SECRETARY'S ADVISORY COMMITTEE
ON
GENETIC TESTING

MEETING TRANSCRIPT

Wednesday, June 30, 1999
Building 31C, Sixth Floor
Conference Room 10
31 Center Drive
Bethesda, Maryland

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I N D E X

P R O C E E D I N G S

WELCOME AND COMMITTEE CHARGE

DR. SKIRBOLL: Good morning. Welcome to the first meeting of the Secretary's Advisory Committee on Genetic Testing. The Department is very excited about this first meeting and we expect a lot and hope this committee will accomplish a lot for the Department and for the Nation.

It is my privilege this morning to introduce Dr. David Satcher. Dr. Satcher was sworn in, in February of 1998, as the 16th U.S. Surgeon General, and he is the second person to hold the position of the Assistant Secretary for Health and Surgeon General.

I should mention who I am and why I am introducing Dr. Satcher. I am the Director of Science Policy at NIH, Lana Skirboll. The management and administration of the Secretary's Advisory Committee comes from the Office of Science Policy at NIH so that is why it is my privilege to introduce Dr. Satcher this morning.

Dr. Satcher, aside from responsibilities having to do with the Secretary's Advisory Committee, you can imagine Dr. Satcher holds a lot of responsibilities in the Department, including a number of high priority initiatives; moving the nation towards balanced community health systems; eliminating racial and ethnic disparities in health, which is part of the President's Race Initiative; and adopting a global approach to public health, including surveillance, food safety and protecting the blood supply.

Prior to his appointment, Dr. Satcher was Director of the Centers for Disease Control for four years. During that time he had many, many accomplishments. Among them, increasing childhood immunization rates by 23 percent and upgrading our capability of responding to emerging infections.

Before beginning public service, Dr. Satcher spent 20 years at the helm of Meharry Medical School. He was also Interim Dean and Chair of the Department of Family Medicine at King Drew Medical Center in Los Angeles. And notable for this committee, he was Director of the King Drew Sickle Cell Center.

Dr. Satcher, needless to say, has been the recipient of many prestigious academic professional public service awards. I promised him I would not go on too long this morning so, without more ado, let me present my boss under these conditions, Dr. David Satcher.

DR. SATCHER: Thank you very much, Lana, for that very kind introduction and let me say that I am delighted to be here with you.

Reed Tuckson looked at me when you said I was President at Meharry for 20 years. The people at Meharry would probably say it seemed like 20 years but it was only 12.

Let me just say that on behalf of Secretary Donna Shalala, I want to welcome

all of you to this first meeting of the Secretary's Advisory Committee on Genetic Testing. The Secretary of Health and Human Services and I are immensely grateful to the members of this committee for the fact that you are willing to assist the Department and, more importantly, assist the American people through your work on this important committee.

You are certainly among the Nation's leading experts on a broad range of issues relating to genetic testing and you were carefully selected for this assignment because of the depth and breadth of your knowledge an insights.

I especially want to thank Dr. McCabe, Ed McCabe, for his willingness to serve as committee chair, a role, which I am sure he knows, always requires extra time and extra effort so we appreciate that.

The Secretary and I appreciate the commitment of each of you to this important and really critical cause and we are eager to see your deliberations begin so I want to be brief.

I do want to say that last night, I thought, Dr. Skirboll, Lana, talked about your role and she talked about the fact that during the time that you are here you are actually federal employees.

Now there are a lot of implications to that in terms -- in addition to the modest way in which we live in the Federal Government. There are a lot of things that people say and think about being federal employees. Of course, it limits your ability to lobby during the time that you are here.

But I also want to say something that Bill Fahey, a former director of CDC, often says about working for the government, and I think about it a lot, and that is that, in fact, government is the only institution that is responsible to and representative of all the people. So it is a tremendous responsibility and opportunity which we have in government, and when you agree to work with us and to advise us, the impact, the tremendous impact that you can have on the lives of the American people all over this country is one to really consider. So we appreciate your being willing to take this tremendous responsibility.

The committee's function is to help the Department of Health and Human Services address a broad array of complex medical, scientific, ethical, legal and social issues raised by the development and the use of genetic tests.

The committee has a mandate to advise the Secretary on the formulation of policies that will ensure the appropriate incorporation of genetic tests into health care practice and public health practice, and to assess the effectiveness of existing and future measures for the oversight of genetic tests. In addition, we expect you to identify research needs related to the committee's purview.

Today, I think we are reaping the benefits of decades of genetic research with the wealth of knowledge that has already had a significant impact on the practice of medicine and on public health. Hundreds of genetic tests are in routine use for the diagnosis of disease. Many more genetic tests are under development and the number

and variety are expected to grow rapidly within the next decade.

Not only are genetic tests enhancing our ability to diagnose disease, they will make it possible to estimate, as never before really, future disease risk in currently healthy people.

This morning, Dr. Collins, Francis Collins, will discuss the progress of the Human Genome Project and will give you some sense of the impact that this knowledge is likely to have on genetic research and on the development and the applications of genetic tests.

For the most part we have good reason, I think, to celebrate the advances in genetic research and test development. The ability to identify genes that cause or play a role in disease holds the promise for preventing disease, better treating diseases, understanding and promoting health, and lowering mortality and morbidity. But at the same time these advances are posing significant challenges to the U.S. health system. At present, our technological capabilities are, in fact, out pacing our knowledge and understanding of gene function, disease pathogenesis and treatment. To this end, new policy constructs are needed to assure the safety and effectiveness of genetic tests and their appropriate use in clinical and in public health practice.

The opportunities and the challenges associated with genetic testing were extensively studied by the NIH/DOE Task Force on Genetic Testing. Later this morning you will hear from the co-chair of that task force, Dr. Neil Holtzman. Neil will review the report's major findings and recommendations. The report found that genetic testing was developing successfully in the United States but that there were some problems in three main areas. One, the way the tests are introduced into clinical practice. There are problems in laboratory quality assurance and in the understanding of genetics on the part of providers and patients.

I think that is going to be a really critical issue. The extent to which providers and patients understand genetics and, therefore, are able to make the best of this technology and how we are going to deal with that.

The recommendations were aimed primarily at enhancing the way in which tests are developed, reviewed and used in clinical practice. Some of the recommendations relate to the activities of educational institutions or professional societies, and other private sector organizations. Others apply to programs and functions in our Department of Health and Human Services.

The Department is already acted on several of the Task Force's recommendations, including, and especially I should say, the formation of this Secretary's Advisory Committee.

We have also taken steps to develop recommendations for more specific requirements for the performance of genetic tests under the Clinical Laboratory Improvement Amendments, CLIA. Later today, you will hear more about the role of CLIA and the work of the CLIA Advisory Committee from Ms. Yost and Dr. Charache.

We have promulgated regulations for components of tests, thereby introducing a degree of FDA oversight of commercial laboratory-based testing services and we are taking steps to ensure that FDA has the advisory expertise needed to review genetic test kits. This afternoon, Dr. Alpert, Susan Alpert, will summarize current FDA regulations on genetic test kits and components of genetic tests and describe the role of the Medical Devices Advisory Committee.

We have established the Human Genome Epidemiology Network, HUGENET, at the CDC to advance the collection, analysis, dissemination and use of peer reviewed epidemiologic information of human genes. I must say that Dr. Khoury, Muin Khoury, has played an outstanding leadership role in that and, of course, will be serving here as an ex officio member of this committee.

The Department is in the early stages of exploring how voluntary public-private partnerships might help encourage and facilitate the gathering of data on the clinical validity of genetic tests. At a future meeting you will hear more about this effort.

While we have taken a number of important steps to address the challenges of genetic testing, there are still many critical questions to be answered. One topic of particular importance is the adequacy of current government oversight of genetic testing.

The Department has a dual responsibility with regard to genetic tests. Given the significant potential health benefits of genetic tests we must encourage their development and their integration into health care practices and public health practice. At the same time we must prevent harm to the public from invalid or inappropriately used genetic tests. A dual responsibility.

The NIH/DOE Task Force on Genetic Testing discussed the question of how tests should be assessed and made suggestions about the need for local and national review of tests and for comprehensive data gathering to establish the clinical validity of tests.

It further called on the Secretary's Advisory Committee to help determine whether some genetic tests should undergo more stringent scrutiny than others and, if so, what criteria should be employed to determine the appropriate degree of oversight. While suggesting that the clinical validity and utility of tests be assessed through outside review, the Task Force stopped short of defining where and how a national level of review of laboratory based genetic tests should occur.

The Department has carefully considered the approaches suggested by the Task Force but deferred further action pending the establishment of this committee and we await your input on those critical issues. The role of Institutional Review Boards and the question of whether further government oversight is needed have significant implications that require further analysis and especially an assessment of the public's perspective on the matter. The public's perspective. I emphasize that because you are going to hear a lot from us about our expectations of this committee in terms of reflecting the public's perspective and some of the challenges involved with that.

Consequently, with a view towards ensuring that our authorities are being applied in the most effective and efficient way possible, we are requesting that as your first task, you review the current extent of federal oversight of genetic tests and in consultation with the public consider whether further oversight is needed and, if so, just what mechanisms should be employed and to what degree.

Now you have received the background paper which was prepared by an interagency staff group that summarizes the current authorities governing genetic tests and poses a number of specific questions that we would like for you to address. In particular, I would like you to solicit and assess public comment on these questions. By December 1st, 1999, prepare a report to the Secretary on the committee's findings and recommendations relative to these comments. The Department staff certainly will be ready to assist you in any way necessary. Obviously, you are advisory to us and in the final analysis you decide how you want to advise us but obviously we have some areas of greater concern than others at this point in time.

Although we have assigned the committee's first task and will no doubt make other assignments in the future, we want the committee to have the latitude to identify issues that you believe are in need of policy deliberations and advice. Indeed, the charter calls on the committee to identify policy issues raised by genetic testing and to make policy and procedural recommendations to the Secretary on how such issues should be addressed. A very important part of the charter charge.

I know that you are devoting time later today to a discussion of potential topics and issues and tasks that you will be identifying as priorities, and organizing a work plan for the next one to two years. Your assessment of the priority issues is certainly critical and the expertise and knowledge you will bring to those issues will be invaluable. There are a lot of issues and potential issues related to genetic testing so, I guess, in the words of Steve Covey, "Putting first things first is going to be a tremendous challenge here."

Before closing, I want to explain an aspect of the committee structure. As you know, the Clinical Laboratory Improvement Advisory Committee and the Medical Devices Advisory Committee have relevant roles in ensuring the quality and safety of genetic testing laboratories and genetic test kits. As I mentioned, you will hear more about these roles later today.

As a way of ensuring coordination and preventing unnecessary duplication of efforts, we appointed current members of CLIAC and the Medical Devices to serve on the committee. Coordination is really critical. Again, I think many of you recognize that from our discussions with you last night.

Dr. Charache is the CLIAC liaison and Dr. Boughman is the liaison from the Devices Committee. As warranted, these members will brief you on relevant activities and serve as conduits of information and advice. This interaction is critical but the committee should be careful to avoid assuming the functions of those other committees, and I think that is a very important point.

The committee also consists of six nonvoting ex officio members whom you will meet shortly. The members represent the agencies within the Department that have

roles in safeguarding public health but also in fostering the development of valid genetic tests and facilitating their availability and their beneficial use for medical and public health purposes.

These agencies must collectively address the broad array of important and complex policy issues raised by genetic testing and the service of their representatives on this committee will have to foster program and policy coordination on these matters, as well as provide you with important sources of information about our policies and programs.

I want to emphasize that because I do not want you to take for granted the presence of these ex officio members. I really think that it represents a tremendous opportunity on the one hand, as I said last night, for input from these agencies and the resources that they can bring but also an opportunity for you to facilitate coordination among the work of these agencies through your recommendations but we are listening very closely to the advice that you give as you give it but also as it is transmitted to the highest levels of the Department to the Secretary.

I am pleased to be with you today to help to open your first meeting and to welcome you here into this role and I certainly welcome the opportunity to work with you and to advance your work.

I regret that -- I am sure you have heard this before -- I regret that other commitments today will prevent me from staying for the rest of the meeting but I look forward to hearing about the outcome of your deliberations today and, as your work proceeds, to receiving your recommendations and transmitting your advice to the Secretary on how we can best take advantage of the promise of genetic testing while avoiding its potential harms.

But I must say that even though I am not going to be sitting through the meeting today and probably a lot of the rest of them and the Secretary will not, we have our best ears here so you can be assured that we are listening to you actively.

The challenges and opportunities of this expanding technology are substantial and we are really pleased that we can now count on such a distinguished group of experts to help us steer the right course. Your role is critical and has critical importance to this nation and I think to the world.

I mean, I have just returned from Geneva, leading the U.S. delegation there for three days, and it is really clear that in so many ways we live in a global community, especially when it comes to medicine and public health so what goes on here has implications globally, and you know that.

So you have my best wishes and the Secretary's as you begin this important endeavor. Thank you.

Later today, I know that Bill Raub, who is leaving with me now to go to a meeting downtown, will be back to participate in your deliberations and can certainly expand on some of the things that were included in the communications that we had directly with you. If there are any burning questions now before we leave -- we have to

leave shortly. And then, of course, you are going to hear from several of the people I mentioned, Francis Collins, Neil Holtzman, and others so I think there will be opportunities to get all of your questions answered.

Thanks very much.

DR. McCABE: I want to thank you, Dr. Satcher for your very clear commitment to the committee and our activities and for outlining our opportunities and our challenges. We appreciate your time with us this morning.

Just to reiterate because I think that when we took on this task I know that I saw that it would take some time for the committee to come together and begin to work towards the common purpose. We have just been given an assignment which will speed that process rather dramatically.

In terms of the dual responsibilities of the Department over this committee then of developing the promise of genetic testing and assuring the development of that promise while also preventing harm to the public, we do need then to come together quickly to begin to have recommendations regarding oversight and the public's perspective on this by December 1st. So just to remind all of you that our feet are to the fire, and we will be talking more about that this afternoon on how we can proceed to accomplish that task.

What I would like to do now is go around the table and have each of you introduce yourselves, the members and the ex officio members, and then have you spend about two minutes each, in order for us to keep on schedule, just talking about what are the issues that are important to you that you bring to this committee. I think it will help us understand each other and will help us move forward.

So if we could start then with Ms. Barr?

INTRODUCTION OF SACGT MEMBERS AND EX OFFICIO MEMBERS

MS. BARR: I am Pat Barr. I am an attorney from Bennington, Vermont. For the last ten years I have been doing consumer and patient advocacy through the forum of the National Breast Cancer Coalition. Actually it is nine -- eight years. And I chair the organization -- I am president of an organization called the Breast Cancer Network in Vermont. I served on the Genetic Testing Task Force. I have also done informed consent work on tissue banking and I have worked with the NCI in their Genetics Working Group.

I think the issue of greatest importance to me is how complex this is as we move from diagnostic genetics to predisposition, and predictive genetics, and how we begin to not deal with one variable but have to deal with increasing numbers of variables, and begin to communicate with the public about risk, and be sure that we have the mechanisms within our public resources to make our medical system, which is still private, as good as it can be, and that good private medicine is dependent on good public information, and that the collection of data now about which genes interact with

which and how they interact, so that people can get good information about risk and make good health judgments is a tremendous challenge, and so that as we look at regulation of genetic testing we want to be sure that whatever is put in place is flexible, is transparent so the public will understand it, and we can talk about it in reasonable and understandable ways with the public because there is going to be a long-term public discourse now about genetics, it has begun and it will continue for a long time, and we have mechanisms to continue to collect very good data, probably quickly and efficiently, and analyze it.

DR. McCABE: Thank you very much.

MS. BEARDSLEY: My name is Kate Beardsley and I am also a lawyer with the Buc & Beardsley in Washington, D.C., where we practice largely in front of the Food and Drug Administration. I specialize in medical devices and have done a lot of work with in vitro diagnostic companies who are either making the test kits or who are making parts of test kits.

I am, I guess, particularly interested in a couple of different things. One is that I think informed consent is a very, very important part of this process and I am really interested in helping sort through some of those issues. I am also interested in the confidentiality and the privacy issues that are involved here. Third, I am really interested in seeing what we can do to make sure that the diagnosis of rare diseases dose not get left behind here.

MS. BOLDT: Good morning. My name is Ann Happ Boldt. I am a genetic counselor. I practice in Indianapolis at St. Vincent hospital. I have been a genetic counseling about ten years actually tomorrow and I am board certified by the American Board of Medical Genetics and a charter member of the American Board of Genetic Counseling. I am also very involved in the education and supervision of genetic counseling graduate students, as well as medical residents and other health professionals. I have served on the board of the National Society of Genetic Counselors for the past seven years and three different leadership roles and am currently rolling off as past-president to the NSGC. During my year as president I actually was very fortunate to go abroad and talk to the European Society about the evolution of the genetic counseling profession in our country and it was interesting to have that dialogue with different countries of where they are in terms of their genetic testing and counseling.

Some of the issues that I really would like to concentrate on are really ensuring quality, pre and post-test, genetic counseling prior to the tests that we are talking about, and also ensuring competence of the health care providers that are ordering these tests.

Again, about two years ago, I had to deal with an individual chiropractor in Indianapolis that was trying to market genetic testing on the web so I think this is something that we have to also address and that kind of ties in with some of Dr. Satcher's oversight issues. He is no longer on the web but I think this is some of the issues we have to be worried about.

Also, I believe it is imperative that we educate all health professionals in

genetics but I think we also have to look at increasing efforts of training more genetic professionals, geneticists and genetic counselors because these individuals are going to have to be around to educate the other health professionals and stay abreast of what is going on. It is also going to be necessary for the lab personnel for the CLIA regulations. And, also, just so that we are going to be able to be the ones that deal with the high complexity cases that we are going to be dealing with in the future. And really, lastly, in terms of reimbursement issues for both genetic counseling services and testing as well.

DR. BOUGHMAN: Good morning. My name is Joann Boughman. I am a medical technologist by training initially and a board certified Ph.D. medical geneticist actually with specialization in population and mathematical genetics. My research has been primarily in the area of neurogenetic disorders, deafness, blindness and more recently periodontal disease and congenital cardiac malformations. I am a founding fellow of the American College of Medical Genetics and I have been a board member of the American Board of Medical Genetics and am past vice-president of that organization. As well as being a federal employee today, I am on vacation today from my state employment at the University of Maryland where I am the Senior Vice-President for Academic Affairs and Dean of the Graduate School.

In my role here I am also the liaison for the FDA having served on the Medical Devices Panel in Clinical Chemistry and Toxicology previously and now in Genetic Testing. I think, although I have been a laboratory geneticist but more recently a population mathematical geneticist and now wearing my role as a more general academic administrator at a complex institution, I think I may be labeled as an eclectic geneticist and have a variety of interests but recognize that one of my major roles here is to make sure that we have a full and open communication between the different branches, and I will certainly do my best to bring information to you from the FDA's side and provide information back to the FDA from the deliberations of this committee.

DR. BURKE: I am Wylie Burke from the Department of Medicine at the University of Washington. I am a geneticist and primary care provider and was the founding director of our University Women's Health Care Center. My research primarily addresses genetics issues in terms of how consumers respond to the opportunity for genetic risk information and how primary care providers respond to the opportunity to use genetic risk information, and in that context how we can most productively provide education to primary care providers about genetics.

In the context of this committee, my interest is particularly in the development of an evidentiary standard for the use of genetic information in both clinical and public health practice and taking into account, as we develop that, appropriate methods for development of consensus, including all interested parties and appropriate methods for implementing and ensuring good evidentiary standards.

DR. CHARACHE: I am Patricia Charache and I think I might be described not as an eclectic geneticist but perhaps an eclectic laboratorian. I am Professor of Pathology, Medicine, and Oncology at Johns Hopkins. I came into pathology through microbiology and infectious diseases. Initially I was a clinician in infectious diseases and I remain a clinician. One month a year I do take care of patients so I have worked at the interface between being

primarily a laboratorian and also in the clinical arena. My research in microbiology has been home brew molecular testing targeted towards viruses but I am very familiar with molecular testing and home brew issues. In 1993, I stepped down as Director of the Microbiology Laboratory to accept a broader role in the Department of Pathology and all of the laboratory sciences primarily in a quality control role. It has been my task to credential now the directors of all of the laboratories who do any patient care testing in our overall institution, no matter what department they are in, and to work on ensuring the quality of any patient care testing that has been done there. Among the 80 units that I now have to address there are six whose primary occupation is genetic testing and I came very heavily into that field, in part, through that role. I am not a geneticist but I am very steeped in the laboratory sciences.

I was added to CLIAC almost three years ago and I am the representative to this group from CLIAC. I had been an ad hoc consultant to the CDC in the late '80s as the CLIAC regulations were being developed. In addition, I have served on advisory -- the Medical Devices Advisory Panel for the Food and Drug Administration and a number of different panels. Since 1996, I have been on the Microbiology Panel and I am now chair of the Microbiology Panel for the FDA. I have worked with HCFA primarily from an educational perspective. We at Hopkins helped design the earliest training programs for the HCFA surveyors and I have continued to work with group, which I esteem very highly, most recently in April with an educational program. So I think I can contribute to the CLIAC perspective some background of understanding of the FDA and HCFA, as well as CLIAC.

My major interest parallels some of the charges that my predecessors have already outlined, which I will not repeat, but I am hoping we can tackle some of the tough questions. Not the ones that are easy such as how you do a lab test but how do we get the clinicians to order an appropriate test? How do we help the clinician avoid the pressure from the patient who wants to know that a test is performed? As well as some of the other issues which are medical, legal and social that pertain to the use of the genetic test and putting it appropriately into the public health arena.

MS. DAVIDSON: Good morning. I am Mary Davidson and I am Executive Director of the Alliance of Genetic Support Groups. The Alliance has long been active in bringing genetic advances to -- we have long been active in the commitment to bring genetic advances to all families and communities and integrated these advances into the health care system. Our mission is to promote optimal health and to promote quality of life for everyone affected by genetic conditions. I am really here to voice the concerns and perspectives of the 270 consumer and professional organizations that make up the Alliance with a reach -- a large membership reach of over three million families, children and adults. I see my role really as linking these family, consumer and public concerns to all the important issues before us. We have worked very hard over the last 13 years to assure that the perspectives of all communities and people of all ethnic, cultural and economic backgrounds, and all genetic related diseases from the rare to the more common are represented in discussions and shape public policy, research and health care delivery.

I would just like to tell you some of our major goals because I think there is incredible harmony with the issues that are facing this committee. Our goals are to improve access to quality, family centered, culturally sensitive, affordable genetic services; to provide parents and individuals who find themselves suddenly faced with a bewildering diagnosis and an unknown future, to provide them with helpful information, support and resources; to

make health care providers and health professionals aware of the unique needs of families, as well as the valuable resources in the support group community; and to actively develop research partnerships between all stakeholders in research, researchers, participants, disease specific support groups and the Alliance; and, moreover, to share consumer perspectives and lessons learned in forums like this to help move the integration of genetic technology into health care services so it reaches our families.

So, like many of us around the table, I am also wearing several other hats and so I wanted to share them with you. My professional training is as a clinical social worker. I worked for about 20 years as an individual, group and family psychotherapist working, in particular, with people with chronic medical problems and, in particular, with people with chronic pain problems, both as an individual therapist but also as an advocate for their particular interests and those of their family.

Another experience that really defines who I am professionally and personally is that I have lived overseas beginning as a student, as Peace Corps volunteer, and as an adoption and foster care worker in Vietnam, as a social worker with a cross-cultural practice in Tokyo. I have lived in South America, Asia and Europe. I just returned, also, from the European meeting and the European Alliance of Genetic Support Groups, and can also see how what we will do here has very large implications. My two children were born and raised in Tokyo, Japan, and spoke Japanese before English. So it very much defines who I am.

My fourth hat -- I think really this is the most important of all -- is that I am here representing also my own family. My son and daughter, my friends and family, through whom I am certainly in close contact and very familiar with a range of rare and more common genetic conditions. I can really feel that I am acting as a voice for them but also for all the families that call the Alliance help line asking questions.

I just want to kind of bring this back home to us with asking questions like: Should I get tested? Where can I find a test? Are there research studies on my disease? What does all this mean to me? What if my HMO finds out? My employer finds out? Where can I find out more information, more resources? Can I switch jobs and insurance companies? Am I to blame for my grandson's problems? Why doesn't anybody know anything? Who can answer my questions and address my concerns? So I think that I am in a position linked to both current consumers of genetic services as well as the public through our programs and our help line to be able to represent their concerns and their perspectives and their lessons learned to this committee.

In terms of the issues and what is important to the Alliance, this is -- I have pondered this for a long time because they are all important to us. They really all define our mission. But I would say that we are currently, in particular, concerned about health care delivery and the fact that one more -- that fewer and fewer families are -- have health care coverage of any kind much less access to genetic services. And that managed care, which is really dominating the market, has yet to really understand or acknowledge or recognize what genetics can bring to greater health and well-being of the families in their care, and that we desperately need federal privacy and antidiscrimination protections so that families can participate in the research that is necessary to know that we have quality genetic tests that can be ready for integration in the health care system. But we want to see the day when everyone in this process, you know, from the lab technician to the lab director to the provider to the insurance agent, the managed care administrator, the health professional, the

public, the employer, the policy makers, the legislators and families, that they really understand and have a better appreciation and literacy in this new science so that it really brings us all of the benefits and we can avoid harms.

MR. HILLBACK: I am Elliott Hillback. I am Senior Vice-President for Corporate Affairs at Genzyme Corporation, one of the world's largest biotech companies. One of our business units, Genzyme Genetics, is the world's largest genetic testing laboratory. We do about 300,000 to 320,000 genetic tests every year. For about five-and-a-half years of my nine years at Genzyme, I was president of that business unit so my knowledge of genetics is really grassroots. I was taught by the folks who worked for me in that business unit. I am also very active in a number of policy related issues. I am Chairman of the Ethics Committee of our trade association in biotech called BIO. I am on a panel of a group at the Whitehead Institute that focuses on genetics and public policy and organized a very large bioethics conference last year. I was with Pat, one of the two surviving members of the Task Force on Genetic Testing, one of the two people that is on this group. I think we learned a lot in the process that we went through there that we will hear more about later this morning in raising some of the issues that we have to deal with.

There are a lot of important issues but I think one of the things that is sort of fundamental to me is that I believe that just the fact that this group exists is an interesting issue. There is not a Secretary's Advisory Committee on Prostate Specific Antigen Testing and there is not a Secretary's Advisory Committee on Cholesterol Testing but there is on genetic testing. I believe to some degree we have, all of us that are involved in genetics, have helped create that environment. We have created a mysticism around genetics. We, I believe, have convinced the American public and maybe convinced ourselves that somehow these tests are specific, they tell the future, they are black and white and not grey, and one of the big issues that I think we have and it is what makes it so difficult for us now is that we have set expectations and we have scared a lot of people.

One of our biggest tasks, I believe, both for the people providing tests, whether they are kits or services, but also the people delivering the information that we create, is to be careful that we talk about what we know and what we do not know, and that we give very honest information. I think Pat said it very well in her first comments. I think that is the biggest challenge, is to find a way to -- for the health care industry side, the test provider, to provide information in a useable form and say, this is what this test does and does not do, and then have practitioners, whether they are general practitioners or geneticists, or genetic counselors, who can take that information and use it in a very clear way so that patients know what the issues really are and are not and they are not told, "Well, this test says you have this disease."

This is not, as one ethicist likes to say, your future diary. This is just a series -- another way to get information like a cholesterol test might be. I think the challenge is for us to get the American people and all of us to accept that this, if well done, can be as routine as a cholesterol test seems to be in most people today. So I think that is a fundamental issue that because there is this mysticism because there is this level of concern, it drives issues about confidentiality and privacy, it drives issues on how it should be regulated, but there is a more fundamental issue I would like to make sure we address.

Thank you.

DR. KOENIG: My name is Barbara Koenig and I am the Executive Director of the Bioethics Center at Stanford University, which is located in the medical school where I am on the faculty in the Department of Medicine. I also, at Stanford, helped begin about a three years ago a program which --

DR. McCABE: Could you use Elliott's mike? We are not picking it up.

DR. KOENIG: Okay. Great.

I also about three years ago started -- helped start a program at Stanford called, "The Program in Genomics, Ethics and Society," which is really designed to take a very multidisciplinary look at the issues surrounding advances in genomics in general. In that program we have done a number of reviews of particular new kinds of genetic technologies. We started out by looking at genetic testing for breast cancer susceptibility because that was a very important issue at that point. We have also reviewed Alzheimer's disease and most recently have tried to broaden our approach to thinking more conceptually about how the technology itself and the ability to do multiple, multiple kinds of tests at once is going to transform many domains within medicine, public health, clinical practice, et cetera. We have the Fellows Program and various other things. So that is my professional hat to one extent. My disciplinary background is as a medical anthropologist, which is a rather unusual perspective I think to bring to this committee. I am also a pediatric nurse by training and perhaps my first experience in genetics was working in a university hospital, which was a referral center, of course, for many, many children with genetic diseases in the upper Midwest. So I have that clinical background, also, which I think constantly serves me well.

In terms of what my own vision and what I think the key issues are, I am very -- when I did my Ph.D. dissertation, lo these many years ago, one of the things I was most interested in was the question of how new technologies transform from the stage of being considered clinically experimental to becoming routinized to becoming a standard of care. So I am a little -- Elliott just said he is interested in these becoming routinized. I want to call that -- I want to sort of -- us to -- I am hoping we can sort of hold that as an important question to really examine and to be cautious about that because my own view is that often our ability to do a particular genetic test in a way is a byproduct of our -- of the basic science questions which we are trying to answer. So I am very interested in terms of how to design research protocols in a way which do not necessarily lead to the quick -- to the idea -- to an uncritical acceptance of the idea because a test is technically feasible or a procedure is technically feasible that it suddenly needs to move out and become a marketable entity out in the "real world."

So that is, I would say, my main interest but I have a couple of other specific interests I just want to mention because I have done some research as an anthropologist trying to look at how families deal with risk. How families, say, undergoing genetic testing for breast cancer understand some of these very complicated issues and how -- as well as just the whole idea of risk is going to be -- is so hard to explain moving from the issue of technical probabilities to how people in the real world understand risk numbers like you have a 15 percent of X over your lifetime. I think we do not really know as much about that as we think we do so I think that is an important area of research.

I also am very interested in issues of what I am calling race/ethnicity genetics and I think another thing this committee needs to be very careful about is thinking about how the ability to do genetic tests has the possibility of transforming the way we think about and understand categories of difference in American society. So one of the things I am interested in is very carefully thinking about the difference between social categories of difference versus those that have their basis in biology and when it is appropriate to use one kind of category and when another kind, and those are very important issues in terms of targeting genetic testing for particular populations, for example.

So I think I will end with those are my interests.

DR. LEWIS: I am Judy Lewis and I am a nurse by training. I am on the faculty of Virginia Commonwealth University in Richmond, Virginia, in the School of Nursing where I am a women's health nurse practitioner and teach graduate/undergraduate and doctoral students. My doctoral work was in the area of social welfare and health policy so I usually when I ask questions I ask them with the health policy hat that I wear. My particular research interests right now are looking at women who become pregnant after history of infertility and for many women looking at some of the issues that relate to infertility also have a strong genetic component because there are opportunities for preimplantation genetic counseling. So those are the particular clinical areas that I am interested in. As an educator, I am very concerned that as we get new knowledge we do not necessarily have faculty that are prepared to teach that so that there is a real lag in terms of getting knowledge to current students. So part of my interests are looking at how do we educate both the current practitioners and also those who are teaching the next generation of practitioners.

As a nurse I am real interested in terms of looking at patient education and some of the issues that relate to how we teach and how we help patients become informed and how we help patients become empowered in the areas of informed consent and also informed consent meaning the fact that it is okay not to consent to something. I think a lot of times once you make a decision to seek health care you end up on some kind of treadmill and people -- I mean, certainly in the infertility work that I do I see people who end up ten years down the road saying, "I wish I had never started this because once I started I could not figure out how to stop." So the whole issue of informed consent to me is informed consent meaning informed decision making, not informed consent, and I think those are two very different things sometimes.

I am also concerned, as a social policy person, with looking at access and making sure that populations -- I agree with you in terms of some of the population issues and populations getting targeted but I also think that as new tests and new technology becomes available, it becomes differentially available, and some people have it and some people do not. So I am wanting to make sure that as we roll things out into practice that we do it appropriately cautiously but also in a way that does not discriminate for or against people based on their health insurance, their ability to pay, where they come from, and all of those issues.

So those are my major concerns.

DR. PENCHASZADEH: I am Victor Penchaszadeh. I was born, raised and educated in Argentina so my native language is Spanish. I got my medical degree and my

pediatric training there and here I trained in medical genetics, cytogenetics and public health. My every day work is I run the Clinical Genetics Division at Beth Israel Medical Center in New York. I am directly involved in delivering the services and care for genetic conditions. I see patients and I do genetic counseling. I order genetic tests. And I have to explain both to, you know, primary physicians and to patients what they mean and what they do not mean. I am also interested in international health. My Latin American heritage brings me to provide consultant services for the development of genetic services and development in general through the WHO and PAHO unit of genetic diseases.

My main concerns have already been voiced by many people. I am concerned about the lack of knowledge of what -- of the reality of genetic testing by many -- by many actors in this field but particularly primary care providers and patients. I think we have to find the right balance between all the market pressures for the implementation on one hand and the real needs and well-being of the populations. You know, many people decide on the basis of wrong or not clear information about what genetic testing is and what does it really mean.

I am concerned about the lack of equity in access to all genetic studies and not only genetic testing in itself but, in general, the prevention and care of diseases influenced by genetic factors in the U.S. Particularly, the needs of diverse populations, ethnocultural, socioeconomic diverse communities that because of linguistic, cultural and economic issues do not have the proper access to knowledge nor to services. And sometimes, you know, I see them steered from service to service when they have the appropriate insurance and when they do not they simply fall through the cracks.

I think that the issues of education are essential not only of professional -- health professionals and public but also of main actors in this field, which are the media. The media can and should play a role that I do not see being played. I see a media largely –- with of course with honorable exceptions -- issues regarding genetic testing which leads to mystification about the determinism of genetic information and so on and so forth.

Issues of quality assurance of genetic testing is another issue. I think that this is probably one of the most technical and restricted things that, as we heard, we have to tackle as a first task and it might be one of the easiest things to tackle. The other complex issues of equity of access, attention to needs of diverse populations and a good balance between market pressures and the need of the public are my main concerns.

DR. TUCKSON: My name is Reed Tuckson. I am a general internist whose clinical interest for years was the care and advocacy of persons with sickle cell disease. I have a long background in public health serving as the Commissioner of Public Health in the Nation's Capitol for a number of years. Prior to that I was profoundly influenced by the thousands of people that I was allowed to serve when I ran the Mental Retardation Developmental Disabilities Administration for the District of Columbia. I have been able to serve as the Senior Vice-President for the March of Dimes Birth Defects Foundation, which allowed me to supervise the research agenda, the legislative agenda, and a 100 and some community based programs across the Nation. Following that, I have been an academician and ran an academic health sciences center in South Central Los Angeles so I am particularly interested in the issues of equity as well as the training of physicians and other health professionals.

Finally, I am now at the American Medical Association where I am responsible for the science, research, technology, public health, medical education, ethics programs of the AMA so that I am looking clearly at the issues of how do we introduce these issues into practice and how do we educate providers, how do we facilitate the patient-physician relationship, and how do physicians work with other members of the health delivery team, and all of those issues in close collaboration with my associates in the various specialty societies and so I am very much eager in collaborating throughout that system.

Finally, I have an interest personally in having served on a number of federal health policy deliberations such as this that combine the interest of science with ethics into public policy deliberations and so I am particularly eager to get at this work.

DR. McCABE: Francis?

DR. COLLINS: Thanks. As the first of the next round of nonvoting liaison members, I am Francis Collins. I am happy to have been chosen by Harold Varmus to represent the NIH on this very important committee and I will have the opportunity to say a bit more to you in a luxurious time frame in a few moments. Just by way of background, I am trained as a physician, an internist, but with a specialty in medical genetics. As a physician, I have spent many hours in clinics counseling families and individuals with genetic disorders. I celebrate the advances that are occurring in that field, which cannot come too soon for families who have lived in uncertainty and ambiguity and lack of hope for far too long. As a researcher, I have been involved in the search for genes involved in specific diseases, particularly cystic fibrosis and neurofibromatosis, and Huntington's disease, and multiple endocrine neoplasia, and most recently my laboratory is involved in a very ambitious and, hopefully, some day successful effort to track down the genes involved in adult onset diabetes. But perhaps I am particularly here as the Director of the National Human Genome Research Institute, which is the lead agency in the U.S. funding the Human Genome Project, and because the U.S. has the largest investment in this project of any country in the world, certainly NHGRI has played an international role as well.

As I will say in a few moments, the advances that are occurring scientifically through this project are truly dizzying in terms of their speed and I share with all of you a concern that we need to link up those basic science advances in a very aggressive way with an assessment of the public policy consequences, particularly as they regard the use of genetic methods testing especially in the practice of medicine.

As far as the issues that I see as particularly important for this committee, I am delighted that Dr. Satcher has given this initial charge, although I am frightened to death by the fact that it is five months from tomorrow that he expects to have a report from this group about what is clearly the most pressing and most difficult to answer question. But I do think what we should consider, and Wylie said this already, is how to implement the evidentiary model for genetic testing.

We have a new field here particularly for predictive genetic testing. We have an opportunity to introduce this new field into clinical medicine in a fashion that is supportable by rational decision making and by data as opposed to some ad hoc approach which might lead us down the path of just sort of a PSA kind of mess, which we would all regret. Here we, around this table, I think, have to figure out how to make that happen so that the

efficacies and the toxicities of genetic testing are reasonably well assessed and we have some means of oversight to be sure that such tests are introduced in a rational fashion. That will force us to face the challenge about how to balance that kind of oversight without quashing a very important field or demonizing genetics, which, I take Elliott's point, is a real risk here if we overdue the statement about the toxicities.

Also, it will challenge us particularly not to do damage to rare diseases because those are, I think, in a particularly vulnerable situation with very few laboratories willing to actually carry out such tests. It is possible we might completely destroy any interest in doing those tests if we come up with heavy-handed mechanisms that small laboratories simply cannot carry through.

So the final thing I would say is I hope we figure out a way to keep this all simple. We will have a lot of acronyms floating around the table today, various agencies, and laws, and regulatory systems. And having been involved in these discussions now for some years it always gets a little discouraging sort of towards the end of the discussion when you cannot quite figure out how did we get in this particular complex network of mechanisms, and if there is some way we can try to keep our eyes on the ball, that would be great.

DR. FEIGAL: Good morning. I am David Feigal. I am here representing the Food and Drug Administration for the Commissioner, Dr. Jane Henney. I am the Director of the Center for Medical Devices. It is a job that I am relatively new at although I have been in the FDA, both in the Center for Drugs where I was the head of the Antiviral Division from 1992 until about two years ago, and also as the Deputy Center Director for Center for Biologics where I worked with blood products and access but also was involved in thinking about the clinical trials and the models for approval of gene therapies.

I think that figuring out exactly what the role of the FDA is, is complex even for older products. We are nearly a century old as a consumer protection agency but we share our responsibilities as a consumer protection agency with the states who have state-by-state rules for regulating medical practice, including laboratory medicine, and medical privacy. We share the responsibility for the oversight of advertising with the Federal Trade Commission and we share in complex ways the regulation of hospital practice and hospital management with HCFA, with the Joint Commission, the American College of Pathology, and many of the other kinds of organizations that have been involved in ensuring quality so it is a complex -- it is a complex environment.

I think if I had to summarize what the theme of the FDA is and how it relates to this group's task is that the fundamental core of our business is to examine claims. What is being asserted about a product? And the radical idea that Congress had is that claims should be evidence-based. The types of claims that we are specifically charged with are claims for things. The claims for tests, for kits that are put into commercial practice, particularly across state lines, although that includes almost everything.

One of the areas that has been challenging in the regulation of laboratory tests has been that laboratory tests often do not begin as things but they begin as services. They begin as information that is shared in the practice of laboratory medicine by reagents that are developed locally and by systems that are developed locally. Already this morning we have heard the phrase "home brew," and that is one of the areas that is one of the challenging ones

to define the regulatory framework.

One of the oldest debates in the FDA is where is the burden of proof in terms of asserting evidence about claims? We began at the turn of the century with the philosophy that the burden of proof for a claim is actually on the FDA's part and so if you could not prove that something was false and misleading or fraudulent then it could asserted. So when there were many possibilities of what information could be used for, almost all of those were promoted. That burden of proof for many things in FDA changed to the claimant and to sort of summarize that philosophy, if little is known you can only claim a little. But I think you see this different standard because the standard for one class of products was changed by Congress about five or six years ago if you contrast the claims that are made for food supplements and the structure of all of the things that you hear on the radio, that is one of the most common commercials for those unsubstantiated claims, compared to those in the drug and device area.

The other area I think where FDA has an important role in early product development and early test development is in our role of assuring ethical research, good clinical practices in the testing of new therapeutic products and diagnostics, assuring early access to products, although reimbursement is not explicitly one of our mandates, although our decision making process of where products are and that is used by other groups. So one of the other focuses really that often FDA becomes judged on is how we affect the process of bringing the products to market. So it is a complex area but I think we can sum it up by saying we are from the government and we are here to help.

(Laughter.)

DR. KHOURY: Good morning. I am Muin Khoury, also from the government. I represent Dr. Jeff Koplan, who is the Director of the CDC. I am the director of a newly form office at the CDC, which is the Office of Genetics and Disease Prevention. This office was formed in 1997 after a couple of years of discussion and strategic planning that was started under the leadership of Dr. Satcher when he was the CDC Director at that time. As a result of the strategic plan and the realization that genetics is going to impact on all areas of public health, our office was formed to try to integrate genetics into the work of the agency to provide the kind of infrastructure both at the federal and state level, provide training and communication strategies along those lines.

A little bit about my background: I am a pediatrician with training in medical genetics, also trained in genetic epidemiology, and I have been at the CDC for almost 19 years now primarily in developing surveillance and epidemiologic investigations around the field of birth defects and developmental disabilities until my new role.

I come to this committee with two hats. One, the regulatory hat because of the CDC involvement in CLIA and CLIAC and you will be hearing about that a bit later, which this is a joint partnership between HCFA and CDC. This is not a natural hat for me and I do not claim expertise in this area. It is not also a natural hat for CDC in most other areas. Primarily CDC is a nonregulatory agency. Our interactions -- CDC has both a research portfolio and a service portfolio so we are one of those agencies that bridges the gap between research and services.

My biggest concern, and I think I want to voice a lot of what I heard this morning, is the transition from research to practice and the impact of genetics on the whole population as a whole. We heard the word "evidentiary based medicine" and public health. This is an area that I feel very strongly about and the need to integrate epidemiologic investigations into whatever we do in the field of genetics and genetic testing. As Dr. Satcher mentioned, last year CDC and a bunch of other organizations started a collaboration, which we call the Human Genome Epidemiology Network, to try to bring some order into a disorganized field to study the epidemiology of human genes as they relate to many diseases. More importantly from a prevention perspective, which is the role of CDC, is to identify the environmental factors for which we have a hook. These could be nutritional factors. It could be chemical factors. It could be infectious agents that interact with the human genome and for which, I think, the field of public health will remain to be an environmentally driven field to try to target our prevention strategies to people who need them while not hurting people who do not need those interventions at the same time.

As I said, our office is new so we have begun a very active collaboration with other agencies and the state health departments, and work with many national organizations. Last year in collaboration with NIH and HRSA we held the first annual meeting on genetics and public health, which will be an annual event. That is going to be this year in Baltimore in December. We have begun a prevention research portfolio, which is an extramural research activity, to evaluate prevention effectiveness of new genetic tests and also evaluate gene-environment interaction. We also have a communication research portfolio in collaboration with other agencies.

And a couple of things I want to mention, that it is not enough to integrate genetics into medicine and find when are we ready, but as a surveillance agency we need to make sure that people are served and that the right services happen. So the evaluation of programs -- an example of that is an evaluation of sickle cell newborn screening programs. Both HRSA and CDC have funded a few projects over the last few years to make sure where the gaps are and who is receiving services. Are there any disparities and how we can serve the public better. So I am looking forward to a very exciting time serving on behalf of CDC and I am delighted to know so many people on this panel. Thank you.

DR. LANIER: Good morning. I am David Lanier from the Agency for Health Care Policy and Research and I am representing Dr. John Eisenberg, who is the Administrator of the Agency. A little bit about myself to begin with: By training and experience I am a family physician and a researcher, and a medical educator. I am currently serving as the Acting Director for the Center for Primary Care Research at AHCPR.

I think probably what I can help you with today in a short of period of time is to tell you a little bit about AHCPR because I think as an acronym that is not quite as well known and not quite as much of a household word as NIH or CDC is. Briefly, what we do is to conduct and support health services research, and that is research that looks at the effectiveness and the cost-effectiveness of personal health care services. We are interested in how best to organize and deliver those services, and also how to measure and improve the quality of those services. So I think a lot of the issues that have been discussed this morning relate directly to genetics.

We are quite a small and new agency, both in terms of the number of employees we

have and our funding level from Congress, and because of that we do not have a distinct division or unit that is devoted to genetics but I think some of our interests overlap greatly with what has been said today, and that is in terms of clinical decision making. That is a huge area of interest for us in our research. We are interested in making sure that consumers have the information they need to make informed decisions and we are also interested that the providers and consumers when they come together have the information and the tools they need to make informed decisions themselves. We also want to be sure that we in some way can measure the quality of those decisions and the outcomes for patients that result from those decisions.

A couple of other things: We, in the past, have supported the development of clinical practice guidelines. We are no longer doing that but currently we have centers that are called "Evidence Based Practice Centers" in which we evaluate all the evidence around a certain field and present that evidence to the public to help in developing guidelines of their own. We also have the Center for the U.S. Preventive Services Task Force, which comes up with recommendations for preventive care throughout the United States. I will stop there.

DR. LLOYD-PURYEAR: Hi. I am Michele Puryear. I am representing Dr. Earl Fox for the Health Resources and Services Administration. Historically, HRSA, as it is known, has been the only federal agency with funding for a genetics program that focuses on genetic services or the translation of those genetic services into practice. This program has been concerned about the accessibility, availability and quality of those services, and we have funded projects that have targeted genetics literacy, consumers, the reduction of ethnocultural barriers to genetic services, the training of public health and primary care providers, genetic technology, the financing of genetic services, and newborn screening programs.

Many of the issues that the present panel or task force has raised have been our concerns. Our current projects include a project with Society of Teachers of Family Medicine, Ambulatory Pediatric Association, and Teachers of General Internal Medicine, around a Train the Trainers Program to incorporate genetic medicine into primary care practice. This is being co-funded by NIH and AHCPR and is being coordinated with the National Coalition of Health Professional Education in Genetics. We also are funding a newborn screening -- a National Newborn Screening and Genetic Resource Center this year to help develop genetics policy for HRSA and the states. We are also funding state planning grants to establish state genetics plans, and we are funding seven this year and hope to repeat this again next year. We hope to fund a cooperative agreement with a national consumer organization next year around issues of genetics. Again this would be done collaboratively with other federal agencies.

About myself, I am a pediatrician with training in molecular biology.

And probably HRSA's primary concern is that genetics be established community-wide and that those genetic services should be integrated again into health care practice and also, I think, echoing Muin, into public health programs.

MS. YOST: Good morning. I am Judith Yost from the Health Care Financing Administration. I am the Director of the Division at HCFA which is responsible for the HCFA portion of the CLIA program and, as Muin indicated, it is a collaboration between

CDC and HCFA and soon to be FDA as well.

I guess the major goal that I have is to definitely ensure that there are comprehensive and consistent state-of-the-art quality standards for facilities that perform genetic testing and that these standards can ultimately be utilized to develop global standards for genetic testing as well. Importantly, also, is that these standards when promulgated will dovetail with the recommended solutions to all the other ethical, social and other types of issues that have been identified thus far by this group.

Specific to the laboratory, a couple things that are important and always a challenge and an opportunity to the CLIA program are, again, things that have been mentioned but are important as far as the balance of access to quality. Also making sure that the standards that are developed are flexible and do not go out of date quickly and that they can support the development of new technology, and the consideration of whether actual regulation or legislation is the answer to oversight versus alternative mechanisms such as professional standards developed by peers. I will be talking about CLIA a little bit later so I will not go on any further. Thanks.

DR. McCABE: Thanks very much. I think this has been helpful certainly to me. Let me just introduce myself briefly. I am Ed McCabe. I am Professor and Chair of Pediatrics at UCLA and I am Physician-in-Chief for the Mattel Children's Hospital at UCLA. I have been involved as a pediatrician in the American Academy of Pediatrics and the Committee on Genetics, the Section on Genetics and Birth Defects, and past-president of the American Board of Medical Genetics, and I am president-elect of the American College of Medical Genetics.

The areas of my interest will be very familiar to you now and I will just single out a few of these but in my role in the college I have been very interested in education so that we can have knowledgeable health care providers and an informed population recognizing the diversity of our population in the United States and being sensitive to those issues.

I do research on rare disorders and I am very concerned, as has been brought up, that we not lose laboratories like mine who provide "services" through a research environment to very rare diseases, and that is a serious concern for many because there are a large proportion of patients who are getting care not getting testing, not through approved diagnostic laboratories but really through research laboratories, and there are major problems with that that we will have to deal with.

I think we need to make sure that we continue the exciting flow of information between the bench and the bedside and that we make sure that that flow is quick and provides access to this important new information but we also need to develop adaptable and flexible approaches to deal with these technologies while recognizing both real and potential risks for these technologies. Finally, the overarching goal, and I think we have heard it over and over this morning already, is to provide accurate and meaningful information to individuals who are tested.

So with that, let me move on to a housekeeping thing that I forgot to mention at the very beginning. First of all, this is an open meeting and was announced in the Federal Register on June 9th of 1999. Also, I will just introduce Sarah Carr very briefly. Sarah is in the NIH Policy Office and formerly the head of policy for NIAID and is the Executive Secretary to the committee and needs to make some -- do some housekeeping things for us.

MS. CARR: Yes. I just need to expand a bit on something Dr. Satcher mentioned to you, which is that as citizens you are serving on this federal advisory committee as a special government employee and as a special government employee you are subject to some of the rules that -- well, all the rules that govern behavior and conduct of government employees. I just want to go through a couple of those things.

You were each provided a copy of a document called "Standards of Ethical Conduct for Employees of the Executive Branch" and other material that explains the rules and regulations. We know it takes a long time to go over those things and we really appreciate the time you have spent doing that.

As you know from your reading, government employees may not lobby the Congress, which is something Dr. Satcher mentioned. This is one of the most important rules of conduct so you must take care if you lobby in your professional capacity or as a private citizen to keep that activity separate from activities associated with this committee.

Another important rule relates to confidential information. If in the course of your work on this committee you receive material of a confidential nature you may not share it with anyone outside the committee and you must take care to protect it from being disclosed. If and when the need arises, you will be given instructions regarding the disposition of confidential material.

Before you were appointed to serve on the committee you were asked to provide us with a great deal of information about your personal, professional and financial interests. This information provides us with a basis for assessing real and potential conflicts of interest or even the appearance of such conflicts that could compromise your ability to be objective in giving advice while a member of this committee.

Under certain circumstances waivers may be granted if the need for your service outweighs the potential for a conflict of interest created by your interests. The information you submitted to us was reviewed by authorized staff to assess whether any of your interests might affect your ability to provide objective advice.

Ethics counsel waived the potential for conflict of interest and is permitting you to participate in matters of a general nature that might involve your interests. If a particular matter comes up that would affect those interests specifically you must recuse yourself and leave the room while discussion of that matter takes place. All of your financial disclosure documents are kept confidential and are seen only by properly authorized staff.

If you have any questions about anything I have said or any other of the other material you have received, Ms. Kathryn Valeda, our committee management officer, will be happy to help you with that. Kay is right here. Thank you.

DR. McCABE: Thank you, Sarah.

I just wanted to go over briefly what our five goals are for today.

We want to provide an orientation to the members regarding the committee's purpose

and function. That is number one.

Number two, brief the members on the report of the Task Force on Genetic Testing and some of the actions taken by the Department to address issues raised in the report.

Number three, develop a plan for addressing and gathering public input on the oversight analysis that Dr. Satcher has assigned to us.

Number four, identify high priority issues and tasks that the committee plans to address over the next one to two years.

Number five, develop an overall plan outlining the time frame and approaches that the committee thinks will be necessary to accomplish the future priorities, issues and tasks.

With that, let me move on to our scientific presentation and we will try and do these with each of our meetings. I do not think that Francis needs very much introduction but in addition to being NIH's alternate ex officio liaison to the committee he is Director of the National Human Genome Research Institute and is a renowned geneticist and physician. Under Francis' leadership the Human Genome Project has accelerated dramatically and is moving ahead very successfully and should finish up well ahead of schedule. Dr. Collins received his Ph.D. in physical chemistry from Yale and an M.D. from the University of North Carolina, has numerous national and international awards, including election to the Institute of Medicine and National Academy of Sciences. Thank you for addressing us.

GENETICS RESEARCH AND THE HUMAN GENOME PROJECT: IMPACT ON THE DEVELOPMENT AND APPLICATION OF GENETIC TESTS

DR. COLLINS: Thanks, Ed. I really appreciate the chance to come before this group at your first initial meeting. I think today is a milestone in the field of genetics and in medicine in general and it is a great honor to have a chance to give you a bit of an overview of the accelerated pace of genetic research, much of which comes out of the Genome Project.

I am going to need some help with the focus because there is no focus control on my remote so you may need to sort of make things come and go.

(Slide.)

So in the next 30 minutes, I would like to cover for you what is the current status of the Genome Project and then move quickly into an analysis of how that is likely to affect the field of medicine, particularly as regards predictive genetic testing, which I think is going to be the area of greatest growth and perhaps greatest importance for this group to wrestle with.

(Slide.)

Just to say from the outset, the Genome Project has from its very origins had interest and a commitment to dealing with the ethical, legal and social implications of genetic research. I do not think it is fair to say the Genome Project has produced any brand new dilemmas. They are dilemmas that we sort of had glimpsed in various ways before the

Genome Project was even thought about but it has accelerated the pace with which those are being pushed in front of the public. Therefore, Jim Watson's decision to put five percent of the budget into research on these issues was a wise one and the formation of the ELSI working group back at the beginning of the Genome Project was similarly a very wise decision. Out of that working group came the Task Force on Genetic Testing, which Tony Holtzman will describe to you in a little bit and which some of you served on. So I guess to some degree since this committee was one of the strong recommendations of that task force, you have the Genome Project to blame for being here today and we will take the credit if you succeed. So we are all connected here.

(Slide.)

Just quickly without going over each one of these arrows, I think it is fair to say that since the origins of the Genome Project back in 1990, there have been a variety of ambitious milestones set and I am happy to say every one of them has been met or exceeded. We can now say here in the middle part of 1999 that we have genetic maps that cover the human genome quite nicely and we have physical maps that do the same. We have finished the sequence of a number of model organisms, including quite a number of prokaryotes as well as yeast, and rather recently the round worm C. elegans, and a variety of other things that I will touch on have gotten under way. We have mapped roughly half of the human genes to precise locations on chromosomes and serious sequencing has gotten under way about three years ago and is now in a very accelerated pace.

(Slide.)

To be more specific about that, the five-year plan, which you have in your briefing books under Tab 5 from last fall, has already been revised and superseded by a new set of goals which you see portrayed here. The original plan from back in 1990 was that we would aim to finish the human sequence some time during the year 2005 and by "finished" I mean really finished, highly accurate, no gaps, no ambiguities, and an error rate of 10^{-4} or better. That time table has now been moved forward because of the advances in technology that have occurred and the experience that has been gained over the last three years. We now, by the way, have done about 20 percent of the work as of today and we now aim to have a finished product some time in the year 2003. Actually this diagram says 2002 because I think we will beat that 2003 deadline. Furthermore, because of an interest in the scientific community in having as much of a sequence in hand as soon as possible we have now made a commitment to produce a working draft of 90 percent of the human genome by next spring -- the spring of the year 2000. And that will all be available on the internet for any investigator who wants to use it.

(Slide.)

In fact, that has also been a topic of some debate and this diagram will indicate to you that there is, in fact, a good deal of interest in the genome as a commodity and we certainly celebrate the involvement of the private sector in genomics because that is the way in which diagnostics and therapeutics are going to find their way into clinical practice. At the same time, the NIH and our international partners in the sequencing effort feel rather strongly that basic sequence information of the genome ought to be out there in the public domain without restrictions on its use in order to maximize the likelihood that it will be used for public benefit. Having the sequence is one thing. Figuring out what it does is another

and we believe that it would be optimum for any investigator with a good idea to be able to use that sequence without restrictions. We also, though, look forward to partnering with private sector enterprises that are involved in sequencing on a large scale if one can see this happen in a way that does not compromise this principle of free access to the information.

(Slide.)

Now how has this changed the way in which we have been tackling the identification of genes involved in disease. For single gene disorders that are inherited in Mendelian fashion with high penetrance, the ability to track down such disease genes has dramatically changed over the last ten years. I would remind you it took a full ten years to find the genes for cystic fibrosis and Huntington's disease, and having been involved in those I can tell you those ten years were not a lot of fun with a whole lot of blind alleys that one had to go down and sort of making it up as you go along.

(Slide.)

As an example of how things go now because I think it is a particularly nice one, here is a relatively rare condition called Pendred's syndrome, which is a recessive disorder characterized by thyromegaly and deafness. Eric Green and a number of other groups interested in this disorder studied families in which the condition was occurring and with the genetic maps that are now easily accessible for any investigator were able in a matter of a few days to map the responsible gene to chromosome 7.

(Slide.)

This is all work that was done about a year-and-a-half ago.

(Slide.)

As it turns out, this is actually a page dumped from the NCBI's (National Center for Biotechnology Information) web site on the Human Genome Project, which I would encourage you to go and look at because there is a lot of useful information there, but this schematic shows you progress in getting the sequence done of the Human Genome and the place where the Pendred's gene was mapped to turns out to be on chromosome 7, which by chance is a chromosome that is already pretty far along because of historical reasons. So this has been a glimpse of the future of what it will be like in another year when 90 percent of the genome is done and all these chromosomes are pretty much colored in. By having that sequence available, Eric Green and his group are able to go into the region of chromosome 7 where they have mapped the gene, searched through it, used a variety of software programs to predict the location of genes that might exist in these large stretches of DNA.

(Slide.)

And basically what you are looking at here is a diagram of a large stretch of DNA, about 100,000 base pairs. Each one of these vertical bars is a predicted exon and the lines here connect what the computer assumed would be a gene, which did, in fact, turn out to be a gene. Sequencing through that particular gene in affected individuals showed different families having different mutations but all of them showing abnormalities in this particular gene. So this is a circumstance where the gene was found based on the genomic sequence

and algorithms that allow you to predict the presence of a gene in that position.

(Slide.)

Having the gene in hand, one then can quickly do a search through the very large database that NCBI operates called GenBank and see whether, in fact, there is anything about this gene that looks like something that has been seen before. Here are the statistical values of the matches. Without going through the details here, I think if you just look down the list of other genes that were in the database that matched this one, they are all involved, it seems in sulfate transport. And it has now been shown, in fact, that the normal function of the gene which is involved in Pendred's syndrome is as a sulfate transport and that in some way is useful for both the thyroid and the development of the ear -- of the hearing mechanism -- and it explains, therefore, why mutations in this gene give this particular phenotype. All of this was accomplished by a single post-doctoral fellow working over the course of about a year. A rather dramatic contrast to the way things used to be.

(Slide.)

Well, you will say that is fine but what about polygenic diseases. If genetics holds promise for diabetes, and heart disease, and schizophrenia, and multiple sclerosis, and the common cancers, how are we going to tackle those given that they are not in general inherited in such simple fashion? They are, in fact, often the interaction of multiple genetic susceptibilities, each one of which is rather weak and with environmental contributions playing a role that is even more difficult in many instances to specify but which we know must also be significant. This makes the problem at least an order of magnitude more difficult for the positional cloner trying to track down the responsible loci.

(Slide.)

But I would like to tell you about a new aspect of the Genome Project which is going to, many of us believe, really move this field forward in a rather quantum leap and that is the ability to track down these complex disease contributions using a catalogue of human variation. Let me explain how this might work.

(Slide.)

This is a new goal of the Genome Project. You will see it outlined under Tab 5. The point here is to try go and find as many as we can afford to find in the near future of so-called single nucleotide polymorphisms or SNPs where you might have a T and I might have a C. You can find one of these about every 1,000 base pairs across the human genome when you compare two different individuals so there is a lot of them out there. Most of them will occur in parts of the genome that are not functionally important and, therefore, will not have a phenotypic consequence but some small fraction of them will affect phenotype and some smaller fraction of those will be involved in disease susceptibility. There is gathering evidence to support the concept that these common variants that occur usually across ethnic groups are likely to be at the bottom of the susceptibility to common illnesses. The paradigm, of course, is APO/E4 in Alzheimer's disease but that paradigm, it seems, is likely to apply to many other disorders.

(Slide.)

So if we had this catalogue of variants, you could set about to carry out case control studies of any disorder for which you think there is hereditary contribution and simply sample -- and I have made this overly simple here but here I have color coded the two alleles that you might be studying for gene A and gene B, and I have ignored the fact that we are diploid in order to make this a simpler diagram. Here you are looking at affected individuals versus unaffected individuals and you see roughly similar proportions of the two alleles for gene A and its particular variant, and you would conclude from that observation that at least in this sample set it does not look as if that variant in gene A is involved in the disease that you are studying. Whereas for gene B you see the orange allele over represented compared to the blue one in the affecteds and the reverse in the unaffecteds. Now obviously you need good statistics here to tell you that is not just a fluke and you need to be very sure that you have matched your affecteds and unaffecteds so that the difference you are seeing here is not actually coming from some other cause such as different population background. But if you have done all that correctly and if your statistics tell you that this has a high p value or a low p value then it is likely that this variant in gene B is actually associated in a cause and effect way with susceptibility to this illness.

(Slide.)

Now why is this an exciting strategy? I will come back to that in a second. Let me first say how are we going to get all this variation catalogue put together. NIH funded back last fall a series of proposals which collectively will produce about 100,000 of these single nucleotide polymorphisms over the course of the next two to three years. And then just two months ago in an unprecedented step, which I think we should all celebrate, a group of ten pharmaceutical companies and the Wellcome Trust got together and raised $45 million to speed up the process of developing this catalogue. The work will be done in the three large genome centers that they chose, namely the Sanger Center in England, the Washington University Genome Center in St. Louis and the Whitehead Genome Center in Boston. They aim to discover another 300,000 of these SNP's over the next two or three years so that will add up to something like 400,000 when you add it with the NIH effort. It is nicely complementary using the same DNA samples for doing SNP discovery. Perhaps most importantly of all, this will all be available to any user where there will be no obstructions to utilization of this information. It will all be there on the internet. And to have pharmaceutical companies come forward and make this kind of commitment, I think, demonstrates how critical it is in many people's view, not just in the academic sector, that these kinds of research tools be widely accessible.

(Slide.)

Now let me say this collection of SNPs will then open the door to studies of virtually any disorder that has a hereditary contribution from this new approach, which does not necessarily require you to go out and collect families and carry out linkage analysis, which has been the traditional way in the past and which is certainly very labor intensive. This will also be labor intensive but it will be more powerful. If you go through the analysis this kind of whole genome association study may require something like one percent or a tenth of a percent the number of DNA samples in order to identify a genetic contribution to illness that the linkage based approach would require. But let me hasten to point out -- this is particular relevant for this group -- that it will also be very susceptible to false positives. If you did not match your cases and your controls you will come up with an association, you will assume that it means something, and later studies will show that it did not and that it was

spurious. Ditto, you have got to be sure the statistical analysis is very carefully done because you are going to be doing an awful lot of simultaneous comparisons and the chance for a coincidental positive has to be dealt with.

In my view, this strategy will tell us a lot over the next five to ten years about the genetic contributions to virtually every illness. I would predict that for things like diabetes, or heart disease, or hypertension, we will find several of the common polygenic contributions to those disorders. Not the rare Mendelian subsets but the actual common forms of those disorders. But it will take quite a lot of difficult and expensive epidemiological research to be sure that you have identified what the relative risk associated with a particular variant is. And you certainly want to know that before you begin to introduce this into the practice of medicine as a predictive test. And that means, I think, somebody has to pay attention to whether that data has been collected and whether it has been validated.

(Slide.)

So all of this is going to lead to a great deal of activity in the top part of this diagram, which is a demonstration or a depiction of what is happening in molecular medicine. We will be finding all sorts of genes involved in all sorts of disorders at a great rate over the coming years. We are already in that situation with over 100 disease genes having been identified in the last nine years using Genome Project tools. But increasingly the diseases are going to be the common ones with an even greater number of potential consumers out there interested in being tested. The first consequence of that over time is going to be in diagnostics and that is why the deliberations of this group are going to be so crucial to see how we usher that phase in. Let me say that I think there are a variety of settings where diagnostics will be going on and they may require different levels of scrutiny and this is certainly something the Task Force on Genetic Testing came up with as well, that not all genetic tests perhaps are subject to the same possibilities as far as misinterpretations and misuses, and we ought to try to figure out which ones deserve the highest scrutiny and focus at least initially our attention on them.

(Slide.)

If you are wondering what the condition is here, those of you who are expert in medical genetics may have figured it out, but these are the typical facies of boys with fragile X. Although they are not all that remarkable, there are some similarities in terms of the facial appearance. Testing for fragile X is often done in the setting of a clinical situation where you are looking at a male who has mental retardation and perhaps other phenotypic features and so the test is being carried out to confirm a suspected diagnosis. Many people would say the test in that situation is perhaps less different than other standard medical tests and perhaps, therefore, less in need of intense oversight. Certainly fragile X molecular testing is being done on large numbers of individuals in this kind of clinical setting right now. On the other hand if you want to contemplate offering fragile X carrier testing to all women, which is certainly something that has been proposed, it is a very different story. It is not just the test. It is the setting in which the test is being offered that may determine our deliberations about what kind of scrutiny is necessary.

(Slide.)

Cystic fibrosis is a topic that many of you are aware has been intensely discussed. There was an NIH consensus conference held about two years ago to deal with the question based upon all of the pilot studies that NIH has funded and others have done as well about is it time to begin to offer DNA based carrier testing for CF to all pregnant couples? Somewhat to the surprise of many people who assumed the answer was going to be no because it had been in the past, this particular consensus panel of a dozen people who were carefully chosen not to have conflicts of interest and to have expertise in the field, came up with their conclusion that this is an appropriate topic for offering to couples who are pregnant or contemplating pregnancy even if they do not have a family history. That has then led to a follow-up conference involving the American College of OB/GYN and the American College of Medical Genetics, and out of that has come a steering committee of those organizations plus the Genome Institute, which is wrestling with how to actually implement those recommendations in a way to make sure that couples understand what CF is before contemplating going through such a test. But it does seemly likely, at least ACOG is certainly committed to this outcome, that CF carrier testing will be offered in the next 18 to 36 months to couples who have an interest in following up on it, although it is likely that it will not be done in an across the board fashion. It will be focused to some degree on self-defined ethnicity. So here is a circumstance where potentially very large numbers of individuals may be tested. It is a circumstance, whereas we all know there is a lot of different alleles present even though one of them accounts for most of the disease. There are many rare alleles. How many alleles have to be tested for – who decides? This one seems to be going down the path of sort of a professional practice guidelines route, which ACOG and ACMG are leading but it might have been otherwise.

(Slide.)

As far as predispositional testing, I think many of you are aware that hemochromatosis is being heavily discussed as the potential most attractive case to begin to initiate a population-based screen for an adult onset genetic disorder. It has many attractive features that might lead you down this pathway.

(Slide.)

As are enumerated here, it has severe consequences. It is genetically fairly much attributable to a single mutation, although there are complexities there that I do not have time to go into. And most important, it is easily treatable by phlebotomy if diagnosed early enough before there is organ damage. As a consequence of this attractive situation, we held a conference some time ago jointly with the CDC and out of that came a recommendation that this should be studied on a pilot basis but that it would be premature to initiate population screening because of the uncertainty of a number of important issues. Most notably, whether the genetic tests would pick up individuals and label them as hemochromatosis individuals but those might not ever people who are going to develop any symptoms, and what is the down side of that and what is the benefit of genetic screening versus biochemical screening. Wylie Burke, who is a member of this committee, led that effort and could certainly tell you more about it. As a consequence of this, there is now a large pilot study getting underway funded by the Heart, Lung and Blood Institute and the Genome Institute, which we hope over the course of the next four to five years will give us answers to this question. So there is a data collection effort of sorts and obviously one that ought to inform the decision making about whether to offer population screening for this

disorder.

(Slide.)

Let me, also, say that a major area that one can anticipate a lot of growth in, which we will have to wrestle with is the whole issue of pharmacogenomics. The SNP's consortium and all these pharmaceutical companies coming forward with cash contributions represents their enthusiasm for the idea that genetic testing may be successfully able to predict responsiveness to drug interventions and, thereby, improve the situation where drug therapies are more effective and less likely to result in a toxic side effect. Here is just one of a long list of examples that are beginning to mount up. This is from the New England Journal about a year ago. They looked at individuals who were at high risk for heart disease. They looked specifically at their degree of coronary artery narrowing over the space of a two-year interval.

First, just look at the yellow bars, which are the effectively untreated people – the placebo controls – and notice that the genotype for this CETP gene, which is cholesterol metabolism gene, had a rather impressive effect on the degree of coronary artery narrowing. So being a B1B1 homozygote led to more severe disease. However, if you look at the treated group who got Pravastatin, you will see they are also the group that got the greatest benefit from the drug intervention, and the heterozygotes and the homozygotes for B2B2 sustained much less of an advantage. So people doing studies of this sort will undoubtedly begin to contemplate the idea and perhaps even make proposals that before writing a prescription for Pravastatin you should get a genotype on that individual for CETP and see whether it is an appropriate step or not. How will we as this committee overseeing genetic testing view that? What kind of data is necessary before that kind of recommendation can be implemented?

(Slide.)

Genetic tests have certainly been proliferating and we obtained this data from the formerly called Helix, now called Gene Tests database. What this shows you is in their database what are the diseases for which genetic tests are offered just over the course of the last six years. You can see a rather remarkable proliferation of such tests from only about 100 in 1993 now to something in the neighborhood of 700. I would say this data, which comes from Bonnie Pagan and this database, which is funded by NIH, might be very useful to this committee. It is clear that this database can be queried in various ways that might be quite helpful in terms of figuring out which of these are tests for predictive purposes. About half of these, by the way, are research based tests that are clearly not ready for clinical application where it is not even clear what is being tested for so you should divide these bars by about two if you want to talk about those that are being used in clinical settings. Most of them are for relatively rare disease. This is a database where additional information could undoubtedly be obtained.

(Slide.)

Let me just by way of illustration to help us think this through as a final comment here to try to ask you to think a little ahead of where we are now. We are going to be all wrapped up in our activities for the next five months but we should not imagine that genetic

testing is maturing at this point but sort of coming at us. Again, I will make the argument that the greatest growth area will be in the field of predictive genetic testing on adults.

So imagine yourself now in the year 2009, ten years from now, and hearing about an encounter between this young man, John, who comes to his physician because on a screening physical for a job he was found to have an elevated serum cholesterol. He reports a family history with a father having died at 48 of an MI (myocardial infarction) and a smattering of other things in his family history as well. In 2009, I suspect, the physician will take a better family history than this, I hope so, do a physical exam and then sit down to talk about what is available to try to identify the cause of this young man's elevated serum cholesterol at the genetic level. In 2009, there will probably be a variety of different genetic tests to sample the various members of the pathway that we already know is involved in cholesterol metabolism and which we will know even more about in ten years.

I suspect that physician or it might be a nurse or a nurse practitioner or a physician's assistant or a genetic counselor -- we have to figure out how this is all going to work in terms of the delivery of services -- may also say to John, "You know, as long as you are contemplating this analysis and doing this preventive medicine thing, would you be interested in also being tested for a variety of other adult onset conditions for which predispositional testing is now available?" And John might very well say, "Yes," and then would like an explanation of what those tests are and he might be given a videotape to take home or perhaps have an interactive CD-ROM that he can take home to learn about what tests are available and what their benefits and risks are.

In our hypothetical situation that is exactly what happens and John comes back and says, "I would like to be tested for those conditions for which an intervention is available. If I am found to be at high risk I can reduce that risk by doing something about it. But I will pass on the test where there is no intervention. I am not so interested in those." I suspect lots of people will say just that.

(Slide.)

So John comes back after having his cheek scraped and the cells gone off to the laboratory and a week later the report is back and he is sitting there getting the results. Now imagine what these results are going to look like. Testing will have been done for a number of conditions. Presumably the ones he will be most interested in are those for which his risk varies by a significant degree from the average, either up or down. And he will also be interested not only in his relative risk but in his absolute risk because relative risk alone is maybe not a terribly useful number for the average person. Someone around the table pointed out, maybe it was Barbara Koenig, how important it is that we figure out how to convey concepts of risk and how poor we are at it right now but, boy, this is going to hit us in the face.

(Slide.)

So this is the kind of result that John might be receiving in the reduced risk category and there will be the ability to make those predictions once we have a full grasp of the major genetic contributions to common illness. He turns out to be at lower than average risk for prostate cancer and Alzheimer's disease because he has low risk alleles for these at risk genes, only two of which I made up; the others we even know about already. And the

reduced risk is demonstrated here as a relative risk. Notice the lifetime risk is still not that low because these are common illnesses. I am not putting error bars on these numbers and, of course, we want to do that because whatever epidemiology has been done ten years from now you can be sure that these will not be numbers that are very precisely known. They will have error bars on them. How are we going to convey that part and how are we going to collect the data to be sure it is right. This is a big challenge.

(Slide.)

Then on the next page is his list of elevated risks, which includes coronary artery disease. Well, no surprise there. That is why he came in, in the first place, and it turns out he has variants in APO/B on that CETP gene I told you about a minute ago that collectively give him a lifetime risk of 70 percent of having symptomatic coronary artery disease by age 65 if nothing else is done. A relative risk of 2.5. He has a fourfold increase risk of colon cancer and it turns out he has a sixfold increased risk of lung cancer if he smokes.

Well, what to do? Again he did not ask for tests for which no intervention was available. The intervention here in ten years is likely to be individualized pharmacotherapy combined with diet to reduce his cholesterol and reduce his risk but focused on his particular genetic version of a high cholesterol.
Colon cancer -- good heavens. We know what to do about that now. If we knew who the people were who were at high risk, we would get them into colonoscopy programs and that would be cost-effective if we focused that effort on the people at highest risk. Of course, the lung cancer risk, he needs not to smoke. I would wager, without being about to prove it, that this kind of individualized genetic information will provide useful ammunition to convince individuals who otherwise ignore our advice about smoking that it really is going to be bad for them.

Is this an image that you like? I hope so. I think it is a very exciting image and there is more about this in tomorrow's issue of the New England Journal of Medicine where I wrote a little piece that goes through this scenario in a bit more detail. But it will only come about if we in this committee come up with the way in which to collect the data to demonstrate that these tests have this kind of value and introduce them into the clinical practice of medicine in a fashion that is based on evidence and not on hearsay. That is the challenge that we face.

(Slide.)

What process should determine if tests find their way into clinical medicine? There is the marketplace, of course, and that will be a factor but, as was already pointed out, one can identify circumstances, whether it is a chiropractor advertising on the web or a surgeon in a northeastern state advertising that he wants to do testing for breast cancer because his main practice is prophylactic mastectomy. We cannot really depend on the marketplace alone, I think, for responsible introduction of new genetic tests. Practice guidelines and professional standards will play a critical role and I think that is something we ought to talk about around this table and make sure that we are not overriding what is a system that in some circumstances may be quite effective. And then cystic fibrosis carrier testing is certainly going down that path. But I do not think there is any way to get away from Dr. Satcher's admonition that we need to look at the need for additional government oversight.

My own personal impression is that we are going to have to deal with that at least for tests that are doing predictive generation of information on currently healthy people.

(Slide.)

Finally, of course, there is this educational challenge. If John was going to get an adequate amount of information from his health care professional that person would have to know a fair amount of genetics and right now one could not be confident of that at all. And in this regard, the National Coalition for Health Professional Education in Genetics is an important organization. It has already been mentioned. Co-founded by the AMA and the American Nurses Association and the Genome Institute but now counting over 120 organizations representing a variety of professions in its membership. This coalition aims to achieve genetic literacy amongst health care providers in the next three to five years. A truly ambitious goal but one which is critical to the success of all of these other things that we would like to see done and obviously closely intertwined with any conversation about genetic tests and their introduction into medicine.

(Slide.)

So not to be sort of gloomy here but we have a stiff challenge in front of us. Genetic testing has been considered by the ELSI working group and then in much more detail by the Task Force on Genetic Testing. Following their conclusions, by an interagency working group at the Department of Health and Human Services that Bill Raub led over the last year-and-a-half. And now it comes to your lap and I think it is all clear that there is a reality here that we need to do something and the question is how do we do this and not let the sort of shadow of confusion and indecision fall in front of us. I think we can accomplish that.

My final exhortation does not come from a poet or a scientist or a physician but from an athlete. My favorite quote and, boy, does it apply here, from Wayne Gretzky -- well, it did not fall down. I can remember what it is anyway. Which is "Skate where the puck is going to be. Not where it is now but where it is going to be." This is a moving target and we have to keep that in mind as we move forward ourselves. Thank you all very much.

(Applause.)

DR. McCABE: Thank you very much, Francis. In the interest of time actually I think we are going to -- you are going to be a part of the group and a lot of these issues are going to come up and people can grab you at the break.

Part of the reason for moving forward is that the coffee service on this floor will disappear in ten minutes so that -- and even more important, before any of you around the table leave, I would like you to assemble in that corner -- in this corner over here, and we are going to have a group photo taken then. So please stay around for the group photo. We will make it quick and get you to coffee before it closes.

(Whereupon, a brief break was taken.)

DR. McCABE: As we heard this morning, we are a consequence very directly of the report of the NIH/DOE Task Force on Genetic Testing, which was co-chaired by Tony

Holtzman and Mike Watson. Dr. Holtzman is here to tell us about that today. Tony is Director of Genetics and Public Policy Studies at the Johns Hopkins Medical Institution. He is also Professor of Pediatrics in the School of Medicine with joint appointment in Health Policy and Epidemiology in the School of Hygiene and Public Health. He received his M.D. degree from NYU and later an M.P.H. in epidemiology from Berkeley. He has had extensive research experience in genetic disorders and I think very appropriate to his role in the task force and also to this committee is his important involvement in newborn screening throughout much of his career. He has been a prolific analyst of health and social policy implications of genetics. And besides co-chairing the Task Force on Genetic Testing, he has also been involved in two previous landmark policy studies. The first, which I think we still refer to quite a bit, is the 1975 National Academy of Science's report on "Genetic Screening," which still has quite a bit of information. If you are not familiar with that, it is something that you might want to look at. And the other was the 1994 Institute of Medicine Report, "Assessing Genetic Risks." So, Tony, if you could now give us the background on the Task Force? Thank you.

REPORT OF THE NIH/DOE TASK FORCE ON GENETIC TESTING

DR. HOLTZMAN: Thanks very much, Ed. When I was preparing this talk, two sayings kept running through my head. The first was the sign that Harry Truman had on his desk in the Oval Office, "The buck stops here." And I think that the buck in this sense that actually Ed partially outlined does stop with this Secretary's Advisory Committee. Ed mentioned that I had served on actually three previous committees. An NAS committee out of which came the volume on "Genetic Screening" in 1975; the IOM committee that published "Assessing Genetic Risks" in 1994; and the NIH/DOE Task Force on Genetic Testing.

Now each of these committees recognized the problems in genetic testing, particularly in testing asymptomatic individuals for risk of incipient or future disease. It may seem that we are just dealing over a 25 year time span with a repetition of one committee after another. But I think that what has happened since the Task Force and happens very historically today with your convening is that we have come a long way and that of the Task Force -- the most recent Task Force's recommendations that this Committee, as you have already heard, represents an implementation of one of those recommendations. And, in fact, two other recommendations have already been implemented and reference has been made to this, and that is that FDA is about to have a chartered committee, a genetics -- will add a genetics panel to its list of advisory panels. And CLIA, partly in anticipation or I should say HCFA and CDC, partly in anticipation of the recommendations that would come out of the Task Force that I chaired has set up a working group on genetics and that has also begun to make additional recommendations that follow from the Task Force report.

Now what is different about these three committees is they are federally chartered committees and they are very close to the seat of power. You have got to be listened to. I think part of that depends on how strongly you marshal your arguments but you cannot be deflected as just another committee as the history of the last 25 years suggests could happen as we go from one committee to the other with some reinventing of the wheel.

I hope you will not -- obviously you need to get a sufficient amount of background information but I hope that you will -- and it seems that you already are on this track -- will

undertake to move quickly for developing real policies that address the issues that have already been mentioned as we went around the table.

Now that brings me to the second saying that reverberated through my brain. Those of you who were on the Task Force will immediately recognize it and recognize its source probably, and that saying is, "If it ain't broke, don't fix it," because this was a question raised by at least one of our Task Force members as we started our deliberations.

And the question is if there are no problems despite the proliferation of genetic tests -- and as you heard from Francis the likelihood that these will continue to proliferate and proliferate at an increasing rate -- if there are not any real problems then we can just as well go home, for new regulations, possibly new laws, might only muddy the waters. But there are problems and, Francis has just given you sort of an optimistic view of how basic research can be translated into laboratory tests and predictive tests that will have an impact. I think what I would rather do, recognizing, of course, the tremendous benefits that are possible from genetic discovery, to indicate to you what some of the problems have been recently in the development of genetic tests and then discuss the policies that could begin to solve the particular problem that I am going to focus on, which is the validity and utility of genetic tests, the issue that was covered in chapter two of the Task Force report.

Now that is not exactly fulfilling my charge because I am not going to run over all of the Task Force recommendations. There were essentially four working chapters of the report. I am told that you all have the report. The first was chapter two, which I have already mentioned. The third chapter dealt with laboratory issues we are going to hear more about this afternoon and I will touch very briefly on them. The fourth was consumer and provider, particularly professional education. And the fifth was rare diseases and the concern of the Task Force was that rare diseases not be forgotten as we concentrate on issues that seem to be upper most today and those are the ones I will deal with primarily common complex disorders.

Now another reason for focusing on validity and utility of the tests and laboratory quality is to keep in thinking that you are advising the Secretary and the Department of Health and Human Services, and it is in these areas of, at least the four that have come up in our Task Force recommendations, on which the Department can have the greatest impact. They are the principal players. When it comes to matters of professional education, as you already heard, there is a coalition, partly involving NIH and other government agencies but where the private sector plays a major role. So I would urge you again, as you set your priorities, to think of where you as a committee advising the Secretary of Health and Human Services focus on those issues where the Department has the major impact.

Now let me then turn to the problem that I think is extremely important, the lack of data on the validity and utility of genetic tests as they become marketed. Now I am going to talk about two examples and they have already been talked about today. The first is Alzheimer's disease and the second is breast cancer.

(Slide.)

In 1994, Geneca Pharmaceuticals made a test for APO lipoprotein E4, APO/E4, available as a predictive test for Alzheimer's disease. People working in the geriatric field immediately saw some problems with this, and in 1995 a consensus panel

under the auspices of the National Institute of Aging and the Alzheimer's Association met to review the situation and in their report the use of APO/E genotyping, determining whether a healthy person had an APO/E4 genotype to predict his or her risk of APO/E, was criticized on several counts.

To summarize those accounts, the first was in 1995, after the test had been on the market already, lack of accurate estimates of genotype specific Alzheimer's disease risk, that you could not tell somebody who was contemplating testing what a positive or a negative test result meant in terms of their chance of getting Alzheimer's disease. The second lack of evidence, if you will, was the fact that our knowledge was incomplete of the factors that might modify APO/E4 associated risk. This was originally done in some family studies. It was late getting some started, some population studies. But it was not clear how age, sex or gender and family history would modify the risk that having an APO/E4 genotype either in single or double dose might have on the future risk of getting Alzheimer's disease. The third concern raised by this consensus group was the absence of a preventive treatment. Why were in indicating to people that we might give them some risk information, we did not know how good it was, if there was nothing we could do about it and what kind of psychological problems would that have and that, of course, raised not only the psychological and psychosocial and medical, and legal problems, but financial problems as well because of the question of insurability which comes up when you have the ability to predict tests for diseases that are not yet treatable.

Now since that consensus panel, at least four other professional groups have cautioned or recommended against the use of APO/E testing to predict risk of Alzheimer's disease. This was after the test was already on the market. And, in fact, it was withdrawn for that purpose. But in 1996, Athena Neurosciences made it available as an aid in the diagnosis of Alzheimer's disease in symptomatic patients.

Now within the neurology community there has been a lot of argument as to whether this is needed or appropriate in patients with symptoms of AD and how much it adds but, in addition, it is a very fine line in terms of defining what symptoms are and there are situations, and the Task Force learned about this, for other late onset diseases where people are so eager to know and their physicians may be so eager to find out whether they are at risk for the disease that the test may be ordered predictably under the guise of being available diagnostically.

Now that -- when that test became available diagnostically the information was still not any greater than -- in terms of answering these points than it was when the consensus conference that I described was held. Now since that time a number of groups have attempted to collect this information, and I think it is worth looking at what the answers to at least some of these questions are.

(Slide.)

So this is a study that came from Dick May's group at Columbia where they actually, as part of that study, followed prospectively a population, primarily white, primarily Italian, of people over 65, 65 and over, mean age of 78.7 years, for over four years to try and get some perspective data on Alzheimer's disease. Now in that community the risk of Alzheimer's disease in this age group, 8.7 percent, was a little lower than in other

communities but they genotyped the entire community. So here is a population genotype study. And found that 19 percent of the people had at least one E4, APO/E4 allele. Based on the study they found a relative risk of 2.3 so that fits into Francis' category of something that might be followed up. But when you do the calculations, and you have got to remember that the calculations of predictive value, sensitivity and attributable risk, will depend not only on the relative risk but on the frequency of the allele you are looking at and the incidence of the disease in the population. When you take all those parameters into consideration, the chance that somebody in this population who has an E4 allele will develop Alzheimer's disease in the remainder of their life, and I comment more on that further, is less than one in five. Those people who have an E4 allele constitute less than 40 percent of all the people with Alzheimer's disease and on a population basis having an E4 allele adjusting for the relatively high frequency of the disease accounts for less than 20 percent of the patients who are going -- of the people who will get Alzheimer's disease.

So the question comes up having collected -- well, let me put it this way: What if we had this information at the time that the test first became available commercially? Would people leap to have a test that had a predictive value of less than 20 percent? Would we encourage it when it was detecting only a minority, although a substantial minority, of people who would get Alzheimer's disease?

Now just to give you an idea of how these variables affect these outcome parameters that are used to measure the validity of genetic tests, if the incidence of AD was 50 percent instead of nine, then the predictive value would go up to one -- less than one in three instead of a little bit less than one in five. Sensitivity would expand to about 60 percent and the attributable risk, that is a proportion of all cases due to the E4 allele, would go up to about 30 percent. And here if you jump the relative risk, keeping these variables constant, you see what happens further. You have got to keep all of these variables in mind so even relative risk is not the only value.

So the point I want to make is that the commercial laboratories who offer this test, who were all licensed under CLIA, the Clinical Laboratory Improvement Amendment, did so without gathering evidence on its validity and utility. The evidence was not there.

Now let's turn to breast cancer. Although BRCA1 and BRCA2 testing was initially done on an investigative basis, there were supposedly protocols available, that the line between what was research and what was clinical practice was very thinly drawn. Some of these protocols were never made publicly available and the marketing of predictive tests for women were not strictly limited to people with a family history or even participation or membership in a high risk ethnic group such as Ashkenazi Jews. Now I mentioned family history as important. Go on to the next slide.

(Slide.)

Because the data that had been collected in asking what the risks were for breast cancer came from the linkage study that was skewed heavily, as it had to be to make its point, and that is that one had to look at families in which there are a large number of cases and which, as it turned out, it appeared that the susceptibility followed a Mendelian dominant pattern. Now those kinds of families, a minimum of four cases per family, are quite different than many individuals who have breast cancer with a family history where they may only

have one or two or possibly three affected relatives, and those lesser families make up the vast majority of families with a history of breast cancer, and they say nothing of what might be going on in the general population of people with or without any family history. Yet these figures that were derived from this linkage study were the ones that were used by a number of organizations, commercial and academic, to indicate to women what their risk might be of getting breast cancer.

Now it was not until Jeff Streuwing and his colleagues at NIH published their study in 1997, which was a population based study, that attempted in an unbiased way to look at what the risks might be in a more general population of people identified with varying degrees of family history. And lo and behold, instead of a risk of one in two, a 51 percent at age 50, the chance in this population based study, and this was statistically significant, was 33 percent instead of 50 percent, and if you go up to age 70, whereas in the linkage study and the data used by commercial labs for telling people their risks, instead of 85 percent it was 56 percent. Now this was limited to three polymorphic mutations. There is little reason to believe that these mutations are functioning in a way much different than many of the other mutations that lead to breast cancer. You see, of course, that in the presence of one of these mutations and "ISM" as I call it, inherited susceptibility mutation, the risks in this population based study were much higher than not having a mutation but still the question comes up as to whether women would make a decision to have the test if they had accurate information on what the risks were.

(Slide.)

Let me also go on and sort of qualitatively indicate to you the kind of information that the organizations that were providing testing in 1996 when I looked at their brochures were providing to people. So Myriad, which is now the primary, if not the exclusive, genetic tester of breast cancer susceptibility today, said in its pamphlet for physicians and consumers, "Early cancer detection provides the best opportunity for reducing mortality from cancer." Now a somewhat more realistic approach was mentioned in Oncor Med's brochure saying, "There is no surveillance or preventive strategy which is proven to decrease the mortality which is associated with carrying the mutation." Now, unfortunately, that still is the case today and yet if a physician was reading the Myriad brochure and using Myriad for the test this is what he or she would think about the utility of testing.

If we go on to what information was provided on prophylactic mastectomy, Myriad said, somewhat more cautiously, "Prophylactic mastectomy does not completely eliminate the risk of breast cancer because surgery cannot remove all of the breast tissue. However, the procedure substantially reduces the risk of breast cancer." The University of Pennsylvania, which had a large testing lab at the time on the other hand pointed out, "There is very little data available as to how effective prophylactic surgery is at reducing breast cancer risk because the mutation will be present in all residual breast tissue. Individuals may be at increased risk following surgery." So quite a difference again and yet this is the kind of variable material that was being made available because of the situation that neither of these tests was being regulated.

So let me turn to the question of policies for requiring data collection and that is essentially all I am asking. I am not trying to make a judgment as to what the appropriate predictive value is or what the sensitivity should be. All I am asking and saying to you is

that in these two cases and many other cases of testing for common complex disorders, and this was a major concern of the Task Force, the data were not being collected before the tests were made available. Now how is that possible?

It turns out that FDA explicitly requires test developers to submit data on the clinical validity, the kinds of things that I am talking about, of tests before a test is marketed. They must submit this as part of the premarket approval process. I just point out to you that was not done for Alzheimer's disease or breast cancer. Does that, therefore, mean that these companies were breaking the law? Not exactly because laboratories who market genetic tests as services, which is the way that Geneca, Athena, Myriad, Oncor Med when they were still in business, was marketing these tests, as lab services do not fall, by FDA's own decision, under things that they choose to regulate.

(Slide.)
So let's skip this.

(Slide.)
And skip the next one, too.

(Slide.)

FDA's policy, and you have heard the term already, on "home brew's" is as follows: The Task Force heard it and more recently Steve Gutman, who is here today and is the Director of the Division of Laboratory Diagnostics at FDA, wrote this in Clinical Chemistry in a summary of some of the task force recommendations. But Steve said, and this is FDA policy, "FDA has always considered tests developed in-house, that is home brews, to be medical devices subject to regulatory oversight." So FDA acknowledges and has acknowledged again and again that they have the authority to regulate home brews. "However, with very few exceptions, the agency has chosen on a discretionary basis not to apply authority in this area." Why not?

The two reasons given were first that FDA lacks resources, and I believe that. The second is that actually many of these tests that are offered as services are regulated. All of them that are offered for clinical purposes are regulated under CLIA. So the question is, is FDA bouncing the ball to CLIA here?

(Slide.)

Now FDA has started to move towards some concern for home brews, and you will probably hear more about this later, because last year they put into effect a regulation on specific reagents that are used in tests like genetic tests, the so-called analyte specific reagents, but those hardly accomplish the collection of data on validity and utility. What they do is to require that manufacturers of reagents that may be sold to labs who are performing tests have to register with the FDA and have to follow good laboratory practices and they have to report any problems that come up in the use of those reagents but these are reagents that are being incorporated into a home brew. It turns out that if a laboratory makes those own special reagents itself, like a DNA probe, and uses it in its own home brew, they do not even have to register with FDA because they are not selling anything.

Now FDA does require data on safety and effectiveness of genetic tests that are marketed as kits but I have pointed out to you already that many of the tests being developed today and in the near future probably will not be developed as kits and, in fact, one reason perhaps that laboratory -- that kit -- that manufacturer -- that labs continue to market tests as services is precisely because they can avoid FDA.

(Slide.)

So what Myriad has said in its prospectus a few years ago, somewhat boastfully in the sense that they were avoiding regulation, was "The FDA does not currently regulate genetic tests developed by the company if used in the company's own testing laboratory (home brews)." So the commercial sector is aware of this and it may be something of a loop hole for them and I think they are burying their heads in the sand, as I will come back in a few minutes.

Now what can be done to improve the situation? The Task Force unanimously agreed that the development of any genetic test needed to go through a pilot or an investigative stage.

(Slide.)

So the Task Force said, "Protocols for the development of genetic tests that can be used predictively must receive the approval of an Institutional Review Board. IRB review should consider the adequacy of the protocol not only for the protection of human subjects but for the collection of data on analytic and clinical validity and data on the test's utility for individuals who are tested." In other words, the Task Force said you have got to collect the data that I just described to you is lacking.

(Slide.)

In terms of how one should go about doing it, doing clinical validation, the Task Force also recommended the study sample must be drawn from a group of subjects representative of the population for whom the test is intended. We know, for instance, that allele frequencies and the risks of what we are calling alleles associated with disease vary from one population to another. "Formal tabulation of each intended use of a genetic test is needed." In other words, if you are going to market a test for diagnostic purposes in symptomatic people but it could be or there is a possibility that people will use it for predictive purposes, data on its use as a predictor must be collected.

Finally, “before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results.” In other words, some data on the utility of tests. Admittedly, the FDA does not really use patient outcomes or quality of life when it decides that a diagnostic device is appropriate. So we still have problems in that area.

(Slide.)

Finally, you have heard this mentioned already, “test developers must submit their validation and clinical utility data to external review.” A number of possibilities are given here. Now, as was also mentioned, the FDA did not -- the Task Force did not go any

further than this. We did not reach a consensus. But let me suggest to you two possibilities that I think are on the table already, and my preference will become clear but this is my personal view.

The first is that FDA do the regulating and extend its authority to tests marketed as services rather than -- in addition to tests marketed as kits. And I have indicated already that FDA does require that when tests are marketed as kits that they do look at the clinical validity of the tests and just by simply saying FDA should undertake the regulation of all tests on the market, whether as services or as kits, that one would at least force the developers of those kits to collect and make available to the public and to providers data on the clinical validity, at least the clinical validity of tests, and that would be a big step forward.

Now it has also been suggested, and this is part of FDA's getting out of this issue, that this is a CLIA issue. I should be very clear that the Clinical Laboratory Improvement Amendments were developed because of problems in laboratory performance. While CLIA is the right vehicle for looking at what we call analytic validity – simply, if you are looking at a test that detects certain mutations, A, B, C, D, let's say, CLIA does have the authority, and probably directly so, and it certainly is getting beefed up, to ask any laboratory doing the tests for mutations A, B, C and D, is when you get a specimen, known or unknown, can you always correctly detect when A or B or C or D is present and always correctly say when they are absent? Now that has nothing to do with whether having mutation A or B or C or D is going to predict future disease and how powerful that predictor will be. It has nothing to say about how many people who are going to get the future disease are going to have it on the basis of having mutation A or B or C or D. I would argue very strongly that, first of all, there are questions as to whether that is under CLIA's purview. It is the issue that I have been talking about for the last 20 minutes and it is very doubtful that the vehicle that CLIA has for enforcing questions such as analytic validity could be applied to measuring clinical validity.

Now how does CLIA measure analytic validity? There are two ways. One is proficiency testing, which again gets at what I said. Does the test correctly measure the presence or absence of A, B, C or D mutations? The second is through the use of surveyors or inspectors who visit the labs and there are now about 18,000 labs that are performing tests in either the moderately or high complex area. These inspectors go through the labs. They look at a variety of questions of laboratory quality. The question is, is this the right venue to get labs to provide data on clinical validity, which means a clinical trial or some collection of clinical data? Now it may turn out, as we are seeing partly because of patenting and licensing policies, that only a few labs are performing these tests. But I would argue that the evaluation of whether even a single lab has adequate data on clinical validity does not tap into the expertise that CLIA laboratory surveyors have. This is epidemiological data. It is clinical data. It is not laboratory quality control data. I would, therefore, argue that CLIA's ability to undertake this task as the FDA has suggested it could when it said it would not regulate laboratory tests marketed as services is inappropriate.

So, in conclusion, I think you need -- this is -- the question of assuring clinical validity and utility is an extremely important one and it should be apparent that my own personal feelings are that you have got to look very carefully and thoroughly at why FDA should not be asked to extend its admitted authority to cover services as well as kits.

I think from the commercial sector's point of view what has happened over the past few years and partly the result of the concerns that have been raised in a number of quarters about what Elliott Hillback has called the “mysticism” around genetic tests that, in fact, demand for genetic tests, particularly for the common complex disorders, has not been as great as certainly many of the manufacturers originally anticipated for a variety of reasons. Some companies and some academic centers have gone out of business partly that is a patent monopoly issue, but partly it is a problem of demand. Now I would suggest that the public, largely thanks to the ability of genetic counselors and other geneticists to want this information, which may be different than is the case for many other professionals and why professional education is so important, but the fact that the lack of this data has been raised has subdued the interest that the public has in genetic testing. It has, therefore, not been to the benefit of many of those companies and laboratories that are offering genetic tests. I think it will be much more to their benefit if they bite the bullet and recognize that we do need rigorous collection of data that will demonstrate the clinical validity and eventually the utility of the tests. So this is only one of the important problems that you are going to grapple with but please remember that the buck should stop here. Thank you.

DR. McCABE: Thank you, Tony. Again, in the interest of time what I would like to do is have perhaps Pat Barr and Elliott Hillback since you were on the committee -- I do not know if you have any brief comments to add before we move on.

MS. BARR: I mean, I can express my personal view and I can also express what I think has been the dilemma or part of the dilemma. My personal view is that if we could design, as we discussed in the report, some system of higher levels of scrutiny, what needs more attention and what needs less attention, that involvement in FDA review, which is not a new regulation but simply an interpretation and decision about what they can do and how they do it, would make a great deal of sense because we would be beginning and insisting on that public accumulation of data, which would not be proprietary. It would be public. The criticism, I think, that we were subject to then and will be subject to again, is why is genetics any different? Doctors every day order useless tests. People are subjected to useless tests. People make medical decisions because somebody is giving them very bad advice. So why should we treat this differently?

As a representative of the National Breast Cancer Coalition and as a woman with breast cancer who has to make treatment decisions where there is not enough evidence on a very regular basis, what I would say is let's push for evidentiary-based medicine. If we have an opportunity to do this because this is a new field then, by all means, let's do it, and let's do it in a way that is flexible and practical, and come up with a good solution. But that is what my goal is. Evidence- based medicine at every turn where it is possible and standards where we cannot get the best evidence that are reasonable and the public can understand.

DR. McCABE: Thank you. Elliott?

MR. HILLBACK: I think Tony certainly highlights the issue that was the toughest issue with the Task Force and that is how do you in an environment where new information is being generated daily or weekly where it is not being generated by one source -- there are a lot of laboratories in this country doing testing on cystic fibrosis, let's take a disease that is supposedly well-known, and I think that you could find that there is new data almost every

day. I think I saw something in the paper in the last couple of days about new information related to a particular mutation in the CF gene.

The problem that we tried to face was how do you deal with -- what I use, and I know Tony is sick of this word -- an iterative process. And I think this is what Pat is trying to -- also getting at, is how do you keep moving forward and not just slam the door on this technology and say, "Well, we will wait ten or fifteen years until we know everything." I do not think that does us any good. So the problem as I outlined earlier is to try to tell people what you know and what you do not know at every moment in time. I think the onus is on both the laboratory where we do have a lab director who signs on every case, whether that is a commercial lab or a university lab, or an independent lab, or whatever, to say this is what is generally known and then the onus is also on the practicing physician to say, "I have done my homework and I understand what researchers in various parts of the world are now saying about cystic fibrosis and the impact of these genes." It is a horrible problem as we get to -- well, you have something -- 900 -- Francis, 900 genes we are having tests for now? How is an average practitioner going to understand all that? So I think the problem has been laid right in the middle of the table. On the Task Force we could not come to a conclusion that we felt would not just slam the door on genetics and say, "Stop, we are not going to use it for years, and years, and years," and that was unacceptable to us. I think that we -- this group -- is going to have the same challenge, I do not know the answer but I think it is the fundamental challenge.

DR. McCABE: Thank you. There are a lot of these issues that we are going to be dealing with this afternoon and we have representatives from various agencies and committees who are going to be taking these up so I think we are going to move ahead because I want to be sure that we have time for public comment. It is going to be an important part of each of our meetings, and we will -- we are running behind and we will just take it out of lunch, and change the schedule in the afternoon because I do not want to short change the public comment.

Right now we have eight speakers who have registered for public comment, which means to fit in a 45 minute period about five minutes each. I would encourage you to try and keep your stated comments, your statements to two, two-and-a-half minutes so that there is time for us to ask you questions but basically you will have five minutes to make your comment. It might be easier if you use the podium for your comments. Our first commentator is Dr. Frederick De Serres from the Alpha One Foundation.

PUBLIC COMMENT

FREDERICK J. de SERRES, Ph.D.

DR. de SERRES: Good afternoon. I am pleased to be here. I am here primarily to discuss what I think is a need to screen for Alpha-1 Antitrypsin Deficiency. This is a disease that originated in Europe. The two major alleles originated in Northern and Southern Europe and, as a result, the disease affects Europeans as well as their immigrants to the United States and all over the world. And as a result of intermarriage of European with other racial groups the disease is spreading. The frequency in Europe can be one out of 1,500 persons to one out of 2,500 and this is true of many population subgroups here in the United States.

To prepare for this meeting, I have produced two different briefing papers, which you can see around the table. This one usually has my business card on it and this other one is a paraphrase of the presentation, the oral presentation that I am about to make for those of you who like to take notes. The briefing paper has the natural history of the disease, the clinical signs, the ability to do therapy in terms of augmentation therapy, as well as the need for avoidance of various environmental pollutants, critical literature references, the most important of which is a WHO publication from a meeting that WHO had on the need to review this disease in 1996, as well as other selected literature references, and on the very last page a very brief CV of my own.

I am here primarily as a representative of the Alpha-One Foundation. I am also a member of the board of the Alpha-One Association. The association is primarily an advocacy group that has support groups all over this country and has about 1,500 members and it tries to teach people who have the disease how to cope with it. The Alpha-One Foundation is a research group. The focus of the foundation is to try to develop better methods for therapy and primarily to find a cure. I am the co-chair of a new group -- well, I am a member of the Medical and Science Advisory Committee of the Alpha-One Foundation and the chair of a new working group for screening and detection of individuals that have Alpha-One Antitrypsin Deficiency.

Around the table this morning, I heard many comments that are similar to the ones that are being raised in the meetings that we have held. When you identify people that have Alpha-One there are all kinds of problems that emerge with regard to ethical, legal, social, insurance issues, family problems. Now that I have got this disease, should I tell other family members? It is a really interesting area of exploration.

I am also here as a patient. I have Alpha-One. It is still hard to admit. I am a ZZ homozygote. I have about 16 percent enzyme activity. I was only diagnosed two years ago when I retired and have a very different future now than the one I had originally planned. I do not know why I am doing this. You think you would be able to face up with the reality that you not only have got this problem but I am one of these rare medical oddities that also has another rare disease, inclusion body myositis.

There are so few of us that have been diagnosed with Alpha-One. There is an estimate that 100,000 people in this country that have Alpha-One and only maybe six percent have been diagnosed. Those that have the problems that I have are so few in number, we do not really know whether I have Alpha-One and inclusion body myositis or whether I have Alpha-One and this is a rare manifestation of the disease.

As you go into the literature that is emerging as a result of the WHO conference, you will see that people that have Alpha-One have many other syndromes that are emerging. Panniculitis is one, Wagner's granuloma is another, cranial and abdominal aneurysms are another, and there is a whole wealth of literature that is emerging where if you want to consider seriously, you know, the need to screen for this disease I will be happy to provide to you in the future.

This is the work of our committee. We are reviewing the literature. We are looking at the frequency of the disease in different population subgroups. We are looking into -- well, there is another thing that is emerging and that is that in addition to maybe about one

out of 2,500 people that are of European origin being affected by this disease, there are new and emerging data. And I was just at a meeting at Haverford College two weeks ago where there was a presentation that carriers for this disease, carriers for the Z allele, so we are talking about 1 out of 25 persons of European origin may also be at risk for higher frequencies of COPD and other syndromes. So this is a frightening statistic that is emerging that we not only have to worry about people who are homozygous for the ZZ allele in particular but people who are carriers of the Z allele as well as carriers of the S allele, which is more frequent in Southern Europe.

So I think I have recovered. I want to offer the work that we are doing in the screening detection working group as a resource because I know you are going to be discussing many of the same things that we are considering in your deliberations during the next few years. The work that we have is ongoing and we are preparing two different reports. One for the American Thoracic Society and the European Respiratory Society so we can educate pulmonary physicians, and the other for the Alpha-One Foundation because they are setting up a registry and we want to be certain that we do not get people into trouble when we identify them as Alpha-One patients. And that is probably all I have time for. Thank you very much.

DR. McCABE: Thank you very much. We will move on at this time to Ilana Mittman, who is Director of Genetic Counseling Services and Assistant Professor of Pediatrics at Howard University, College of Medicine.

ILANA SUEZ MITTMAN, M.S., C.G.C.

MS. MITTMAN: I am going to read my comments to save time. Good afternoon. I am here to testify before you on the issues facing diverse communities, in particular ethnic and racial minorities, with regard to genetic testing. in doing so, I represent myself as an ethnic minority and an immigrant; a genetic counselor of seventeen years, dedicating more than a decade of interventions to vulnerable populations; and a member of the academic staff at Howard University, the first and largest historically Black academic institution in the nation, and the only such institution nationally to offer graduate training in genetic counseling.

There is no question that the numerous revelations made in the past decade through the Human Genome project have forever revolutionized the approach to disease identification, treatment and prevention. Hence, this rapidly growing and most promising of scientific technologies has traditionally failed to reach out to a substantial and growing part of the U.S. public -- members of ethnic and racial minority groups, a population that according to the latest census data approaches one third of the U.S. population. In spite of the fact that ethnic/racial minorities suffer poorer health as compared to other populations, and are affected by an array of genetic conditions, members of these groups are vastly under-represented among consumers of genetic services, genetic providers, genetic scientists and policy makers in genetics. Furthermore, ethnic/racial minorities are vastly under-represented in studies set to ascertain consumers' prior knowledge of genetic risk and services, as well as preferences and attitudes regarding these services.

In summary, minority communities not only fail to reap the benefits of genetic technology, they have very little influence on the way this technology is developed and used.

Unless remedied, this discrepancy stands to further increase the health status gap between minorities and nonminorities, an outcome in direct contradiction to the recent Presidential initiative set to eliminate health discrepancies experienced by racial and ethnic minority populations by the year 2010. In order to better understand the issues facing diverse communities with respect to genetic services, a nationally inclusive dialogue on genetics took place in the spring of 1998 in College Park, Maryland. The dialogue called "The National Dialogue on Genetics" intended to promote the assurance that the rapidly advancing genetic technology, which costs taxpayers billions of dollars, will address the needs of every American community. More than 100 scholars and community leaders from around the Nation participated in the two-day dialogue, representing grassroots organizations, consumers of genetic services, professionals such as genetic counselors, molecular geneticists, medical geneticists, anthropologists, social scientists, ethicists, legal experts, and representatives of government health agencies.
The National Dialogue on Genetics was spearheaded by Howard University and funded through grants provided by the Maternal and Child Health Bureau of the Health Resources and Services Administration, and the National March of Dimes Foundation.

As a result of the dialogue, important recommendations were made with regard to means of increasing inclusion of ethnic/racial minorities in the new genetics. These recommendations are included in a meeting's proceedings published in March of this year, and it is my privilege to present them to all committee members today. The main highlights of the dialogue were as follows:

Ethnic/racial minorities face multiple barriers to genetic testing and education, including ethnocultural, economic and educational barriers.

Unfavorable previous experiences with biomedical research have led to an existing sense of lack of trust in genetic research and services, compounded by the fact that few genetic providers are of ethnic/racial minority background, or are truly culturally competent.

As ethnic/racial minorities are not likely to be among those surveyed for their preferences and attitudes regarding genetic services, or to be among those shaping genetic policy, diverse communities play a rather passive role in the new genetics. It was, therefore, the consensus of the dialogue participants that informed consent and community education are crucial but not sufficient alone. Until ethnic/racial minorities are able to achieve equity in participating in the initial design of genetic research and shaping policy leading to genetic testing, genetic services will benefit only a select part of the U.S. population.

As this distinguished panel sets out to review and establish policies pertaining to genetic testing, it is my hope that every possible effort be put in place to encourage all American communities to voice their concerns, views, experiences and desires pertaining to genetic testing. Thank you for giving me the opportunity to speak to you today and best wishes for productive deliberations.

DR. McCABE: Thank you very much. We have time for one or two brief questions. I just would point out, first of all, that Victor is one of the guest editors on the issue of Community Genetics along with Ilana that was just passed out. Also, that this -- anyone who has heard Dr. Satcher speak -- it came up this morning and it is certainly very high on his agenda -- this issue more globally in terms of access to care and certainly in

terms of access to genetic health care would be right up there, too. Yes?

DR. TUCKSON: Dr. Mittman, what is -- do we have any statistics that tell us what is the percentage of genetic counselors who are from ethnic communities?

MS. MITTMAN: Yes. The latest professional staff survey from 1998 indicates that -- I think it was only 4.5 percent were members of ethnic/racial minority groups. To be more specific, they were only .7 percent of all members were African Americans and another one percent were Hispanic Americans. The American Society of Human Genetics recently started to collect data about their membership, and it was very similar there that this was about one percent for African Americans and .7 percent for Hispanic Americans. This is really astounding given the fact that these two populations alone, African Americans and Hispanic Americans, comprise almost 20 percent of the U.S. population. So I think that a lot more needs to be done in order to bring all communities to become a part of the profession so that we are really empowering all Americans to have a say in this technology and not just simply be on the receiving end of this technology.

DR. McCABE: Thank you. I think we will need to move on now.
Our next speaker is Dr. Jane Lin-Fu, who is former Chief of the Genetics Services Branch, Bureau of Maternal and Child Health, which is part of HRSA. I will pass these around for the panel.

JANE S. LIN-FU, M.D.

DR. LIN-FU: I will have the slides at the end, so could I have the lights, please. I do not read too well in the dark. I am a pediatrician born with an advocacy gene and so here I am today. I hope some day someone will clone this gene.

I come before you today as a member of the public, an Asian American, a racial minority, who cares deeply about equity for racial and ethnic minorities in the United States in genetic testing. No longer do I speak with constraint as a civil servant so I speak freely as a private citizen. The one question I want to pose before you today is can one size fits all color blind public policies on DNA-based genetic testing assure equity for U.S. racial and ethnic minorities?

In traditional public health programs, while the outreach approach to each community must be culturally appropriate and somewhat different, the tests used in screening is generally the same and, therefore, we use the same HIV, blood lead and cholesterol tests for all populations. But genetic testing is different. Color-blindness, one size fits all public policies may not work. It is not so much because the frequency of genetic disorders differs widely among different racial and ethnic groups but more importantly because common mutations for the same genetic disorder often differ widely from ethnic group -- from one group to another. Using the same DNA-based genetic testing for our highly diverse U.S. population can pose a serious ethical issue of equity for minorities because a proportion of detectable alleles and test sensitivity can vary widely in different populations.

The 1997 NIH consensus statement on CF testing provides a prime example. The statement acknowledges that the current CF test sensitivity ranges from a low of 30 percent

in Asian Americans to 90 percent in U.S. Caucasians and 97 percent Ashkenazi Jews. Yet, in recommending that CF testing be offered to couples planning a pregnancy or a woman seeking prenatal care, the statement gives no specific or special consideration to minorities for whom the test sensitivity is of unacceptably low level. Nor does the statement recommend further attempts, further efforts be made to achieve comparable test sensitivity for minorities.

Is it really ethical to offer a genetic test of 30 percent or 57 percent sensitivity to minorities when such levels are deemed unacceptable for the majority population? For Asian Americans, among whom CF is relatively rare and the test sensitivity is only 30 percent, does anybody worry about the mass chaos that offering such a test can create when two-thirds of this population are foreign born and more than one-half of this population do not speak English very well. The same question must be asked about the Hispanic population among whom CF has a higher frequency but a test sensitivity of 57 percent. Thus the 75 percent test sensitivity in African Americans, while higher, nevertheless reflects a double standard, one for the Whites and one for the Blacks.

Do we really care about ethics in genetic testing? This statement prepared at taxpayers' expense issues a clear message that it is acceptable to have different standards of test sensitivity in genetics testing, one for the majority population and one for the minority population. Is that what we want? I respectfully urge you to examine whether one size fits all DNA-based genetic testing, public policies can assure equity for all U.S. populations, and whether a comparable DNA test sensitivity for all groups is a realistic goal. Given the severe under representation of minorities in the genetics community, how can Americans be assured that a single standard of test sensitivity is applied in all -- to all regardless of race and ethnicity? While it is politically expedient to stress that regardless of race and ethnicity, human beings are overwhelmingly alike genetically, we must be honest to acknowledge that the small differences in our genes are very important because they cause us to be at different risk and also to have different mutations for the same disorders.

In closing, let me point out that during the past three decades minorities have grown at a rate three times that of the total U.S. population and six to eight times that of the non-Hispanic White population. In May 1999, the minorities stood as 76.4 million or 28 percent of the total population. By the year 2010 minorities will make up one-third and by 2050 one-half of the U.S. population. The genetics community, which has little color, has shown little sensitivity to issues of deep concern to racial and ethnic minorities. I urge you to examine whether one size fits all color blind approach is ethically acceptable and scientifically sound in DNA testing public policies. Above all, I hope that you will assure the American public that with or without due representation by minorities on federal and other panels, equity is not an empty word in public policy or programs on genetic testing. I sincerely hope that the outrage we Americans have demonstrated over ethnic discrimination in Kosovo is not just for international display, that we would have the same compassion and a sense of social justice for our own racial and ethnic minorities inside the United States. Thank you.

Let me show just three slides very quickly. Could I have the three slides, please?

(Slide.)

This is a slide to demonstrate how fast the minorities have grown. Three times the

total population and six to eight times that of the non-Hispanic White population.

(Slide.)

Okay. This slide gives you some idea of the different rates at which minorities and majority population have grown. The last slide?

(Slide.)

Okay. This is a slide that shows you how fast the minority population will grow in the next many years. Thank you.

DR. McCABE: Thank you. Moving on, our next speaker is Dr. Edward Furton, Director of Publications and Staff Ethicist from the National Catholic Bioethics Center.

EDWARD J. FURTON, M.A., Ph.D.

DR. FULTON: Thank you, Dr. McCabe, and thank you for the opportunity to talk to this very august group of scientists, physicians and attorneys. What I will do is just speak very briefly -- I have two parts here -- announcing where we stand on the broad issues in connection with genetic testing and maybe a bit of an exhortation to you to take the moral dimension of your deliberations here very seriously.

We represent at the Center that part of the Roman Catholic tradition which is dedicated to reason and its application to public policy matters. Of course, we have our religious faith elements as well but we understand they have no place in a committee like this. But we also hold that certain theological and moral truths are evident to reason and that is the readers that we have for our publication, Ethics and Medics. And, as we like to point out, that is also very closely connected with the American founding and that famous phrase, "The laws of nature and nature is God." That phrase does not come from any sectarian religious tradition but from the recognition in the West that human reason can know certain theological and moral truths.

We also accept evolution. We see it as a theological event as part of the divine concursus. And that God is working is will through creation through the laws of nature in random variation. That causes us to see germ line therapy as something of a trespass on the order of nature and we are very alarmed about the possibility of testing to advance any kind of wholesale changes to the human genome. We hold that every human being has a natural and God given right to enter the world with his genetic material untampered with by preceding generations. Somatic cell therapy, by contrast, a great good and we wish the committee well in advancing tests that can lead to those kind of therapies.

We, also, at the Center, as you would expect, are shocked by the routine use of genetic testing for the purpose of abortion. That came through very clearly at the conference put on in part by the Whitehead Institute, work with Christine Eng and others showing how routinely that is done. We realize it is legal in the country but we would point out to you that women are subject to coercive policies, possibly through insurance companies and maybe even government policies, when they are encouraged to have abortions or when insurance companies say, "We will not cover the birth of your child because that child has a genetic defect." That is also alarming to us.

But I think the main point I want to make to you, and this is the exhortation as I bring these brief comments to a close, is the issue of -- and I guess this issue has been a part of the West for a long time. I do not really know how to even describe it too well, but the kind of disconnect that sometimes happens between religious believers and the scientific community. And I thought maybe the best way to just draw your attention to that is to point to the work of another committee, the National Bioethics Advisory Commission, which is coming out shortly with its report on embryonic stem cells, and the difficulty -- of course, we disagree with many of the conclusions -- but it is the moral reasoning of it that is, I think, problematic and maybe a lesson to you, and something to watch for in your deliberations. Let me just give you the element that strikes us as so odd and tell you the consequence of it.

That committee decided that they could not tell what a human embryo was, whether it is a human person or not, but that embryonic stem cell research should go forward because when you put human embryo and the benefits of research into the scales, utilitarian scales, they took a very utilitarian standard, the research outweighs the human embryo. But how can you say that when you do not know what the human embryo is? You are not sure whether it is a person or not. And they would not answer that question. They would not tackle it. And that, I think, opens up that commission to serious criticism as I am sure we are likely to see over the coming several weeks as this debate heats up with the announcement of the report.

So I think what I would say to you as an organization that tries to reach out to the medical and scientific community, certainly among Catholics but hopefully among all others as well, we try to be completely open to science, but you really need to apply as much care and concern to your reasoning about moral issues in this committee as you do about scientific issues. That I think is the key point that I would like to make to you. Thank you very much.

DR. McCABE: Thank you, Dr. Furton. We need to move along to Joseph McInerney, who is Director of the Foundation for Genetic Education and Counseling.

JOSEPH D. McINERNEY

MR. McINERNEY: Thank you very much. It is never good to speak right before or after lunch so I will try to be brief. I am not here to convince you of the importance of education. I have worked with many of you and I know you understand that. My purpose is to convince you to make education a priority and not to make it an after thought here. I know you realize that education is important and I have been involved in genetics education for more than 20 years and I am still frustrated that sometimes our approaches remind me of the Greyhound bus driver who announced to his passengers, "The bad news is we are lost, the good news is we are making very good time."

We know intuitively that education is important and so we do something. We act. We make good time. We generate lots of information in many forms, print, radio, television, and we often continue the dangerous and wasteful illusion that information and education are coequal. We fail sometimes to do the necessary and difficult intellectual work first and so we remain lost conceptually. We fail to develop consensus on the goals of our educational programs and having failed to do that it is little surprise that we fail to evaluate effectively

whether we have succeeded because we often do not know what it was we were attempting to do in the first place.

The Task Force on Genetic Testing noticed that public education about genetic testing is important and Dr. Holtzman and Dr. Watson and their colleagues appropriately said that the Task Force report was not the place to determine exactly the nature of that education and I think they were correct to do that. But the genetics community has not done that yet either and it must at some point do that and it has to do it in concert with individuals who will be affected by genetic testing.

Now let's assume for a moment that the audience is the public for a particular education program. We can bring some cohesion to these kinds of efforts by asking three very simple questions. What do we want the learner to know and why? For example, do we really want the average person to know the details of genetic tests or should we focus on more basic concepts related to genetic variation, notions of risk and susceptibility, and uncertainty and certainty, as Mr. Hillback indicated this morning.

The second question: What do we want the learner to value? Perhaps, for example, we want consumers to value the ability of genetic tests to provide information that can help inform their decisions about health. Maybe we want them to value, as well, their right and their ability to protect that information from abuse.

Third, what do you want the learner to do as a result of your educational interventions? Particularly health related education often has as its objectives some change in behavior on the part of the learner. What do we want the public to do differently as a result of educational efforts about genetic testing? For example, do we want all people to begin asking their primary care providers about the availability of genetic testing when appropriate?

I do not know what the answers are to these three questions but I suggest that we do that kind of difficult work before we embark on the development of educational programs. Having answered those kinds of questions we can begin to develop educational strategies to address the answers and equally as important to develop evaluation strategies.

Now I am representing a foundation that came into existence only this month but, as I said, I come to you with more than 20 years of experience in developing educational programs. We are hopeful that this new foundation can serve as a focal point where we can begin to answer some of these questions for a variety of audiences in concert with the genetics community and in concert with individuals who will be affected by genetic testing.

I will point out that during the last five years I have been a member of the ELSI working group and then we had sort of a speciation event under selective pressure from the Spence Rothstein report and we emerged as ERPEG. I think the only thing the Genome Project generates more rapidly than sequence data is acronyms but anyway here we are as ERPEG. Last October as part of a new five-year plan for the Genome Project, ERPEG released a new five-year plan for the ELSI program. That plan identifies a lot of issues that overlap with the interest of this committee. Each of the areas of emphasis specified by ELSI -- and I hope you have read that plan, you notice there are research and education questions. We support the clear message that ERPEG is sending about the importance of education and we are very hopeful that we can contribute in a productive way.

Our nascent foundation already has some broad objectives in mind for genetics education. Our philosophic objectives are embodied in the lessons that evolution teaches us about the nature, extent and value of genetic variation. We look forward to working with you and to hearing your answers to some of these questions.
Thank you.

DR. McCABE: Thank you very much. Moving on, our next speaker is Dr. Tom Tonniges, who is from the American Academy of Pediatrics where he is Director of the Department of Community Pediatrics, and will talk about the recent newborn screening meeting task force that was held.

THOMAS F. TONNIGES, M.D.

DR. TONNIGES: Thank you, Dr. McCabe. Newborn screening is a preventive public health program for the identification of disorders whose early recognition can lead to the elimination or reduction of mortality, morbidity and disabilities associated with the natural history of these conditions. Its efficiency and effectiveness is governed by the smooth transition and integration of sample collection, test analysis, follow-up with families, diagnosis and timely treatment.

This mass screening program of over four million infants per year has been heralded as a successful program, as cost-effective, and reduces morbidity and mortality associated with these inheritable conditions. Newborn screening programs in the United States were the first population based screening programs for genetic disorders and signaled the integration of genetic knowledge into public health programs.

Underlining principles of newborn screening programs are (1) the condition has a high incidence within the population; (2) an effective treatment for the condition is available; and (3) an effective sensitive and specific screening test is available.

Newborn screening programs are based at state and public health agencies. Therefore in America today we have 51 different programs. Interesting from some of our studies of these programs, we found that some states test for three conditions and other states for up to 21. Each state has established some infrastructure to ensure that there is follow-up of positives. The emphasis is on some, meaning that one of the things that we are finding is a very marked inconsistency on how follow-up takes place and it is far too often in America today that children who test positive do not get appropriate follow-up. Because of this, infants do not have an equal access to newborn screening and its potential to prevent impairment and disability.

Differences will likely continue unless a nationally acceptable standard is in place. To address these and other issues, a Task Force on Newborn Screening was convened. The American Academy of Pediatrics served as the convener at the request of Maternal and Child Health Bureau and HRSA. Co-sponsors of this event were NIH, the CDC, the Agency for Health Care Policy and Research, the Alliance of Genetic Support Groups, a consumer group, the Association of State and Territorial Health Officers, the Association of Maternal and Child Health Programs, and the Association of Public Health Laboratories.

This task force, I think, was really developed and had there significant components that were different than a lot of meetings that have been held in the past. First is connection to the concept of a medical home. Medical home is family centered, community based, coordinated, comprehensive, culturally sensitive for which the health care professional shares responsibility with the family. This was the underlying -- underpinning concept of this meeting.

The second was the very important role of families. I know some of the members of this group have said that they have had personal experience except one thing that is different is when you have a family member who does not have any other association background. We have found that is an extremely and important and, yet, different perspective.

The third was the role of primary care health provider. As a part of the preliminary work for the task force we surveyed over 1,000 pediatricians and did focus groups with pediatricians. I think they really represent the whole field of primary health care, meaning nurse practitioners, physicians assistants and family physicians and internists, that they really want to be involved in the discussion and the follow-up and the support of families who are impacted by these conditions.

Five work groups were set up, one being newborn screening and its role in public health. The second, the medical home and systems care. The third, economics and screening. The fourth, ethical, legal and social issues. And the fifth, implementation and assessment issues. These work groups met for six months, collected data, and spoke to various state and public health agencies, health labs, maternal and child health programs, involving pediatricians, families and consumers, bioethicists, scientists, and other health service researchers, and then in May of this past year presented their work for public comment and papers along with specific recommendations.

This -- the results of the task force will be completed over the summer and we are hopeful that you will be able to, as the Secretary's Advisory Group, review this information as you make your decisions and deliberations. Thank you.

DR. McCABE: Thank you very much. Our next speaker then is Dr. Russel Enns, who is Vice-President for Regulatory Affairs of Vysis.

RUSSEL K. ENNS, Ph.D.

DR. ENNS: Thank you, Dr. McCabe and the committee. I guess I represent the manufacturing sector. My background is I am a Ph.D. biochemist with 25 years experience in the biotechnology industry having worked for five different manufacturers representing Fortune 50 companies, three start-up companies.

(Slide.)

It was my good fortune to put the first DNA probe products through the FDA in 1985 starting with legionella for legionnaire's disease and another half dozen products in '86 for infectious diseases. Over the course of my experience with DNA probe technology I had the good fortune of having over 20 products reviewed and cleared and approved by the FDA for use in DNA probes. I will read the rest of my comments and you can kind of follow along the major points or concerns that I have.

On behalf of Vysis, as a leader in the emerging technology with six FDA cleared and/or approved products for genetic testing, it is our vision to develop and market genomic disease management products with the greatest near term medical/clinical value. Our long term goal is the continuing expansion of clinical genomic products and systems. As an ethical manufacturer of in vitro diagnostic products approved or cleared by the FDA, we have a very strong interest in the efforts and future recommendations of the SACGT on the subject of genetic testing.

We have closely followed the previous efforts of the NIH/DOE Task Force on Genetic Testing and its positioning statements on this subject. We have several specific concerns about the carryover of these specific statements and possible negative influence on the work of the SACGT. We are also somewhat dismayed that none of the technology leaders, the manufacturers of these in vitro diagnostic products, is included in the committee membership, representing manufacturers.

We believe that our industry is leading the way in reducing the discovery of critically important genes in disease processes to fully functional in vitro diagnostic products with clinical validity of data. Representatives of our manufacturing industry could significantly enhance the overall effectiveness of the SACGT. I am sure as I am volunteering, other members of our manufacturing sector would be at your disposal if questions come up on manufacturing, quality assurance and controls.

Our first and foremost concern pertaining to the SACGT is that the committee will not restrict the definition of genetic testing, as suggested in some sectors, to inherited diseases only. Today, the majority of genetic testing that occurs in diagnostic testing laboratories that are accredited by CLIA from cytogenetics laboratories to pathology labs represents testing for somatic cell mutations associated with disease, whether the disease is cancer or birth defects, et cetera, and not only just inherited disease disorders. Our apprehension is that the medical professions, let alone the public, as a whole, do not yet clearly appreciate these significant distinctions between inherited disorders and somatic cell mutations.

The NIH/DOE Task Force on Genetic Testing focused its attention on predisposition genes, as we heard Dr. Holtzman speak earlier on BRCA1 and breast cancer. The primary concern, I believe, as you heard this morning, was the potential of the invasion of privacy and discrimination against a patient or their family members and there was also this concern that Dr. Holtzman discussed about the abuse and misuse of these predisposition tests and the inadequate regulatory oversight of test use. Part of this concern is due to the less than optimum treatment options with respect to results from tests like BRCA 1 and 2.

However, if the SACGT focuses only on predisposition tests, it is likely that the committee recommendations will unfairly apply to somatic cell mutation tests as well. Due to lack of knowledge my many health care professionals they are unable to distinguish between the clinical utility of these test types, the more stringently regulated predisposition test standards will inappropriately apply to the routine somatic cell mutation tests by default.

This will greatly impede the progress being made in the delivery of new and better somatic cell mutation tests which do not represent the same level of concern pertaining to

patient and family discrimination as inherited disorders. Therefore, Vysis prefers that the SACGT adjust its focus to commenting and recommending upon all types of genetic tests for public clarity. That is if you make the distinction that you are only going to deal with inherited disorders then define what other genetic tests are and what you are not proposing policies and regulations for.

For example, our most recent product was approved by the FDA in December of '98 for the PathVysion HER-2/neu DNA probe kit with the following intended use statement:

"The PathVysion HER-2 Probe is designed to detect amplification of the HER-2/neu gene via fluorescence in situ hybridization in formalin-fixed, paraffin-embedded human breast cancer tissue specimens. Results from the test are intended for use as an adjunct to existing clinical and pathologic information currently used as prognostic factors in stage II, node-positive breast cancer patients. The kit is further indicated as an aid to predict disease-free and overall survival in patients with stage II, node positive breast cancer treated with adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil chemotherapy."

So this test represents the detection of somatic cell mutation in the HER-2/neu oncogene. It is not an inherited disorder. It might in the future be found to have polygenic variables but they are not known today. With the results of this test a clinical oncologist can discuss very specific chemotherapy options with his or her patient.

The same FDA regulations and guidance documents for all in vitro diagnostic products were developed from the 1976 Medical Device Amendments to the Food and Drug and Cosmetic Act, also the Safe Medical Device Act of 1990, and the FDA Modernization Act of '97, and these should all apply to genetic tests. The same regulations and guidance documents were applied, for example, to the recently FDA approved free PSA antigen test for use in prostate cancer, and specifically this is not measuring DNA but it is measuring the protein antigen. So these -- I think these results -- these same regulations should be applied.

Vysis would like to go on record with the committee stating that the current FDA regulations and guidance documents for in vitro diagnostic products works well for somatic cell mutation type genetic tests. The FDA could continue improving upon its recent record for handling in vitro diagnostic products if given access to additional resources, especially for the anticipated flood of new genetic tests. These same regulations and guidance documents should apply to predisposition genetic tests made by in vitro diagnostic product manufacturers. The committee could and should recommend more stringent FDA regulations for predisposition tests.

However, the potential for abuse and misuse of predisposition genetic tests comes not so much from the manufacturing sector that submits their products to the FDA for review and approval. Instead, the potential for improper use derives more from the laboratory sector, as Dr. Holtzman has shared earlier, that overzealous attempts to be the first to offer the public a new genetic test. In many instances, the lab fails first in adequately validating the clinical performance of the new test before offering it to the public. The FDA does not typically regulate these laboratories becasue they do not fall under the current laws, regulations and guidance documents that pertain to the interstate commerce of medical devices.

Congress enacted the Clinical Lab Improvement Act of '88 giving HCFA and the

CDC jurisdiction over the regulation of clinical testing laboratories. Unfortunately, CLIA '88 probably did not go far enough in defining specific criteria for adequately qualifying the use of new clinical tests, not only genetic tests but all tests, developed by the testing laboratories. In contrast, the FDA requires that in vitro diagnostic part manufacturers meet certain minimum statistical standards in clinical trials to validate the clinical utility of their new tests. The requirements established for laboratories that implement new tests under CLIA '88 are far less stringent than the FDA requirements for manufacturers of in vitro diagnostic products.

DR. McCABE: Dr. Enns, could I ask you perhaps to summarize the rest of your comments?

DR. ENNS: Sure.

DR. McCABE: And submit your written comments to us?

DR. ENNS: I have two more paragraphs.

DR. McCABE: Okay.

DR. ENNS: I guess, I can follow up. What I have already said is in bullet point of CLIA '88 regulations and I believe from Dr. Charache's experience with the CLIAC. I do want to make -- recommend more specific stringent requirements for validating laboratory tests that are not submitted to the FDA.

I would also say to listen and act upon the patient advocacy group now. You have good representation on your committee. Because as we continue to develop more and more genetic tests, we are going to continue to subdivide patients into smaller and smaller categories where each one of us will be waving a flag for special interests and now is the time to get the system in place that works. Then, finally, just again I would like to just say we are at your services if you need the perspective of the manufacturer. Thank you.

DR. McCABE: Thank you. If you could, give your written comments to Sarah Carr.

DR. ENNS: I believe I have 25 copies.

MS. CARR: We have them.

DR. McCABE: Okay. I am sorry. They are here already.

DR. ENNS: Thank you.

DR. McCABE: Thank you. Our next speaker is Chris Asplen, who is Executive Director of Attorney Janet Reno's National Commission on the Future of DNA Evidence.

CHRIS ASPLEN

MR. ASPLEN: Thank you, Dr. McCabe. Very briefly, I would like to, on behalf of

the Department of Justice and on behalf of the National Commission on the Future of DNA Evidence, I would like to offer our encouragement to you and our services to you as we attempt to interactively -- have a better interactive relationship with our fellow Federal Government agencies.

The National DNA Commission was established at the request of Attorney Janet Reno for the purpose of maximizing the value of DNA evidence in the criminal justice system. As such, we are, I believe, significantly limited in the scope of our review as compared to what it is that this committee is doing. However, there may be some things that we have already talked about in the past year-and-a-half that may be of some benefit to you. However, quite frankly, I think that some of your discussions may be of even more benefit to us.

There are a couple of issues that the commission is in the process of considering and will continue to do so that members of this committee and attendees may well be able to provide valuable information to us on. There are issues such as phenotypic profiling and what our capabilities will be in the future but also what that means in the criminal justice context.

This morning, Dr. Collins' comments and vision of predictive genetic testing has significant implications for the criminal justice system. Quite frankly, I think it is fair to say that the complexities of the application of DNA technology to the criminal justice system simply regarding identification technology will pale in comparison to the complexities of the issues that will arise in the context of using DNA to determine or predict human behavior.

The application of predictive genetic research to the concept of human responsibility, not human identity, are going to be very significant for the criminal justice system. Again, I think that those questions will be even more difficult than the questions we have had to answer over the last ten years in terms of human identification by nature of DNA technology.

Another issue that is of significant consideration for the commission right now is the issue of data-based sample collection and storage and retention, and the privacy issues and considerations that accompany that proposition. We now have a national database of convicted offenders that is in the process of being developed and the issue arises as to what we should do with DNA samples after they have been tested, profiled, and put into the system. It is a question that the attorney general has asked us to address very specifically and it is one which members again of this committee may well be able to offer some guidance on as to what the pros and cons are of keeping those kinds of samples.

Again, we encourage your work here and we offer our services. The commission is comprised of representatives from the broad scope of the criminal justice system. We have -- it is chaired by Chief Justice Shirley Abrahamson of the Wisconsin Supreme Court. However, we have experts such as Dr. Philip Riley, who some of you may know, and also Dr. James Crowe, who some of you may know, but we also have representatives from the defense community, prosecutors, laboratory personnel, a victim advocate, as well as law enforcement and law school professors. As such, we have tried to identify those issues necessary to maximize the value of DNA in the criminal justice system.

Fortunately, the commission is blessed with a deputy director who is actually a real

scientist in all of this and understands infinitely, better than I, the discussions that you have and will continue to have. That is Dr. Lisa Foreman in the back of the room there. I am, by trade, an Assistant United States Attorney in the District of Columbia. However, I wanted to point her out because she will be here this afternoon and if you have any questions about the commission rather than doing it now if you would like to approach her with what we are doing or some ideas that you may have as to what you would like us to consider, please do not hesitate to contact her.

Thank you, Dr. McCabe.

DR. McCABE: Thank you very much. One quick question?

DR. BOUGHMAN: Could you comment on the relationship of the commission to the DOE and ELSI supported educational work being done in health science in the courts and the educational programs for the judges?

MR. ASPLEN: Yes. We are strictly limited right now towards -- we have five working groups on the commission. One on legal issues, one on post conviction issues, crime scene investigation, laboratory funding, and research and development. In the context of those, individual educational issues have arisen but it is not as specifically education oriented. I would support that proposition and also Dr. McInerney's request that this body consider even more the issue of the education, particularly from the public standpoint, because especially in the forensic context the issue of creating a database system that is based on public trust and public understanding is the key to its success.

DR. McCABE: Thank you. I would like to thank all of our commentators for the important information and insight that you have given us. We are now going to take a lunch break. It will be a half hour lunch break so until 1:30. The members of the panel are to meet in conference room 9 for lunch.

(Whereupon, at 1:02 p.m., a lunch break was taken.)

* * *

A F T E R N O O N S E S S I O N

DR. McCABE: Okay. Let's go ahead and begin to move towards our seats.

We have heard a lot this morning about CLIA and the FDA and HCFA and where the lines are drawn, and as somebody who has been involved to some extent with this in the past it is still a bit fuzzy. So I think I am beginning to get the hang of it but we thought it would be good, especially given the role of genetics in this and past role, that we review that this afternoon. So the topic will be "Overview of Clinical Laboratory Improvement Amendments (CLIA) Regulations and Role of the Clinical Laboratory Improvement Advisory Committee (CLIAC)," and that will be by Judy Yost. I will introduce both of our speakers at the outset.

Ms. Yost is Director of the Agency, HCFA, Division of Outcomes and Improvement, which is responsible for the administration of many facets of the CLIA amendments of 1988. She began her career as a bench technologist in a microbiology laboratory. That seems to be a common theme here. A number of people have done that. And then went on to direct hospital laboratories and progressively larger organizations. She is a certified medical technologist and holds a graduate degree in hospital management from Central Michigan University.

Following Judy, Pat Charache is going to talk about the CLIAC recommendations on genetic testing. It does not look like I have one on Pat but I will tell you Pat has already given her introduction as part of the introduction this morning and we know that she comes to us also from microbiology and with more of a clinical lab base and that has moved her into genetics and Pat is from Johns Hopkins. So, Judy, could you then go ahead and begin? Thank you.

OVERVIEW OF CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA) REGULATIONS AND ROLE OF THE CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC)

MS. YOST: Good afternoon. I have the dubious distinction of trying to keep you awake after lunch and, wow, what a topic. Okay.

(Slide.)

I promise to be as quick and fast and as painless as I can. I do have an extensive laboratory background and so I came to HCFA actually about the time that the final CLIA regulations were published in 1992. So that is about seven years ago and so you are going to get in about 15 minutes seven years of implementing CLIA and you will all be experts by the time I am done.

What I am going to do, again, is give you an overview of CLIA and to prepare the way really for Dr. Charache, who will then take the recently recommended recommendations of the CLIAC regarding CLIA to dovetail the two together. So I am going to give you CLIA as it is and then just a tiny bit of the role of CLIAC, which I am sure after today will be very familiar to you because it is very similar. Both of us will be happy to answer any questions that you may have.

Since your task has already been complicated by all of the issues that were presented, I would like again to provide you some items that -- for contemplation at least in regard to regulating laboratories. Again there is the issue, and you will see it again in guiding principles for our regulation, of balancing access with quality as well as to ensure accuracy and reliability.

There is also the need to be sure again to have flexible requirements because every lab is somewhat different so there is flexibility versus prescriptiveness and also the need to ensure that we encourage new technology as time progresses.

We also need to consider whether or not a regulation is the answer to an issue or whether there are other alternate mechanisms available versus standards or guidelines and so forth.

The other thing we need to consider when looking at CLIA because that is just one narrow piece of all the issues that have been brought forth this morning and all the other ones that are yet to come that we do not want to give the laboratory responsibility for something that it has no authority or control over. So that is also an important thing to keep in mind.

Dr. Holtzman really did not give us a whole lot on what the task force recommended but actually out of the 14 recommendations, about four or five of them deal exclusively with quality of laboratory testing. Let's go ahead with -- you should have a handout that is going to follow my overheads.

(Slide.)

These are some key features --

DR. McCABE: Yes. The first one.

(Simultaneous discussion.)

MS. YOST: Got it? Okay. Standards are based on the complexity of testing. Meaning the more complex the procedure, the more stringent the requirements under CLIA. All the aspects of CLIA that I am going to provide for you today do apply to genetic testing. That is an important thing to keep in mind as we go through this.

The law applies to virtually all clinical laboratories in the country. Right now we have registered actually about 170,000 laboratories and I think all of us think of a laboratory as a university laboratory or a hospital or an independent laboratory. We regulate ambulances, schools, community clinics, physician office laboratories, all those types of things are covered under CLIA. That is why the number is so high.

The impetus for CLIA was problems in cytology labs where there were actually deaths from incorrectly performed tests and clearly you have a direct patient outcome and that was the impetus for CLIA.

There are sanctions provided under the CLIA requirements for laboratories that

cannot meet the requirements. However, the basic approach for the CLIA program has been educational. It is our intent to really show the laboratory how to do quality laboratory work and not to put them out of business. It is only when the laboratory cannot or will not provide quality testing that we apply the sanctions.

CLIA is somewhat unique for a government program in that it is completely funded by user fees and the laboratories themselves pay the costs and the entire cost of the program, which sometimes can be quite challenging.

(Slide.)

Just a wee bit of history. What we are going to focus on today is 1992 where the final rules with comment were published. We are going to really just look at the standards piece, not all the rest of them because those are the things that are directly applicable to what you will be dealing with as far as the quality of laboratory testing.

(Slide.)

Again the intent of the CLIA statute was to ensure accurate and reliable testing regardless of where a test is performed. Another important thing to remember as we progress again is the definition of a laboratory under CLIA, and I am going to read this one. I do not want to read all these for you because you can read, too, but this one is really important.

"A laboratory is a facility for the examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of disease, or the assessment of the health of human beings."

(Slide.)

There are actually a few areas that are not covered under CLIA. One other thing that is covered, by the way, are government laboratories so they are not excluded for those of you who might have an interest. But forensic testing, legal type testing. For example, if an individual is on probation and drug testing done is as a criteria for permitting the probation to continue that testing is not at this time covered by CLIA because it is for legal purposes only. And then research. Research is a very near and dear thing to our hearts in that there are permutations of research. When research is done strictly for the purpose of just providing aggregate information, it is not covered under CLIA. However, just because you call yourself a research lab, if you individually identify specimens and return the results of that testing back to an authorized provider or to a patient, that facility then becomes covered under CLIA.

(Slide.)

The complexity model for CLIA is pretty straight forward. There are waived tests and there are moderate complexity and high complexity. And, again, as the complexity of the test increases so does the stringency of the requirements. A simple test are those where there is minimal risk that if it is performed incorrectly -- that it can be performed incorrectly so it is a very simple one step type of test with a direct specimen. Examples under CLIA are a glucose done on a meter or a urine dip stick test. The moderate complexity tests are

primarily the automated tests in the laboratory like a complete blood count that is done on an automated instrument. The high complexity tests are those tests that have many steps and require extensive training to perform, and have perhaps preanalytical processing, and have interpretation to be done with the results. Examples of that are like a cross match that is done for transfusion or pap smears where judgment, individual judgment, is required.

(Slide.)

It is very interesting to look at the proportions of the tests. At this point CDC has categorized about 23,000 different tests under CLIA because each methodology by each manufacturer becomes an individual test under CLIA but you will see that three percent of the tests are waived, 70 percent are moderate, so you have almost a sort of bell curve, and then 27 percent are high complexity. By contrast, however, since many of the most frequently performed tests in say a physician's office laboratory are now currently waived, 50 percent of the labs in the country will only do waived tests and, thereby, are only subject to very minimum criteria and requirements.

(Slide.)

These are some of the things I mentioned earlier. They are more less goals for the CLIA program. Again to assure access and balancing that with the quality requirements. Be sure that the program -- because it is user fee funded, the program itself has to be cost-effective so that we are using the laboratory's money that we collect very prudently. And we also want to be sure not to inhibit the development of new technology.

(Slide.)

And, again, today we are going to focus on the quality standards and they are thus listed. And they include proficiency testing, which is an external type of quality control, patient test management, which is just really an audit or record keeping system, quality control, personnel qualifications and, very importantly, personnel responsibilities, as well as quality assurance which is really the over arching quality principle under CLIA.

(Slide.)

Just a little bit more information about each of those. Actually private organizations or states can be proficiency testing providers under CLIA and they actually go through a rigorous review annually to be sure that they are meeting the standards to provide these services to laboratories. As well under CLIA, there are certain requirements for the laboratory to meet for proficiency testing and some of that is listed here for you. We have about 18 proficiency testing providers, which are organizations or states, currently approved. And currently the operative word in this overhead is "regulated." There are a list of about 83 different tests listed in the regulations currently that must have proficiency testing performed on them, that is if the laboratory does that test. And then there is an actual frequency and grading level that the laboratory must achieve in order to meet CLIA requirements. This is an external assessment of the laboratory's accuracy of its results.

There are, however, as you know, about 1,000 analytes in the world at least so you are seeing only 83 listed here. There is an alternate requirement under CLIA that actually

falls under quality assurance but it is applicable to this in which if a lab -- if there is no required proficiency testing, every other test that the laboratory performs has to have an accuracy check of that test two times every year to be sure again that the laboratory is providing quality services. That is just one arm of the CLIA requirements for quality.

(Slide.)

Again, patient test management is the audit trail or the record keeping system. It primarily consists of requirements for the preanalytic process which start at specimen collection. Those are the test requests and specimen -- and possible specimen handling and then through the post-analytic system, which is essentially reporting the result to the appropriate authority.

If you have read any studies about laboratory testing you will note that most of the errors in laboratories do not take part in the analytic part where the analysis is actually performed. The errors in laboratories are actually primarily -- like 80 percent of them -- in this preanalytic phase because that is the phase where there is a lot of human hands and a lot of manual steps, people handling and collecting specimens, labeling them, handling them, putting them on instruments, and so that is where the errors actually occur in laboratories. And that has been proven several times over in several studies as well as again in result reporting where the wrong result goes to the wrong patient or to the wrong -- and so forth.

So that -- and there are also requirements under CLIA to keep records for certain periods of time so that the laboratory can go back and check if there is a problem as well as, of course, for the inspector to be able to review what the laboratory has been doing.

(Slide.)

There is within the patient test management a key piece that is really pertinent to this group and that is that there is a requirement for confidentiality of all patient information. It is a very broad blanket requirement but it is already in the CLIA requirements. But the rest of patient test management is essentially documentation requirements.

(Slide.)

Quality control is the real time assessment of whether a test system is working and there are specific requirements under quality control. You can see that the laboratory has to have a procedure manual. They need to check their equipment to make sure that it is working, their reagents must be in date. I am just giving you examples of these. And there must be some mechanism to check the environment, the competency of the personnel that are doing the testing, as well as the test device or test system itself as part of that quality control mechanism, and then there are requirements for calibrating where calibration applies if an instrument is used and not a kit.

Quality control also has -- it is broken down into general requirements which apply to everybody in all the tests and there are also specific requirements for certain laboratory specialties. Again because cytology was the impetus for CLIA, there are very, very stringent proscriptive requirements for cytology.

(Slide.)

There are also fairly detailed requirements for the qualifications, the education, experience and training of the individuals in the laboratory. There are also required positions for the laboratory as well and they are listed here. And, again, as we mentioned before that they are by complexity. The more complex the test the more stringent the requirements, the higher level of qualification is needed, and the more types of personnel. Now if an individual in a laboratory, say in a physician office lab, meets all these requirements, they can be that position. It does not have to be five different people as long as they meet the qualifications.

The most important part, to me, I believe even more than the qualifications, are the responsibilities under CLIA for the personnel in the laboratory from the director, who has the overall responsibility for the quality of the laboratory testing, to the individuals who perform the tests. Those responsibilities must be met in order for the laboratory to be in compliance. It is not enough to have the piece of paper on the wall that says I am whatever degree. It has to be that that person is actually doing the job of the director, especially in the area of quality, because the laboratory director again has the overall responsibility to ensure that the tests that are selected in the lab are appropriate, that the results that go out of that laboratory are appropriate for the diagnosis of a particular patient. So it is a very broad responsibility. Interestingly enough, that responsibility ties directly into -- and you will see this in CLIA as well -- that all the requirements are not stand alone. They are all interwoven to give you a complete type of quality assurance package.

(Slide.)

So that the -- again the over arching requirements, the laboratory director responsibilities, you will see, directly correspond to the quality assurance requirements in the laboratory and that is very important. The quality assurance requirements encompass all the things we talked about so far, as well as some additional things. Again, if the laboratory is not enrolled in proficiency testing, for example, or they do a test by two different methods, they need to make sure that those two methods are correlated so again the laboratory is providing quality results.

Quality assurance is really an ongoing mechanism that that laboratory develops for their own operation to ensure that on an ongoing basis it is providing quality testing. That is they have mechanisms to correct their problems and to assess even the fixes that they implemented for their problems. They need to do -- say, for example, again if proficiency testing is not available, a lot of the genetics folks do inter-lab comparisons. So that is an excellent way to supplement the quality assurance in the laboratory. There needs to be mechanisms for communication and complainant investigations as well.

(Slide.)

So now that you know all the requirements, I just took 113 pages of regulations and gave you five overheads. I will just quickly run through these, show you these rules because as we mentioned earlier, HCFA and CDC share the responsibility for CLIA and we will soon be adding FDA. HCFA is more the administrative operational stuff. We register the labs. We collect their money. We impose enforcement if we need to. We do the approvals for

accrediting organizations which are allowed under CLIA. We approve the proficiency testing programs.

(Slide.)

CDC is the scientific and technical experts, although HCFA now does also have technical expertise as well so it is often a collaboration. However, CDC has the lead on the quality standards. They currently categorize the tests and they assist HCFA in all the other parts of approvals under CLIA. CDC has the exclusive responsibility for CLIA studies that were mandated to assure that the standards are really monitoring quality in laboratories and to also support the Clinical Laboratory Improvement Advisory Committee, which are the folks that Dr. Charache is going to tell you about what they do.

(Slide.)

We have a new player coming in, in the near future, where FDA is going to take over the role of test categorization under CLIA from CDC, and that was by law.

(Slide.)

Just a tiny bit about the CLIAC committee. They were chartered right when the regulations were published in 1992 and have been meeting ever since and have promoted a number of recommendations to both HCFA and CDC, most of which have been published in regulations so I think that is an admirable record for CDC particularly to ensure that those recommendations go somewhere and action is taken on them and that they are -- and if they are not in regulations, often times they might get implemented administratively so that they truly do have a very important role in this program, and also to keep it current, keep it up-to-date and so forth.

(Slide.)

There are a couple of things that jump out and they actually are right out of the recommendations from the Task Force. Things that still need to be looked at particularly in the area of genetic testing but not exclusively. Some of the recommendations that the work group made under CLIAC for genetic testing are actually applicable across the board to all laboratory testing but there is not enough required proficiency testing in the area of genetic testing but then again that might not be feasible for every type of genetic test. So, I mean, there is a balance there.

Quality control for the current methodologies. That has got to be updated. It needs to be state-of-the-art. And other pieces of the quality control requirements Dr. Charache will talk about, as well as specific personnel qualifications and responsibilities and the discussion of whether a separate genetic testing specialty needs to be implemented and so forth, and also discuss where and how informed consent and counseling fit into CLIA.

But, again, as you can see, many of the aspects of genetic testing are already covered by CLIA. That does not mean that they cannot be better, that there is not another way to do that and so the first step will be clearly to go through the recommendations from the CLIAC and we hope to clarify those recommendations in future regulations. What has happened,

again, is we have -- we are currently working on a final quality control regulation that encompasses quality assurance, as well as the patient test management, and the quality control.

Many of the recommendations in the area of genetic testing from the CLIAC are very much applicable to the broad base of all clinical laboratory testing and are very much a logical outgrowth of existing requirements so they will be incorporated into a final quality control requirement. However, many of the other recommendations of the CLIAC are new or very specific and so thereby have to be put into a proposed regulation that will be developed by HCFA and CDC.

So, I guess, now it is up to you to tell us where to go from there. Thanks.

DR. McCABE: Thank you. Why don't we move ahead to Pat Charache? Dr. Charache will talk about the CLIAC recommendations from the genetic testing perspective.

CLIAC RECOMMENDATIONS ON GENETIC TESTING

DR. CHARACHE: How much time do we have?

DR. McCABE: We have another 25 minutes but if we can have some time for some Q&A at the end that would be good.

DR. CHARACHE: Thank you. I am going to -- I would like to start by making the point that I certainly also agree that there is a very major need for a change in the way the genetic testing oversight is done and I just received by fax a copy of a report that I really would like to read this group. It is from one of the two or three large commercial laboratories in this country. This was for a test of familial polyposis. The result says, "The results for this test are for investigational purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure." For this entity, the only diagnostic approach is the colonoscopy on an annual basis. The charge for this test, I learned from calling the company, is $751. So I certainly would agree that we have to make changes.

Now as a result of the discussions this morning, I would like to emphasize the complementary and overlapping important roles of the various groups that are concerned with this entity. We had a conference call, thanks to Sarah Carr, as a result of a need to see whether the FDA, with Susan Alpert, and the people from CDC -- I was at CDC at the time -- along with Dr. Robert Martin, who is Director of the Laboratories Division, and Judy Yost from HCFA. We talked about the roles of these groups. I think that -- I later made a summary of what I thought we had said in a few words and sent it to everybody and said, "Is this what we agreed upon?" And there was concordance.

I think the point we should make is that the FDA is responsible for test approval and it does this primarily now through premarket and post-market reviews but also through any other process or procedure that they elect to introduce. CLIA is responsible for laboratory practices, including defining personnel requirements and responsibilities of the various people who work in the laboratory. Now as Judy showed with her overhead, CLIA has

responsibility for any laboratory that does work with material taken from an individual for the purpose of diagnosis, treatment, prediction of disease and so on. It is a very broad responsibility. HCFA's responsibility is enforcement. It is to carry out the policies that are developed and agreed upon that should govern the handling of material that comes from a patient for medical purposes. You have seen that there are very few instances where this is not covered.

The strategies that are used are also overlapping. Here I think we have to disagree with the impression that may have come out of some of the Task Force discussions that CLIA is only concerned with what has been called analytical validity. CLIA is concerned with laboratory tests and throughout the CLIA regulations it makes it very clear that there are three components that are the responsibility of CLIA. Preanalytical, analytical and post-analytical. What is covered by proficiency testing and what is covered by just an analysis of whether a test can be reproduced or not or can detect an analyte or not, that is a part of the analytical part of the test but the preanalytical, the analytical and the post-analytical are all covered in exactly that way by CLIA.

(Slide.)

Now what I had planned to talk about was just the extended requirements, those which the Genetics Working Group had said should be added to current regulations or clarified. It is either clarified or expanded. But what I would like to do is also be sure that there is understanding of what the current regulations now say because they are powerful. I am going to come back to how we can help the FDA and HCFA in their parts of expanding and ensuring that the policies which are set up for CLIA, in fact, can be carried out.

(Slide.)

Now one of the things that I will show you is a current regulation for the responsibilities of the director of a CLIA laboratory and this is only one and there is a whole list of them but it emphasizes the point I just made. The laboratory director must ensure that the testing systems developed, if they are making home brew, and used for each test performed in the laboratory provides quality laboratory services for all aspects of the test performance, which includes the preanalytical, the analytical, and the post-analytical. As I show you overheads of the changes and recommendations made you will see what is encompassed in that. You cannot meet the post-analytical requirements if you do not know the predictive value of your test. This says that you do not do a test if you do not know how to interpret it.

(Slide.)

Now in this discussion -- and I am going to skip quite a bit but I will try to give you a sense of how encompassing the work of the Genetics Working Group has been if I cannot detail some of the points made. And then as these subjects come up, I can address them in discussion as we go. But what I am going to do is summarize the approach used by CLIAC, the Clinical Laboratory Improvement Advisory Committee, and its Genetics Working Group, summarize the recommendations, and I will go through this very quickly, and then the current status of the implementation of these recommendations. There has been a great deal done very rapidly as a result of the working group and I will tell you how that happened.

(Slide.)

What CLIAC did at the request of Dr. Baker, who is head of that unit at Public Health Programs at CDC, was to review the status, the current status of genetic testing and decided that it was inappropriate, reviewed the regulations, determined the need for special requirements and voted to establish a Genetics Working Group, which was done.

(Slide.)

The Genetics Working Group included 15 people. There were 11 genetics people. I had 12. I could not add very well. There were three people whose background -- and I was one of the three -- who was in the laboratory sciences so we could put the genetics together with how laboratories work. Then we had one lawyer who was a specialist in legal ethics and was a very positive contributor. We added clinical users to our pre and post discussions.

(Slide.)

The strategy that the working group followed was in this order: We defined the genetic test and we will show you our definition which varies a little bit from the Task Force one, although we looked at a lot of people's definitions. We defined specific issues that apply to genetic testing. We did not look at what the regulations were. We just said these are issues we have to attend to. These are preanalytical issues. These are issues that have to be addressed for genetic tests. I did not bring that list but I can tell you what they were. And then we defined what policies and strategies would be appropriate for CLIA addressing those issues. And then, finally, with the help of people from CLIA, we established whether new regulations had to be written or whether they were already there but needed to be enforced.

(Slide.)

We define genetic testing by two definitions. A molecular test and a biochemical test. They both have the same last sentence pretty much.

(Slide.)

The molecular test was defined as an analysis of human DNA, RNA or chromosomes to detect inheritable or acquired disease related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or processes. So this does include the noninherited markers and I wanted to point that out.

(Slide.)

The biochemical testing, the definition is analysis of materials derived from the human body, including human proteins and certain metabolites predominantly used to detect inborn errors of metabolism, inheritable genotypes or mutations for clinical purposes. And that word "predominantly" is very important, which is why the bracketed phrase was added at the bottom of the next one, which is tests that are used primarily for other purposes but may contribute to the diagnosis of a genetic disease such as a blood smear, certain chemistries, such as cholesterol would not be covered by this definition. And we knew that the whole system would sink if we tried to cover -- did not define it as a test that is used predominantly for detecting genetic disorders or mutations.

The reason for requiring the biochemical testing and not just the molecular testing for DNA and RNA or chromosomes is very important and multifaceted. It is -- we know that many new tests will be measuring gene products, not the genes themselves. It is cheaper and it is easier. You can measure all kinds of things by measuring proteins immunologically as opposed to looking for the gene responsible for manufacturing that protein. In addition, there can be and has been a disconnect in which a true genetic test was not protected by the FDA or others because it was easy to run and it was a biochemical test yet all the other aspects of genetic testing apply, including heritable implications for the family, insurance and all the rest of it.

(Slide.)

Now we wanted it to apply the patient care test and we wanted -- needed to define what a patient care test is. This is my wording. The CDC is still working on it. But we defined a patient care test, and we have done this -- I said at Johns Hopkins -- this is what is applied to say what is a research lab that can do what they want and what is a patient care test. And a patient care test is any test whose results are provided to a patient, a patient's family or a health care provider. And we do that for, as an example, the report I read you to begin with. That was described as a research test but it was provided to a health care provider. So we say that anyone who is doing a patient care test by this definition needs to meet standards appropriate for providing that kind of genetic information.

(Slide.)

Now we looked at each component -- sorry.

(Slide.)

We discussed in order topics that apply to all aspects of testing and those which apply to each of the three phases of testing, preanalytic, analytic, post-analytic. So that is the order I am going to show you some of the questions that were addressed and recommendations that were made. We also divided into three sub-working groups. We had a preanalytical group, an analytical group, and a post-analytical group. You could belong to more than one. I chaired the analytical group and belonged to the post-analytical group. But that way we could focus attention on each topic.

(Slide.)

So, first, then are topics that apply to all tests. We did cover informed consent. We felt that this should be added to CLIA regulations, not to every test but to those tests whose sensitivity demanded it. We did not prejudge that every test should be handled the same way but said that because of the sensitive nature of some genetic tests the laboratory must have assurance that an authorized person has obtained appropriate informed consent from the patient, that at the request of the authorized person the laboratory shall assist in developing the appropriate informed consent, including the limitations and consequences of the test result.

We thought that should be added, also, issues pertaining to the re-use of specimens and I am not going to show you the whole discussion here but there is a major discussion

going on now, including in Congress, as to whether you have to destroy all laboratory specimens or products within a given length of time. For genetic testing, for many reasons, this would be extremely destructive. So we listed when you had to have consent to retain the sample and when it was permissible to use the sample without requesting signed consent.

(Slide.)

We considered whether to include in the regulations that due to the sensitive nature of certain genetic test results the laboratory must have a policy in place which deals with the confidential nature of test reporting. Now this is kind of a global statement but I put this here to ask this group also, as you think about confidentiality, does this mean that you can or cannot fax the results of a genetic test, can you put it on an electronic cumulative report, and so on? These are the issues being considered.

(Slide.)

The next group are the preanalytical requirements. We wanted to add to the CLIA regulations that appropriate information must be provided on the request form. You need the data. Any information you need to interpret the result or to know whether the test should be performed in the first place needs to be on the requisition. If it is not there the laboratory is proscribed from performing the assay. If there is a request for Alzheimer, you need to know it is not the pediatric patient. If it is a request for the colon cancer gene, you need to know it is in the appropriate ethnic group.

(Slide.)

We want to add the responsibility -- and what is in italics is what was also considered a discussion point and important. "When deemed necessary the laboratory shall assist its clients in ordering tests to meet the clinical expectations, including suggesting follow-up tests when appropriate." Nonwritten requests for additional tests must follow confidential and informed consent requirements just as the original one. We know that those who order these tests are often not as aware as they might be as to what they are ordering and it is the responsibility of the laboratory to guide them.

(Slide.)

The next group are the analytical phase recommendations. There are added responsibilities, which I will not show you, added for technical supervisor and clinical consultant, which increased the amount of training and education experience that they had to have in order to be permitted to do genetic testing. This is all associated with the recommendation that there be a separate requirement for genetic testing that is different from the general requirements for a high complexity laboratory.

(Slide.)

The three groups that we were most interested in were the lab director, the technical director or technical supervisor, and the clinical consultant. Now I am skipping because of time certain information but there are a couple of other things I will show you. For the analytical qualifications we want to add to the regulations that a specimen should be stabilized until clinical information for accurate testing is available. That is what happens if

you get an unstable sample and you do not have the genetic information required to do the test, you still do not do it, you take the specimen as far as you have to, to stabilize it so if you can get the information you can still do the test. This applies particularly to some of the more fragile samples in which you have to grow the cells and you do not have the information. You stabilize the cells, do not do the test until you have the information required to interpret it.

(Slide.)

There are additional recommendations that have to do with the specimen and specimen integrity, and so on.

Proficiency testing was specifically detailed in its requirements and is already being implemented but that is if there is no proficiency test available it specifies how you must meet that need.

(Slide.)

Validation of tests: Laboratories must verify or establish reproducibility for each method. Methods must be appropriate to the condition of testing. Reagents must be validated and so on.

(Slide.)

And there were specific recommendations for the number of probands that have to be tested prior to saying that you can validate a test and offer it for patient care. So I am not going to go through all of these details because it is extensive and we have limited time but the sense I want to give you is that the recommendations made by the Genetic Working Group were quite detailed and very extensive in terms of ensuring quality.

(Slide.)

I guess I want to emphasize it is not just that you can detect an analyte but the laboratory must define predictive value in terms of ethnic populations. I want to give you the sense that this really is a comprehensive set of recommendations. There are post analytical recommendations that include this, and this is the only one I will show you on this.

(Slide.)

The laboratory director, clinical consultant or technical supervisor must ensure that reports of test results include pertinent information that is meaningful to a nongeneticist health care provider. And there are details of that should be including the number of genetic sites you tested and variants that you tested if you report a disease like cystic fibrosis. Any disease that has more than one.

(Slide.)

This is the only other example I will show you of this, which says that these are the things that must be included in the report. Now the advantage of this approach is that it does go further than just saying the test is good to do. It really addresses preanalytical, analytical, post-analytical.

(Slide.)

Added considerations. The FDA oversight responsibilities for tests and a validating test we consider to be essential. And I said must be protected. This is my wording now. Remove it from CLIAC. We are very concerned about the starvation of the FDA about the fact that they have exempted tests that we consider very risky to exempt from premarket review, including all control reagents. So if you get a kit that has good reagents for establishing a curve, the controls you often have to purchase separately. Those control reagents are no longer being reviewed in any way so you do not know if the curve -- it may be a nice curve but maybe it should be somewhere else. Those have been exempted and actually the CLIAC is going to review a couple of test strategies. Some of this is congressionally mandated and compromises the FDA. Even so, I understand, they approve 300 tests per day so we think that the FDA needs to be supported.

We think that HCFA needs to be supported. They certainly need training to carry out these new policies. I am not really worried about HCFA. They are a good group although they also need resources but they are a defined group. I worry more about some of the groups that have deemed status. One, in particular, is like rounding up cats. It is no stable group. So I think it may be necessary for HCFA to define which groups have deemed status for genetic tests as opposed to deemed status for other types of tests.

The IRBs, I think we need to recognize, are a very weak reed. It took me about three years to get our IRB to agree to have a review of the material that goes through Hopkins and we found a lot of people who were doing genetic testing and other testing in which they said that if the family asks we will give them the results. Well, then it is no longer research, it is patient care. These laboratories were all over the map in terms of their ability to offer the information at that stage so we know that IRB is important. We need to know their limitations as well as their strengths. And we need to know that just looking at testing for genetic tests is not the whole story. We have heard a lot of that already today.

(Slide.)

Now I am not going to go over all the things that CDC has already acted on but what they have done is to determine what of our recommendations of the working group they could implement without having to go to the Federal Register and they found some very significant ones, which are already in the process of being implemented.

(Slide.)

So they are going to be emphasizing all three parts of testing as is now stated in CLIA. They are going to require confidentiality of patient information and they are going to facilitate work processes within the laboratory which are easy to introduce. They have been drafting recommendations that do have to go to the Federal Register that address others of our recommendations.

So I would like to stop at this point but give you a sense that CLIA is taking this seriously and, as Judy pointed out so nicely, many of these changes, although they apply to genetic testing, will have immediate beneficial impact on a whole bunch of other tests which affect people in the same way, whether it is tuberculosis or cancer markers, or whatever.

DR. McCABE: Thank you. I think, unfortunately, we are going to have to move ahead and come back to a discussion of this in the open discussion at the end of the day. Our next talk is the "Status of the FDA's Regulatory Oversight of Genetic Tests and Role of the Medical Devices Advisory Committee" by Dr. Alpert, who is the Director of the Office of Device Evaluation at the FDA, Center for Devices and Radiological Health. This office is responsible for premarket review of safety and the effectiveness of medical devices. Dr. Alpert joined the FDA in 1987 as a medical officer in the Division of Anti-infective Drug Products. She also received a degree in medical microbiology from NYU and an M.D. from the University of Miami, School of Medicine, and will summarize FDA regulation of genetic test kits and components, and will describe the role of the Medical Devices Advisory Committee.

STATUS OF FDA'S REGULATORY OVERSIGHT OF GENETIC TESTS AND ROLE OF THE MEDICAL DEVICES ADVISORY COMMITTEE

DR. ALPERT: Thank you. Good afternoon.

(Slide.)

What I want to do in the next few minutes, and in the interest time I will try to be brief, is to focus down on the way in which the oversight of FDA applies to genetics testing. I think I have to back up one step and say that the Medical Device Amendments went into effect in 1976 and laboratory diagnostics are considered medical devices. What that means is that the FDA has oversight for those products, their design, their manufacture, their market entry, and monitoring them through the lifetime of the product in what is called the post-market period. That, as I said, includes in vitro diagnostic tests, which many people do not recognize as being medical devices but they meet the definition because they are used to diagnose a disease or a condition in man. That puts them under our jurisdiction.

(Slide.)

We have different types of controls. What we call general controls that apply to all medical devices, things like the quality systems approach to good manufacturing practices, the reporting of adverse events that happen to patients in association with the use of any medical device, the follow-up in the field if there are failures of products that get reported in our monitoring of the manufacturer's responsibilities to either recall or address in the field the failures of any medical devices. All of those general tools apply to in vitro diagnostics as well as to heart valves and surgical tools.

In the premarket arena, we also have a menu of options in the way in which medical devices are regulated and I am going to go through those a little more specifically as we go forward but I will point out something that I know was already discussed this morning, and that is that the agency has not exercised regulatory authority from a premarket standpoint for laboratory tests that have been developed in-house, the so-called home brew tests. They meet the definition but the agency has, in fact, elected not to regulate them in the same way as we do those tests that are manufactured and provided and distributed and sold to laboratories for their use.

The last item on this list was the analyte specific regulation and that is on there so that I can point out a number of things. One is what we are doing to provide a threshold of oversight for tests that are, in fact, home brewed and it also gives me an opportunity to give you a real example of the FDA regulatory paradigm for medical devices because we have used just about every tool we have in looking at analyte specific reagents. All of the premarket tools on the manufacturing and quality systems approach, as well as the reporting tools for analyte specific reagents so I will come back to them as well.

(Slide.)

When you look at the tools that the FDA has to apply to the premarket evaluation for in vitro diagnostics, including those genetic tests that are manufactured for distribution in the marketplace in the U.S., we have a number of different ways in which we provide regulatory oversight.

The first one is what I put up there as device classification. We do not have a one size fits all regulation for medical devices. At the time the amendments were enacted it was recognized that medical devices can come in a variety of flavors. They may be very low risk and well understood. They may be of moderate risk or have special characteristics that need to be evaluated or they may be novel or high risk and require a full evaluation of their safety and effectiveness each time a new product goes to market.

So the statute and, therefore, the regulations provide for three levels of medical devices. Those of the lowest risk, the best understood, those where it has been determined the least oversight, regulatory oversight, is necessary are considered class 1 medical devices and they are subject to the general controls that I described. Things like quality systems, good manufacturing. They have to be labeled accurately. Any adverse events that are reported to the manufacturers of those devices get reported to us, and the companies, of course, and we are responsible for the lifetime of the product.

In class 1 we have two categories of devices. We have devices that -- as Dr. Charache pointed out -- are exempt from premarket review. What that means is that all of the other general controls apply to those devices but they may enter the marketplace without coming to the FDA first and getting a letter that provides them an authorization for marketing. They market on the basis of the fact that the manufacturer has determined that they meet the description of the device. For example, unassayed control reagents are exempted class 1 devices. They have to be manufactured well. They have to be labeled accurately. But a manufacturer of an unassayed control does not need to come to the FDA for permission to market. They just have to meet all of the other requirements.

Other devices in class 1 are, in fact, reviewed in the premarket -- from the premarket point of view and that means that the sponsor, the manufacturer, who wishes to put that device in the marketplace brings the data to us demonstrating that, in fact, they meet all of the requirements, all of the general requirements of the law, and in class 1 that they are substantially equivalent to a device already marketed for that use that is considered in that category. What does that mean?

What was classified were the uses of medical products. Not an individual manufacturer's product but a claim for a specific type of test, for example. So unassayed

controls as a category were placed in class 1 and then exempted from premarket notification or 510K. Assayed controls, on the other hand, are also classified but they are not exempt from premarket notification. They do come into the FDA and are, in fact, reviewed.

What that substantial equivalents review entails is a sponsor showing how their brand new product that has yet to be marketed compares to an already marketed product in its design, in its testing and sometimes even in its clinical impact so that we can reach a determination that it is expected that it will be as safe and as effective as the predicate to which it has compared itself.

The same is true for class 2 medical devices. That is the moderate risk category. The ones where we need some special testing. But in addition to all the general controls there are special tests that might have to be performed or special labeling that might be needed to be applied to those devices. So they are a moderate risk category. They come in through an abbreviated system, the premarket notification system, where what they are demonstrating to the agency is that they are equivalent to a device in that same class for that same use that is already in the marketplace.

Those are the two mechanisms. That mechanism for the two lower classes, class 1 and 2, we consider an abbreviated application. It contains just sufficient information to demonstrate how this new product is like an already marketed product and then they assume safety and effectiveness from all of the previous experience with products in that same category.

In the highest risk category or for novel products, it places them into what we call class 3. Class 3 products have to demonstrate everything to the agency in order for them to be approved for placement into the marketplace and that includes design, manufacture, bench testing, animal testing when it is required and clinical testing as required to provide evidence of a reason -- that provides a reasonable assurance of safety and effectiveness for that specific product from that specific manufacturer.

So it is quite different. It is a full application and not abbreviated and each and every manufacturer of a class 3 device has to independently demonstrate safety and effectiveness for that specific product. That is part of our menu for how we regulate medical devices. Classes 1, 2 and 3 from lowest to highest risk, abbreviated premarket notification applications or full-blown premarket approval applications.

(Slide.)

And where do genetics tests fit over the entire spectrum of medical device testing or the way we regulate <u>in vitro</u> diagnostics? There are some tests which have been in the marketplace since before 1976 that look at the products of genes. Those tests were classified in the early days of the Medical Device Program and many of them are in class 1 or class 2. In addition, there are brand new diagnostics that are looking at gene products that were not in the marketplace prior to 1976. They became new products. They were classified into class 3 by statute. Anything that was new is a class 3 product. And they have -- those products have moved into the marketplace with a full premarket approval application, soup to nuts, demonstrating the reasonable level of safety and effectiveness for their intended uses. So genetics tests that move in commerce that are manufactured and sold to laboratories for their use are the subject of -- some are the subject of each level of regulation in the medical device

arena.

(Slide.)

We move now to laboratory testing service. The so-called home brew. As I stated earlier, the FDA has chosen not to regulate those services in the same way that we regulate marketed tests. However, several years ago we were approached by the laboratorians raising the concern about the quality of specific reagents that are used as the building blocks for home brew tests and after much discussion, including discussion with the public advisory committee, the agency promulgated and finalized a regulation that we called the analyte specific reagent regulation that deals with the business end of home brew tests that are bought on the market from manufacturers. Again the manufacturers we are looking at are those that manufactured the reagent, the monoclonal or polyclonal antibodies that are used as the business end for many home brew tests. I know you have the regulation in your packet so I did not repeat the entire definition but just highlighted the fact that it talks about -- the regulation speaks to receptor proteins, ligands and nucleic acid sequences, and identifies those as being used in diagnostic applications, identification, and quantification testing.

(Slide.)

The way we chose to regulate analyte specific reagents was to take advantage of that menu that I gave you of classes and of levels of oversight on the part of FDA. All manufacturers of analyte specific reagents are subject to the quality systems regulation, to the good manufacturing practices. They are all subject to appropriate labeling, and I am going to come back to that, and they are all subject to reporting of adverse events that happen in association with those reagents. It is kind of funny because they are not marketing a test. They are marketing a reagent.

The focus of the regulation was to provide well manufactured and consistent reagents, batch to batch consistency, which was the subject that the laboratorians brought to our attention that prior to this regulation you could buy the same reagent from the same manufacturer but were not sure exactly how it was going to test out, whether it was going to have the same amount of reagent or not, whether you were going to need to redesign your home brew test each time you bought a new batch, significantly change your home brew test because the batches contained very different amounts, very different concentrations of the specific ligand, and it had different performance. So the focus of this regulation is to provide quality reagents to the laboratory that is developing and utilizing that reagent in a test used to diagnose a disease or condition of patients so that the patient testing that Dr. Charache spoke to.

(Slide.)

As we looked at these reagents, we recognized that since we were not regulating the end test and the laboratories that created the tests and that, therefore, provide the testing were different laboratories with different performance, with different tests, using different mixtures of reagents in different ways, their outcomes were all different. So we were not regulating the outcome from these reagents. Therefore, the manufacturers can only provide information about what is in the vial of reagent that they supply. What is it? Its identity. Its concentration. Its batch number. But no information about its performance because the

performance is based on the full test and they are not marketing the test so there is labeling restriction on these analyte specific reagents.

Again since the focus was good manufacturing and accuracy in the representation on the label of these reagents, most of these reagents were classified into the lowest risk category, class 1, and we exempted them from premarket notification because there is no data that would be available that we would review. It is basically a quality system look and a labeling look at these products. Therefore, they are class 1 and exempt from premarket notification.

We did reserve some into classes 2 and 3. Into class 2, the category that needs more than general controls, that needs some special testing, and would require premarket notification, we placed analyte specific reagents that are home brewed for use in blood banking because of the special concerns and the special risks associated with the performance of tests for the blood supply. So we require that those tests come into us, those home brews that are for blood banking purposes come into us. Those analyte specific reagents, they need to provide evidence that used in testing, therefore they have to be working with a laboratory and have test results to provide to us to establish that they are, in fact, capable of performing tests accurately and, therefore, being safe and effective for that use but that is through a premarket notification and abbreviated application. Mostly performance data in the laboratory.

(Slide.)

We reserved yet another category. Those reagents that are used in home brew tests for contagious diseases highly likely to result in death that are of high impact on the public health. Good examples are tuberculosis testing and HIV testing. So analyte specific reagents that would be used in those types of tests are in the highest regulatory category for oversight. Those reagents need to come in with a full premarket approval application, a full characterization of everything from the initial laboratory work all the way through manufacturing and testing in order to go into the marketplace and be distributed to laboratories. So we have used all of the tools. In addition, we have another authority.

(Slide.)

We have an authority called the "Restricted Device Regulation." This regulation allows us by notice and comment rule making, we cannot do it by ourselves, we have to do it with public participation in a rule making process, to not only look at the tests but to put limitations on the user, limitations on the user of the medical device. We felt that that was extremely appropriate in this situation for all analyte specific reagents. This applies to all of the categories, those in class 1, those in class 2, and those in class 3. And it is intended to be sure that those who order the tests as well as those who buy the reagents know what they are getting when they purchase the reagent or order the test.

We limited the sale of analyte specific reagents to CLIA high complexity laboratories where the personnel and the oversight exists to assure that home brew testing would be overseen well, that the tests will be appropriately developed, and that they will have the appropriate reliability even though they are home brew.

I already mentioned labeling requirements. The reagents cannot claim outcome

measures unless they have been through the PMA process. Only in class 3. All other reagents can only describe the quality of the reagent in the bottle.

(Slide.)

There are required language -- there is required language for the reporting by the laboratory to the ordering physician. For these tests, the ordering laboratory needs to specifically identify that this is a home brew test and that it was -- that the data, the information about the performance of the test is the responsibility of the laboratory. It is not a test that has been verified outside of that laboratory. The limitation on ordering has to do with who can send the samples to the laboratory for these types of testing. And that limitation is health care professionals. There are many types of tests that may be freely ordered in this country by anyone. You can walk into a laboratory and order anything you want in about half the states in the country. These tests, the laboratories are restricted from providing this type of testing except on order of a health care professional because of the concerns about the performance and understanding the reliability of the results of this type of testing.

Those are the kinds of tools that we have in place to regulate genetics tests. All of the different types that were described and that have been described and discussed this morning.

Again, just in summary, we have a classification procedure where those tests that are going to be manufactured and sold to laboratories are classified into class 1, the lowest risk with general controls, class 2, moderate risk with some special controls, or into class 3, needing a full premarket approval application. We have all of the general controls for quality manufacture and so forth apply across the board to all of those tests. And we have already received numerous tests that are used to identify most commonly gene products. So some have come through our premarket notification and some have come through premarket approval applications.

(Slide.)

Our step into the home brew environment has been in the analyte specific regulation, which I have just described, where we have categorized the business end, the reagent, and assured quality manufacture for all of them, good information transfer for all of them, appropriate labeling for all of them, and premarket notification for a reserved small set that have great impact on the public health.

In addition, we recognize that there will be more tests that look at either genes themselves or markers of specific genes that will be coming to us. We also recognize that the expertise that we need to evaluate these tests is very specific and so we have empaneled an advisory committee under our Medical Device -- a panel under our Medical Device Advisory Committee -- I will get the words right there -- that will be one of 17 panels that we have that assist us. These are our expert advisory panels that assist us in evaluating our processes and many of our class 3 medical devices. This panel has yet to meet. It is a new panel. We will be meeting with them for training purposes. They will be named and it will be meeting, we believe, in September as a -- for their first meeting.

Their role and the role of all of our advisory committees is very specific. They provide advice to us on classification when we are evaluating appropriate classes for medical devices. They provide advice to us on premarket approval applications, particularly first-of-a-kind tests or first-of-a-kind devices going to market. They work with us on the development of guidance documents. They provide a public venue for discussion of guidance documents and policy that are specifically focused on the premarket review tools that we use.

I hope that has given you an overview of what the FDA's current level of regulation is for genetics testing.

DR. McCABE: Okay. Thank you very much. What we are going to do now is take a break until 3:15 and we will reconvene at 3:15 and begin to have some discussion of what we have discussed today and begin to plan how we are going to respond to the oversight request for recommendations as well as what our prioritization is for our other activities. Thank you. So we will be back at 3:15.

(Whereupon, at 3:05 p.m., a brief break was taken.)

DR. McCABE: Okay. Let's get to work. The next session is going to run from 3:15 to 4:00 so we are going to have 45 minutes for discussion with an hour then for the last part in terms of priority testing.

DISCUSSION OF OVERSIGHT OF GENETIC TESTS

This is a discussion of oversight of genetic tests, our rapid assignment. I would like to introduce Bill Raub, who is going to join us at the table. Dr. Raub is Deputy Assistant Secretary for Science Policy and Director of the Office of Science Policy within the HHS Office of the Assistant Secretary for Planning and Evaluation. He has a long and distinguished record of service for the government. He has held a number of high level government positions, including a two-year service as an Acting Director of the NIH. Among many of his -- among his many current responsibilities, he is the leading -- has a leading role within the department addressing genetic testing issues and he has played a key part in developing the oversight document, which is under tab 3 just for your reference. Kate Beardsley is going to lead this discussion. Our goal is to develop a plan for addressing and gathering public input on the oversight analysis and I will let Kate begin that discussion.

MS. BEARDSLEY: Well, we have certainly heard a lot today about what the government is doing and some things it is going to be doing, and lots of opinions about what it should be doing, and I guess it is time now for us to go to work and think about how we are going to advise on this topic given Dr. Satcher's charge to us.

We have -- I guess Dr. Raub and his colleagues have put together a list of questions that they have asked us to address, and they are in tab 3. You may want to take a look at them as we go through here.

I think we probably all have some thoughts, more or less firmly held, on the answers to the questions that we have provided. I think probably what our job here today is less to think about what the answers are than to think about whether we understand the questions,

whether we think they should be clarified, and also especially to figure out whether we think we need more information to address them. And most importantly, as Dr. Satcher said this morning, to figure out how we can help gather public input and help understand what the public would really like to see here today.

So I am hoping we could maybe divide this discussion into three parts if it suits the committee. One being to take a look at these questions to see if we think that they need clarification. I do not know -- I do not think it is within our charter to decide whether we think they are the right questions. I think we have been given the questions but I will ask that question. Secondly, to think about what additional information we would like that we can gather, that we can ask the staff to gather. And, third, to think about a plan for gathering the information from the public that we have been asked to gather and get it processed, and somehow manage to get a report to Dr. Satcher by December 1st, which seems to me to be a pretty challenging task. I know that as an FDA lawyer, when the FDA comes to your company and says, "We need something by X date," the first thing generally you do is ask for an extension of time. So I would just like to say I have a lot of experience with that.

Unless anyone has another idea about how to do this, maybe what we ought to do is take the three questions, one at a time, and see if we think that we understand what they mean and also if we think that the public if we pose them to the public will understand what they mean and that we will get meaningful input if we ask these questions. Is that satisfactory to everyone so far? Okay.

The first one involves, obviously, IRB's, Institutional Review Boards, and their role in the oversight of genetic tests, particularly during the period when a test is being developed or evaluated. This appears to me to be limited to that phase and not to the phase in which it is in routine use. We are told here that at least some subsets of investigations of tests, those that are regulated by FDA at least, generally are -- the test is -- or excuse me, the study is conducted under the oversight of an IRB. I would have -- I think that IRB's generally are involved even in tests that are not necessarily overseen by FDA, although I do not know the answer to that question. There is some question about what the scope of an IRB review ought to be in approving and overseeing the conduct of these test protocols.

There is a discussion here -- so that is the first question that is being asked. Is the current degree of IRB oversight the correct degree? Should their responsibilities be enhanced? For example, I think there are questions about whether IRB's generally concentrate basically on the risk to research subjects or whether they can also have something and do have something to say about the scientific merit of a particular protocol. Whether those things are linked? Whether priorities ought to be skewed and whether IRB's ought to be doing a different thing on protocols involving genetic testing than they are on other kinds of protocols. I think that is basically the first question. If everyone has had a chance to look at the write-up, do we all understand that question? Do we agree that those are the right questions to ask?

DR. CHARACHE: I would like to see one thing added to the question. It says, "Should their responsibilities be modified?" I would also wonder if their composition should be stipulated because IRB's frequently do not have people experienced in laboratory testing on them, and they can be evaluated in other things. We had IRB proposals in which they wanted expedited review because all they were doing was drawing one extra EDPA tube and

that would not cause harm to the patient but what they were using that tube for was not necessarily asked.

DR. COLLINS: I hesitate to be unduly disruptive so early in the process, particularly as a liaison member, but I must confess to some sense of puzzlement about why we are suddenly jumping into a question about IRB's. It seems to me that the fundamental questions this committee needs to deal with really come under perhaps the second one here about do all genetic tests deserve the same degree of oversight or is there a subgroup that we would identify as in need of particular attention. If we could agree that there is a subgroup, we could probably figure out what the characteristics would be that would put a test in that subgroup, and then we need to figure out, well, what would that oversight look like and it might or might not involve IRB's, and to plunge immediately into that question seems to me preempts a much more important and larger discussion about what pathway of oversight would be ideal in this circumstance.

MS. BEARDSLEY: Let me refer that question to Dr. Raub because I know that they have given a lot of thought to the way these questions have been written and ordered, and what is in them.

DR. RAUB: I think the simple answer is this one is first because if we put them all at the top of the page we would not be able to read them one out of the other so they had to be sequenced in some way. I think the general thinking was not the intent of driving the consideration on this issue perhaps either to the exclusion of or to the warping of the others but rather trying to identify something that was really quite fundamental to the process in stating that and then going on to some of the things that were more specific to the regulatory processes either with CLIA or with the FDA. But certainly there is the license for the group to pursue any number of strategies for addressing these questions.

(Simultaneous discussion.)

MS. BEARDSLEY: So you are proposing that we reorder them, is that right?

DR. COLLINS: I think the most important thing for this group to do is to figure out what paradigm we think ought to be followed for oversight of genetic tests that require high scrutiny and then after we have decided that to figure out how the existing mechanisms, be they FDA or CLIA or IRB's, might be utilized to implement that pathway but to start with the mechanisms is going to get us all bollixed up.

MR. HILLBACK: I think I would agree with Francis for another reason as well. It is not obvious to me even in any of the approaches we might come up with how pivotal a role IRB's play in the core questions which get back to the issues of validity and whether analytical validity, which I do not think they play much in or clinical validity, their role, it seems to me, is quite different and people do not usually go back at the end of a study and ask the IRB did I do a good job on this study and did I prove that the test works. The IRB is usually at the front end of the process rather than the back end, so I do not think spending much time on IRB's is a good use of our time. I guess, I would agree with Francis.

DR. COLLINS: Then I will have to reconsider my position.

(Laughter.)

DR. LEWIS: I agree with what has been said. It seems to me that the IRB plays a part in a very significant but small part of the whole process, which is looking at monitoring patient safety during the development of the science but in terms of oversight it seems to me that is just one small part of it but there is also the part of post-the-research piece in terms of looking at how this -- how the knowledge that is developed in the research, then gets analyzed and implemented into practice, and I am not sure that the IRB is the appropriate organization to do that.

DR. McCABE: Remember one of the mechanisms that has been discussed and is in our materials, and I think may have been discussed today, is also to have institutional oversight committees that are different than the IRBs to look at the evaluation of the data. IRB's are supposedly looking at evaluations downstream as well in terms of the annual reports but we have discussed already about how they really function, which is at the front end, which is where the most stringent review is. So, you know, perhaps there needs to be review perhaps if it is not only an IRB. Again that would fall out of the discussion of questions two and three.

The other point is that my understanding is that while many of us come from academic backgrounds and we are used to IRBs governing everything that we do in test development that when you move into the private sector that IRB's play a very different, if any, role because the IRB process has to do with federal funding and if you are not using federal funding then you may not have an IRB process, and that is also something we do need to address, I think, but again it could be in position three here rather than position one but I think we need to address that. Are tests different if they are developed in a university setting versus in a private setting? If we are concerned about the risk, the risks are there to the individuals no matter where it is being developed.

MS. BEARDSLEY: Dr. Feigal?

DR. FEIGAL: There may be an opportunity now to actually have some influence on IRB's and although the -- because the broader questions are being asked about IRB's, about the Office of Protection of Protection from Research Risks. So I think -- but I guess one thing that strikes me in terms of getting into the discussion today is we really have not had a presentation about that system and, in fact, it is very complex and it is very international. There have been long and large meetings to discuss having uniform standards of human protections across international borders. And nonfederally funded research that is done under FDA has to be done according to the same rules as the federally funded. So I think since we started about talking about not trying to answer these questions today but identifying the process, maybe the part of the process is for us to revisit this and learn a little bit more and have some of the informational presentations on IRB's and some of the current findings based on some of the reevaluations and critiques of the current systems to see how this specific issue might play into that.

DR. McCABE: May I just point out what our deadline is -- December 1st. My understanding is that we have possibly moved into November in terms of our next meeting so that we -- one of the things we need to do in terms of developing process is looking at whether the large committee is really the appropriate way to address this.

DR. KOENIG: I have one further question on the IRB issue. I agree with Dr. Collins and Mr. Hillback about the general issue. However, there is one way in which IRB's are crucially involved and what I said before is that my interest with just the issue of movement from experimental to routinized stage of these tests, and that is the way in which the IRB's are involved in the issue of whether it becomes mandatory to disclose the results of tests to individuals in a research setting. I think that is a very fundamental issue, which if we do decide to not -- that is very important because I think that is one of the things that leads to the sort of rapid adoption of the use of tests that are still highly experimental, that some issue that goes on within IRB's that it becomes almost seen as a moral imperative to disclose results. So I think that one part of what IRB's do is very important.

DR. CHARACHE: I would point out again that IRB's are totally different between institutions. There are some IRB's that preclude providing information until the data is available that permits you to make a good decision and others that require it. So I think we do need to think through the heterogeneity of that mechanism.

DR. BOUGHMAN: Whether intentional or not, I find it actually interesting and important that the order of the questions was, in fact, presented to this group the way it was. I think there is an underlying message here. If you look at questions two and three, it focuses on the test, on the laboratory, on these important issues that we have been talking about, independent of the patient or the patient's family. Number one says to us, do not forget the patient or the family the way the information is transmitted, the way -- and the implications of that information. It has been couched in IRB language because that is one of the mechanisms that assures that we do not forget the patient or the individual and the protection of those individuals. But, in fact, when we went around the table this morning many of us addressed all of our issues from that perspective and it would seem to me that we would be meeting Dr. Satcher's charge this morning if, in fact, we reminded ourselves, whether we get the answer to that question or not, that that part of the process is paramount as we go forward with the federal level or recommendations on oversight of the testing process.

MS. BEARDSLEY: Yes, Dr. Tuckson?

DR. TUCKSON: I am a little -- I need to be oriented a little bit. I am a little confused. We are determining now appropriate questions and a structure for those questions to be able to receive public comment from somebody other than us?

MS. BEARDSLEY: I think what has happened is Dr. Raub and his group have told us what they believe the questions that they would like us to answer and to get public input on are, and we are figuring out whether we understand those questions and whether we think that those –

DR. TUCKSON: Are we participating in the process of eliciting the public input?

MS. BEARDSLEY: Yes.

DR. TUCKSON: It happens through this committee?

MS. BEARDSLEY: Yes. Right.

DR. TUCKSON: So we will convene some group of people who will come and make testimony around a range of questions, which we are starting to work through here?

MS. BEARDSLEY: I think that is one of the things that we have to decide within our 45 minutes is how we want to proceed to gather the public input and what to do with it when we get it.

DR. TUCKSON: So now I am getting clear. And then, finally, the purposes of that public input is designed to influence our ultimate report or some other user body?

(Simultaneous discussion.)

DR. RAUB: Well, I mean, we would like you to be the final common path --

DR. TUCKSON: Okay.

DR. RAUB: -- of that. So your analysis and synthesis of that information. It may or may not influence your collective view about some of these but having done the process of having the benefit of the public comment solicited by you, interpreted along with your own best judgments --

DR. TUCKSON: And the --

DR. RAUB: -- is the advice the Secretary would be looking for.

DR. TUCKSON: -- the questions that we are getting public input on are questions that ought to be high in our own minds in terms of things that we are trying to work through and we are getting the advice of others to help shape questions that we are struggling with. So these ultimately become fundamental questions about which we are trying to resolve and then getting input from the public that will in some way influence us. Is that the logic of it all?

MS. BEARDSLEY: I think that is right. Also, high priority questions in the mind of Dr. Raub and the people who we are advising.

DR. RAUB: And, in particular, having worked with representatives of our regulatory agencies, from their perspectives, these are very important questions. That is not to say these are the only questions. That is not to say you should not pursue variations of these themes or additions such as the suggestion from Dr. Charache about composition as well as function.

So your extension and refinement would be very helpful but we would hope that the core did not disappear because from the point of view of having to implement these things, these are important considerations from the regulatory agencies.

DR. TUCKSON: So then, ultimately, overall, I think that I -- I think I understand Francis' question better. It is that we are ultimately trying to decide in over the full range of genetic testing issues, you know, do some of these tests require more oversight than others and if they do what are the available ranges of mechanisms by which you accomplish that, of which one is what occurs in an IRB, of which one has to do with the discussion that we had

just now that we have not resolved, and that is whether or not the changes that CLIA has made to respond to the concerns are appropriate, whether or not the changes that FDA has made are appropriate. So once we put that grid together and once we have some debate about that, we will understand more clearly in our own minds whether or not the problem has been resolved or whether there are outstanding issues that remain to be addressed. And then the question is based on our understanding collectively of that, we then will say we seek other information or a test of whether our -- we are comfortable because whether others are comfortable or not with our comfort -- in fact, we have comfort if that is comfortable.

(Laughter.)

MR. HILLBACK: Can I -- is -- let me ask if you are saying what I think you are saying. It seems to me -- it seems to me what you are saying is that we have listened -- we have done a lot of reading and we have listened to a lot of people tell us what is happening and what should happen, and what has happened, et cetera. We have not had any chance for us to debate those things to try to come to grips with, as a group, trying to talk -- I mean, consensus is too nice a word, but trying to come to grips with as a framework how do those things all fit together, where might the holes be, where are not the holes. We have not done that on our own and we also have not asked the public. But I think what you are saying is it is kind of hard to ask the public to help us figure that out if we do not even know how we feel about it and how we want to phrase the questions.

I think this comes back to something that I said to you earlier, you know, to do this with one more meeting before we meet with -- before we do the report is almost -- is very difficult. I do not know how we are going to do it. I would almost propose that we find a way to get together sooner and digest what we heard today where we can really scrap about it and get it up on the table and talk about it and get our own -- there are lots of opinions of the committee members that have not been put on the table besides my own. I am always shy about putting mine on the table -- but -- and then go forward from there. I think that is what you were saying.

DR. TUCKSON: That is precisely what I am trying to get at, is I think we are jumping into a big pond of water and we have not even decided how we are going to swim together yet. I think maybe for the chairman's sake that perhaps a part of this has to be done or, you know, I think something -- either a conference call -- I mean, it sounds like that we are going to have to commit ourselves to a great deal of work outside of the meeting. And, for one, to make it easier for you, sir, I am proposing that -- you know, we take this assignment seriously and we will work our tails off but I think we have got a little bit of pre-work to do here.

DR. BURKE: I just really want to follow up on the comments that have been made. I think that we should recognize right now that question two is the first priority question and that we really cannot address these question without -- any of the other questions that are posed -- without getting into the questions under the questions that are grouped under do all genetic tests warrant the same degree of oversight. If not, what are the characteristics? And what are the different mechanisms that are available? It seems to me that we have to address those questions first to give -- and seek public input on those questions. We have to take a body of information from within and without this committee first to then begin to integrate those concepts, what we are coming up with, with what we heard today about CLIAC and

the FDA and potentially other regulatory mechanisms, including the IRB.

DR. LEWIS: Yes. I just also struggle a little bit when we talk about public input, who the public is. I mean, is it members of our professional communities? Is it the average citizen? And, you know, depending on how we define the public, I think it is really going to depend on how we go about gathering the information because it is pretty easy to get information from sophisticated users, from professional associations, but I am not sure that is a really good snapshot of who I think the public is.

MS. BEARDSLEY: Yes, right. Well, I guess, we either need to say here that we feel that number two -- and I guess I would add some parts of number three are really -- are our critical mission here and we are comfortable with the idea that that -- that we have to ask those questions or we need to decide that we need to have more discussion before we can figure out what the questions are.

DR. CHARACHE: I would like to also second the fact that I think it is going to take a lot of work but I think that we would be doing a disservice if the imprimatur of this group were superficial. I think that we really do need to have a discussion among the members and formulate a better understanding and get input from each other too.

DR. BURKE: It may be that that is a necessary first step before we figure out how best to access public opinion.

DR. CHARACHE: Yes. I would hope that we can get together before November so that we can try to meet Dr. Satcher's goal but not be superficial.

MR. HILLBACK: I would make one other comment. I wish Pat was still here. I am sorry she had to leave. I think one of the things that is very obvious over the several years or two years that the task force existed is that there is no solution we will come up with that does not involve a huge number of trade offs. And until you get into an open discussion which not only includes the full members but also the ex officio members and where the trade offs become obvious where you are really trading off, you know, how long you want to wait for information versus taking information that is not complete. Those kinds of issues are really the gut issues that we struggled with. Tony was there. I think he would also agree with me. We struggled with it for two years and we never came to a consensus and that is why we did not recommend a final approach on regulation. So without getting into that give and take, I think it is going to be hard for everyone to have a touch, have a feel of the fabric of what the real debate is about. We all have opinions about it because we have been involved with genetics some but to not have the give and take, I think, would be very difficult to try and make a recommendation without that give and take.

DR. COLLINS: I think basically what that will come down to is a need for this group to get comfortable with what we think the major questions are and I think maybe there are really four and they overlap a bit with what is in front of us but maybe if you will permit me just to put out a suggestion of what those four might be.

First of all, are there genetic tests that require greater scrutiny than the current system or offers? And how do you define that stringency criteria? So that is question number one. If the answer is, yes, there are some that need more scrutiny, and I suspect it

will come down to that, then what kind of data is needed before such tests become utilized in clinical as opposed to research activities? Is this clinical validity or is it going beyond that to clinical utility? Third, who collects that data? Who holds the responsibility? How is that data going to appear? Where is it coming from? And, fourth, who is going to review it and decide whether or not it is convincing and, therefore, that this test is ready for application in clinical medicine?

Those -- that is where it all centers, I think, and again I would appeal to this committee not to get too distracted by whether or not the mechanism exists in one of the existing HHS agencies to make one of those things happen tomorrow, and we need to figure out what the pathway ought to be and figure out how the agencies can perhaps adapt themselves to meeting those needs, and not the other way around or we will get all tangled up.

MS. BEARDSLEY: If we were to build on a base of those four questions, would we be capturing what the agencies need to know?

DR. RAUB: I think it certainly goes a long way to do it but again I would urge you to have the discussion that several of you have suggested to ensure that not only is your comfort level there but, indeed, that in this formulation there is capturing of the questions that have been raised here. I think in the end those who need to work either within the current statutes, regulations or proposed modification of them, you know, need to be able to deal with the questions that they have formulated.

MS. BEARDSLEY: Right.

DR. BURKE: I think I would just add to Francis' four questions that the first two that he has posed, are there tests that require greater scrutiny than is currently available and, if yes, what are the criteria that we would apply, do get to the core points under question two. And the last two questions, who collects that data and who reviews it, I think, could be modified to what are the options for collecting that data, what are the various options for collecting that data, and what are the various options for reviewing that data, which would encompass the discussion we need to have about different regulatory options.

DR. TUCKSON: Do you mean to suggest by the options, by the way, that at the end of the day we would make recommendations about –

DR. BURKE: Absolutely. We need to have a discussion with different options and then agree on what the best option is.

DR. KOENIG: I agree with the four questions and Wylie's comments with one addition, which is I just want to keep -- I will probably keep putting this idea on the table, which is that data are not going to answer these questions, data alone will not answer the questions. Perhaps at the level four in terms of who reviews it, we have to accept the fact that there are going to be value and other considerations and that is where the public input comes in. There is not just a straight forward issue of collecting data and we are not going to go from data to policy without something complicated in the middle.

MS. BEARDSLEY: All right. Well, where should we go from here then? Should we be asking -- go ahead.

DR. McCABE: Well, could I propose a mechanism? First of all, Sarah has been reviewing the calendars and we can capture most people but not everyone September 1st and 2nd. So that the issue is should we try and have an earlier meeting so if we need a second meeting before December 1st then we do it? And it looks like that is the best date, so we should think about that. Secondly, I would propose then that even before that meeting, knowing that the summer is difficult but still recognizing that we are under some pressure and that is two months away, that we put together a subcommittee and I have, you know, quickly jotted down a subcommittee of four who I would be happy to share with you and then invite others to participate. I would not have anyone feel left out, though. There will be plenty of work during the time of our charter. So do not feel that you have been left out, and this was done very quickly.

Kate, I would ask you to chair the subcommittee. You have thought about this before this and you have the experience with the FDA and regulation, and you have already told us you are good at appealing for extensions, so I think that you would make an ideal chair.

(Laughter.)

Then just going through the list, Joann Boughman from the University of Maryland with experience in epidemiology, and certainly as we get into clinical validity and clinical utility and epidemiology. Wylie, in terms of your experience and background, and some of the comments that you have made. And then Elliott to represent the private sector in these discussions as well. If anyone else wishes to volunteer -- and I would propose that these -- this is a small enough group even if we add a couple more if some of you are just adamant that you must be a part of this, that could be handled by conference calls so that we could begin to put some things together.

DR. CHARACHE: I would be happy to volunteer. I would like to see someone with a background in laboratory sciences.

DR. McCABE: Okay. Fine. That is obvious with your work on the CLIAC. And then I will sort of serve as an ex officio but not let my schedule interfere with the activities of the subcommittee.

DR. TUCKSON: And we have the option of sending them some thoughts to –

(Simultaneous discussion.)

DR. McCABE: We will keep you in the loop. Sarah is very good. Other people will be in the loop and if someone feels that they need to be a part of any of these discussions you can certainly join in.

DR. PENCHASZADEH: So what will be the charter for the group?

DR. McCABE: The charter for the group would be to begin to address these questions, whether we couch them in terms of the four questions and the variation on those four or not, but begin to develop a framework to bring back to this larger committee in early

September so that we could have a discussion and really begin to hammer it out. So, in essence, it is an outline. I would propose that we have a fairly complete outline. The thought being that it is easier to react to something, to generate something in a large committee, and I would charge the subcommittee with having something for us to react. So try to have it to us before September 1-2, hopefully before the night before we arrive, but recognizing we may have to digest it here because it is a short time frame. So an outline -- I think ultimately if we do it in terms of the four questions that Francis has proposed, we are going to have to convert it back to the three questions here because that is what we have been asked to do but if it is more comfortable to do it in the four questions that is fine.

DR. TUCKSON: Well, let me just doubly make sure, Dr. Raub --

DR. McCABE: And, again, I am proposing something --

DR. TUCKSON: Right.

DR. McCABE: -- and feel free to come up with alternatives.

DR. TUCKSON: I just wanted to make sure I understand the certainty with which your good provocative questions have been delivered to us. I mean, do we need to do this reverse transcriptase or are –

(Laughter.)

DR. TUCKSON: -- we allowed to -- if we, in the body of our discussion and deliberation come up with a pretty nice -- our own framework, do you have, you know, editorial rigidity on this?

DR. RAUB: Oh, no, not at all. In fact, I think the chances are good we will be able to figure out how to do the transposition given the inherent overlap of the questions.

DR. TUCKSON: The second thing would be is that I was -- I found that I was impressed by not only the four questions but the addendum about the policy implications and it would be, I think, just fun if we might get a little e-mail from the proposer of that to flesh some of that in terms of what they were thinking because I think it resonated around this side of the table anyway as being a useful thing. So if we could sort of add that, whatever that implication was, so the committee would have that, it might be helpful.

(Simultaneous discussion.)

DR. TUCKSON: Somebody said about policy implications.

MS. BEARDSLEY: That was Barbara.

DR. TUCKSON: Barbara, okay. Yes.

MS. BEARDSLEY: All right. So we will --

MS. DAVIDSON: I just wanted to -- Joann, on your comment, I have been thinking

about it because I think it is very important for us always to keep in front of us the fact that we are here for families to be sure that quality tests are the end product. I am just wondering whether -- these four questions certainly make sense, I think, in terms of the way we should progress but that there might be some kind of statement up on top in terms of the purpose of this that would clarify that the real objective is always -- is, of course, for quality testing, to improve quality health care.

DR. McCABE: I had seen the draft of this and I added some things. It was already -- it was not -- at that point we did not have the license to alter the verbiage but I added after the first sentence, which I have to look back and see if it is still the first sentence -- yes. That -- well, it actually was something that is not in here about notice and inviting public comment but said the goal was to provide accurate and meaningful information to individuals who are tested. I mean, that is ultimately what we are trying to do with this and I think that captures what Joann was saying. And it also talked about a -- that -- "looking at regulatory framework appropriately tailored to current emerging needs and technologies to protect and to benefit those undergoing testing" so we could include some sort of language that in our preamble that gets it back to why -- why we are concerned about analytic validity. It is not that we want to get good grades on the test. It is that we want to assure that the patients -- the individuals -- are getting a quality product in terms of the test . . . but we can do that in our preamble I would think.

DR. COLLINS: We should be so lucky as to be writing a preamble. We have got a lot of stuff to fit into the middle.

DR. McCABE: Well, but I think it is an important point.

DR. COLLINS: It is an important --

(Simultaneous discussion.)

DR. McCABE: The laboratory is an end in of itself.

DR. LEWIS: I think that is the point I was trying to get at when I talked about who our public was. I want to make sure that the public becomes broader than just health care.

MS. BEARDSLEY: Go ahead.

DR. KOENIG: I was going to ask you if this was the appropriate time to talk about the issue of how to incorporate -- first define, and then incorporate public comments as part of this effort or -- I mean, in terms of this first specific charge with the December 1st deadline or, you know, over the course of our work. Is that going to be the next --

MS. BEARDSLEY: Maybe one thing we could do in the hope of speeding the process along is that in addition to providing a statement of the issues, we can at least come up with a list of options for generating input from the public at the same time so that maybe we can do both things in September.

MR. HILLBACK: Maybe some of the questions -- because I think the way you phrase questions to the public is very crucial –

MS. BEARDSLEY: Yes.

MR. HILLBACK: -- if we really want to get the broader public involved, and as we look at trying to write this outline that the boss has asked us for if we could also try to define some of the questions to be asked and circulate that around through email or whatever.

MS. BEARDSLEY: Yes. Are we reasonably clear at this point about where we are going?

DR. KOENIG: I am clear about the subcommittee. I am still not clear, though, about the public comment issue because I guess by that are you meaning -- and maybe Sarah could help us address this -- are you meaning formal sessions where they are advertised and people who have the interest come and give public comment or are we truly interested in going -- in perhaps going further out and perhaps even doing something like a little empirical research of deciding who we really want to hear from and perhaps even commissioning some focus groups. I do not know what the budgetary issues are about that. Or, you know, just being more -- a bit more creative. I mean, obviously you want to have interest groups, disease specific interest group representation, professional group comments, et cetera. But I am real -- it just strikes me I am very -- I am sort of interested in what really are people's interests in the regulation of genetic tests. You know, people who do not already have a stake in this, especially when you start talking about predisposition testing.

MS. BEARDSLEY: Sarah, did you have particular things in mind?

MS. CARR: Well, the classic way, of course, is through the Federal Register, but I think if the committee feels strongly that we should look to other mechanisms like focused groups, which are a complicated thing to do, I think because you need to provide a lot of background information to the group and so forth, but if you feel strongly that we should consider that, we will consider that. You know, we will try to see if our budget could accommodate that.

DR. McCABE: Is there any experience with electronic accumulation of these sorts of data, some bulletin board posting? Is there any mechanism within the Federal Government on any of your web sites for gathering that kind of data?

DR. FEIGAL: FDA when they open up a guidance or a regulation or something for comment have dockets which can be submitted to either in paper or electronically but I do not think we reach the different people. I think the same people write to us, just write to us electronically. I think that one mechanism that has been fairly successful with advisory committees is to post the meeting, but then to notify selected groups that have taken interest in the past of the opportunity of the meeting and even doing selected invitations but at least letting -- actually inviting has budgetary implications but at least letting people know that there will be a meeting and an opportunity to discuss, and then I think you just need to work through some of the issues of who the constituencies are. But there is always -- there is always going to be a great mass in the middle that is not represented and hard to reach.

MS. BEARDSLEY: Does anyone know whether you are likely to capture different people by holding, for example, a public hearing outside of Washington, somewhere else?

DR. FEIGAL: FDA was mandated by law to have stakeholder meetings and regional meetings, which we have been doing for about a year-and-a-half, and we have done them across cities, and we again almost exclusively do not draw in the public. We tend to get industry and then groups that have interacted with us in the past. It gives us more of them if they do not have to travel but that has been our experience. It may be different with other groups.

DR. McCABE: I would think, though, getting back to the point that was made that there are a number of individuals in the population who have concerns about this, that if we go -- if we go outside of Washington that we will open it up and broaden the base of representation. We may have some of the same people who would come to the meeting in Bethesda, but we may get some input from some others. I would encourage us not to have all of the meetings on the NIH campus, but again that is open to discussion. It will make it hard. A lot of the liaison people, not all, but a lot are based here and so that will make it harder on them.

DR. LEWIS: I am also wondering in terms of not just, you know, formal testimony by the public but that each of us, you know, is a member of a community and how much information -- you know, just the average people we can get by just connecting with individuals rather -- I mean, and I do not know how legitimate that is in terms of rather than the formal testimony structure, just talking to people and hearing their stories, and getting their concerns in a less formal way and then bringing that information back because we are pretty geographically diverse and we have the ability to reach different populations too outside of the public, I mean, is that something that is reasonable to do?

MS. CARR: It could be valuable, yes.

MS. BEARDSLEY: Are there other thoughts on how we ought to make -- sorry, I could not see down there.

DR. LANIER: Yes. I think we ought to give a little thought about the timing of asking for responses to -- just as you mentioned -- having a sort of straw paper or something that could be shot at is useful to this group. I think it is useful for the public as well. What we -- our experience has been that if we -- when we were doing guidelines, we actually published some of the draft recommendations. We got a lot of responses back quickly from people that were very focused and clearly related to what we wanted rather than sort of scattered comments. So that would be -- another alternative would be to actually put something in the Federal Register that indicated the direction we were thinking about and got public reaction from that.

MS. BEARDSLEY: Other thoughts about this?

DR. HOLTZMAN: Yes.

DR. McCABE: Could you come to a mike, please, so we can capture your words?

DR. HOLTZMAN First of all, let me say, to go back to Francis' four questions, I think they are right on target and will capture a lot of the issues. I hope I did not give the impression this morning that the Task Force on Genetic Testing did not reach a consensus on

many issues. In fact, we reached consensus on an overwhelming number of issues, including many that are embodied in those four questions. The one area that we did not reach consensus on, Elliott referred to this, was the specific regulatory stance for approving new genetic tests marketed as laboratory services before they were made available to the public. The Task Force had no difficulty with FDA's regulation of kits. So there is a very specific area where we did not reach agreement.

What I am worried about is perhaps the third saying that I might have mentioned this morning, and that is that this -- your Secretary's committee does not waste time reinventing the wheel. And I think there are many things in the task force report that you all had that deserved careful reading, particularly in chapters one and chapter two where the answers to many of these questions can be found. So I would urge you all to read that.

For instance, in terms of Francis' first question, are there genetic tests that require greater scrutiny? The Task Force debated this for quite some time as the members here know and on page 33 of the Fask Force report we actually came out with eight possible points for how to decide which tests need scrutiny or how to prioritize tests for answering those questions. In regard to the second question, what kind of data are needed before tests go into practice, again there was enormous -- there was consensus, I guess you cannot have enormous consensus. There was consensus embodied in chapter two on the data that need to be collected in terms of clinical validity and clinical utility.

There was also -- there were several -- the issue of who collects the data, Francis' third question. Well, it was not up for debate. I mean, again it is a combination of public and private, CDC, Dr. Khoury has got a new unit that is very interested in this, and I think here it is a matter of categorizing and being complete. But again following what we have got in the Task Force is sort of at least a skeletal outline of where the answers lie.

And then, finally, the fourth question, who is going to review it? Well, that gets us -- a small part of that question gets us to the dispute about FDA. But again the Task Fforce agreed that there needed to be both internal review, namely that when an organization collected data on clinical validity and utility that itself, within the organization, should review that data, possibly or preferably by a group or subgroup within the organization that was not the same as was collecting the data. And that in addition to that there had to be external review. There had to be review by an organization outside of that which was performing or developing the test. Where we broke down, where we did not reach complete consensus, was on the matter of the role of FDA for tests marketed as services.

So again you have got a great foundation there and obviously I have got a vested interest, and I do not want to see it wasted and squandered, and I do not want to see you waste and squander your time because time is precious, and I hope you will take off where the task force left off. Let me say one word about the analyte specific reagents because even there a majority of the task force did submit its comments to FDA and, in fact, FDA's own panel that reviewed the ASR, analyte specific reagent proposals, did also recommend that genetic tests for predictive purposes, looking at one level of prioritization, not be ever exempted under the analyte specific reagent panel but considered either class 2 or class 3 devices and, therefore, for class 3 have to go through premarket approval.

So the point is you have got a tremendous foundation there. Obviously I am proud and committed to it. There are relatively few issues but they are important and there are

critical regulatory issues where you really should begin if you use the foundation that we laid for you, and that was our intention by recommending this committee.

DR. McCABE: I think we are going to need to draw this to a close pretty quickly. Do you have guidance?

MS. BEARDSLEY: I think we have guidance. Let me try to restate briefly what I think we are going to do and that is that we are trying to take the questions that we have been given -- we are going to recast them somewhat on the basic framework that Dr. Collins gave us. We are going to try and take advantage of what has already been done, and we are going to try to make sure that we try to capture as much as we can in a short document some of the policy gloss and we are also going to write a little bit of background to make sure we know why we are asking these questions. We are going to try to get it to -- oh, and that is job one. And our second job will be to come up with a list of possible ways to solicit public input that the committee can debate at our next meeting, and we will do our best to get it out the door to everyone enough in advance that everybody will have a chance to think about it and react to it before the next meeting in September. Is that basically right?

DR. McCABE: Muin, quickly?

DR. KHOURY: Yes, a very quick comment because Tony mentioned it, and I know the committee today has been bombarded with a lot of input and even myself, I have heard this stuff at least three or four times before, and it is really mind boggling to hear all the details. I think the task force recommendations were quite thoughtful and very extensive. And one of them about the data collection, I just want to follow-up with you and give you this additional information, which I will be happy to share with the subcommittee that you form that there is an interagency subgroup of the group that Dr. Raub has been heading that has been looking specifically on the data issues in terms of data formats, collection, dissemination. We have been doing quite a lot of work and this committee is sort of an HHS-wide committee, and I would be happy to share the progress, the challenges with you guys, with the subcommittee, and we can discuss them next time.

DR. McCABE: Okay. Well, good. We have got that. At least we have a plan for dealing with that. So good.

DISCUSSION AND PRIORITIZATION OF OTHER ISSUES AND DEVELOPMENT OF OVERALL WORK PLAN

DR. McCABE: Now let's move on to the last order of business, which is a more general discussion. I think that having this as an exercise -- I know it is more than an exercise to Dr. Raub and the Secretary, but for us it will definitely be an exercise in coming together. I think that it will help us focus on the next task, which will be the rest of what we do and we will have some framework on which to hang the additional issues.

Our goal is now to really identify five to ten issues that we think warrant attention over the next one to two years and try to outline fact finding and analytical approaches that will need to address the issues. Some criteria that we might think about in terms of ordering this, what are issues that are unique genetic testing -- are there issue that are unique to genetic testing -- and what are pressing in regard to their need for resolution. So what are the high impact areas? What issues are not being addressed elsewhere by another agency,

another committee, another professional organization? In other words, where are the gaps? And can we identify those gaps and begin to fill them in? Or even if they are being addressed, where we do not think they are being addressed adequately or vigorously enough. And then issues that are in need of enhanced public awareness and understanding. We have talked a lot about education today, so that is definitely something that we need to consider.

I would have you look at tab 4, which was a listing that was generated by staff, but then there was input from all of us when we reviewed that so that might help us but feel free to come up with things that are not under tab 4. Part of the reason of going around the room this morning was getting to know what our agendas were but also so that would really be somewhat of a preface to this activity at the end of the day.

So who would like to start off in terms of what you think are the burning issues? What are the things you heard more than once as we went around the table today? There were certainly quite a few. Okay. I have -- there is a listing. We already have a bit of a transcript so I can tell you that education was talked about four individuals and professional education. There was information tools, informatic tools were discussed by a couple, the quality of the tests. Rare diseases came up. Quality and access, the role of the consumer, diversity as an issue, informed consent, quality of testing, reimbursement, evidence-base for decision making, data collection and developing models. So that there were a couple of things that came up over and over so someone -- Elliott?

MR. HILLBACK: I think we can spend a lot of time on the topic we talked about for the last hour and there may be several different approaches that could work and I do not think that we can come up with the best one of those and, if we do, we can still fail, and genetics can fail in this country, and that is if we do not address the issue of education and how this technology gets accepted by practitioners and by patients. I go back to my demystifying genetics point that I have gotten into the -- that phrase many, many times -- because I know there are a lot of efforts that Kathy Hudson, who is here in the audience, and some other groups are working on. Education, I know the AMA, Reed, you guys have tried a lot. There is a lot of things going on. I do not think we are making much headway and I think the problem is only going to get worse before it gets better. The amount of data we will have five years from now for people to try to understand is exponentially greater than what we have now. So I do not know. I do not have suggestions at this point. I am frustrated by what I see as lack of real impact. And it would seem to me that somewhere as we come up with a few major recommendations to make, if this is not one of them somehow that really then marshals federal resources to help get something done, even more than what is being done now, I think we are going to have a real problem so I would like to make sure that one is put on the table.

DR. McCABE: Yes. I think I was one of the people that raised education, but the opposite side of that is that I do not think we are doing a very good job. So I think maybe it would be worthwhile having a bit of a discussion about how we could improve education. Rather than just saying we need more education, we will talk more to each other about it, and that will improve the situation. I do not know. Francis, ELSI, one of the issues that ELSI has taken up is education, and I do not know if there are any good models there that have come out of any of the projects.

DR. COLLINS: Yes. There is a whole lot of effort that has gone on both funded by

DOE and NIH. Not nearly enough, though, I would say. It has been focused on NIH's side primarily on health professional education, DOE more on the public. Part of the problem with the public is deciding, as Joe McInerney was saying earlier, what is the message. What is the thing you are trying to say to the public about genetics, and I do not think we quite know yet how to formulate that, which is one of the reasons, I guess, that there has been maybe more of a coalescence around the idea of preparing health professionals to be the people who explain genetics to patients in the not too distant future.

Again, I think the National Coalition for Health Professional Education in Genetics, which is still a fledgling organization, may be a good mechanism to achieve this if it can accomplish its current effort of acquiring substantial funding from Robert Wood Johnson, which is something that is under study and, therefore, can build up its staff and develop a really vigorous effort at both undergraduate and graduate education, as well as practitioner education and developing a centralized clearing house for validated and edited information that practitioners can find when they are in a hurry. This is a very tough problem and certainly any input is welcome. I am not sure that we can get much further than saying this is really important without digging into the details of what the various groups that are already working on this have done.

DR. McCABE: Wylie and then Pat.

DR. BURKE: I want to concur with the high priority of this topic and just mention from some work of my own I am aware that we probably need to do something very similar to what we are talking about in seeking public opinion. That is we really need to go out to the health care providers and particularly the primary care providers and ask them because when you look at a lot of what has already gone on in the way of genetics education, it is people with genetics expertise getting together and deciding amongst themselves what primary care providers need to know. But actually the landscape looks quite different from the perspective of primary care and so I think we need to -- I think this committee might help to spark a very productive dialogue where we try and frame what seemed to us the most cogent, urgent genetic problems but then as opposed to telling others what they should know about these urgent problems, engage in a dialogue that helps us to understand how cogent they look from the other side.

DR. McCABE: Pat, and then Muin.

DR. CHARACHE: One of the initiatives that has been introduced by CDC is a program being developed in association with Dartmouth, which is described as a multimedia program aimed at educating primary care providers about commonly encountered issues related to genetic testing. I did not have a chance to show some of these activities in a longer way but I can learn more about it and provide more information next time, and perhaps coordinate it. I think coordination is one of the things I would like to emphasize. There's a lot going on. I would like to be sure that just as Tony has pointed out, there was a great deal of information that is already available through the Genetics -- NIH Genetics Task Force and similarly there is a lot of work that has been done that was just covered the tip of the iceberg by the Genetics Working Group associated with CLIAC. I think we should be sure that we meet Dr. Satcher's recommendation that we not reinvent the wheel.

DR. McCABE: Muin, then Judy, then Victor, and then we are going to move on to

another topic.

DR. KHOURY: I would like to concur with what was said earlier, and I think this group is likely to both learn and contribute tremendously to a lot of interagency coordination because I know all the federal agencies around the table talk about education. They talk about training. And I am glad Pat mentioned this particular CD-ROM project that the Division of Laboratory Systems has. But, also, CDC in a global sense is part of a strategic planning effort that went into the formation of our office identified communication and training as very important for this issue because everything we do here will require a major training of a lot of work forces. For us, we concentrated a lot on the public health work force for now, both from the official side and the researcher side of things. We are getting ready to finalize a communications plan in coordination with -- we will be collaborating with other agencies. So, I think as you move forward with this stuff that you might hear from all of us what we are doing and provide input into the ultimate coordination of these efforts.

DR. McCABE: Judy?

DR. LEWIS: I would just like to support what Wylie said in terms of getting out to where the rubber meets the road and I think a lot of times when knowledge is new and it is highly technical it tends to stay at the specialist level and I think if we really want to impact the public health we have to look at doing the education to get things to the generalists level, to the health care providers that, you know, interface with the public and spend a lot of time with the public.

And that we look at a bunch of different levels so that there are certain levels of information that all providers should know, not just highly specialized people but that we then look at -- when you get to certain levels of having some kind of a referral network so that we've got generalists and we've got specialists, and that we do not waste the time of highly trained -- not waste the time -- but we do not dilute resources and use specialized resources to do some of the primary prevention and some of the public education but that we look at groups at primary health care providers like nurses, like science teachers, and that we get people who are -- can have a certain level of knowledge, and that we focus our education in a multifaceted way, and I think that would help with the public health issues.

DR. McCABE: Victor?

DR. PENCHASZADEH: I agree with all that was said regarding education and taking the issue of giving attention to what the providers need, the generalists or the primary care physicians, I would also think that we should also have to encourage education of the public. I think that -- and by education of the public, I also mean a two-way thing. So we should try to learn what the public really wants or what the public really needs. Particularly in terms of things that have to do with personal values and cultural values, and this happens whenever you deal with genetics and it will happen more and more with predictive predisposition tests. So I would link that with the issue of attention to diversity. I do not know -- are we still discussing the --

DR. McCABE: Well, that is what we are going to do next. The next thing -- I know that a lot of people have their hands raised. We will be coming back to this. This is not the only chance for this. What I want to do is I do not want to get hung up on education because we need to come up with several other topics. So you want to move on --

DR. PENCHASZADEH: I wanted to move on to --

DR. McCABE: -- and that will then shut down the people who have their hands raised. I apologize but we have to move on.

DR. PENCHASZADEH: Just two quick things. One, I think we should always stress the need to look at genetic testing as part of a larger genetics service and be careful not to focus specifically and exclusively on the tests but all that goes with -- all the counseling, pre, during, post, and all the intervention. So, you know, to see this as a comprehensive genetic service.

The other issue I think is of primary importance is that of access. I mean, we can have the best regulations and the best tests available but if people do not have access because of insurance issues or whatever, you know, organization of medical care we have in this country, that may pose a problem. So I think that those issues will have to be looked at. Not that genetics from that point of view is different from health care in general but I think that we have a stake to look at how -- what is the accessibility and what are the barriers to genetic service in general.

DR. McCABE: Is there anything that the two people were waving vigorously at me here -- either very briefly on education or can we move it beyond education?

MR. HILLBACK: Very brief. I would like to make a suggestion of how we would approach this because there are lots of people, many of them in this room, that have spent a lot of time working on this. I would rather think that we are -- that we, in theory, have clout. We are reporting through Dr. Satcher to the Secretary. I think the biggest service we could provide is to somehow under our auspices serve -- convene a summit of the various organizations that are working on education in this area. CDC has programs, AMA has programs. I know that NIH has, the Genome Center, has programs. And to try to bring together everybody and say, look, we all have the same objective, do we have enough resources, what is the overall view of this, and can we bring everybody together, and then, in effect, make a recommendation going forward of here is where we are short, here is where this does not fit together, and serve more as a coordinator -- I hate to use that word -- more as a catalyst than to go start again out at the bottom. I do not disagree with the need to understand what physicians need but I suspect those surveys have been done. We ought to know if they have been done or not. I would rather serve as the catalyst than start all over but there are a lot of people here who have spent a lot of time on this topic.

DR. McCABE: Mary?

MS. DAVIDSON: Yes. I just -- I wanted to just pick up and remind all of us that, of course, it is not as if the public is out there waiting to be educated about genetics. I mean, attitudes, feelings, you know, the willingness to participate in research, to use genetic services, I mean those attitudes are being formed now I think on a very ad hoc basis. Even with all of the -- the certainly considerable efforts that various ones of us are putting forth. But I think -- you know, I just -- I was very excited this morning to hear so many people talk about public education. In the three years that I have been at the Alliance, you know, I have felt sometimes like I was the only person in the crowd waving my hand. And I think the time has definitely come. In particular, I guess I am thinking about the whole issue of

integration of genetics into the health care system and managed care, and I felt like that is really an issue that was not very clearly delineated in our list of issues.

In our experience -- we have a managed care program at the Alliance -- and our experience is that one of the big problems is the lack of understanding by the managed care administrators -- and the lack of any kind of genetics training within the managed care system, considering how many people now receive health care. So, I would like to have us think about education but not in a broad sense but in a very specific, strategic sense, because I think that it -- particularly as it relates to managed care and health care and health insurance systems, it will be a determinant as to whether -- and the success that we have in translating genetics into real every day care.

DR. McCABE: Michele and then Judy.

DR. LLOYD-PURYEAR: I agree that we need to do a lot more with provider education. However, we actually are doing a great deal and I think rather than -- and there already is a national coalition for health professional education in genetics, and I think that we should keep reminding ourselves of that and recognize that all of those efforts really should be coordinated through that. You know, there is a great deal of effort that went into creating that coalition and I think it is important to keep it viable. But I agree that we could -- I mean, there could be a report on what is being done and what maybe needs to still be done.

I agree with Mary that we need to do a lot more with public education and we keep hearing about that but I think what Mary offers actually is targeted public education around issues because I think that goes a long way to demystifying it. It puts genetics in a context, a very practical context.

And as far as access to health care, I think that is a problem in general with American health care but I think that genetics will either be a great equalizer or you will see real disparities there depending on what kind of health care financing we have when someone tells me that the tests were -- I cannot remember what it was, it cost $700. I mean, that is clearly outside of everybody's -- mostly everybody's pocket. And clearly health care financing -- currently the way it is structured -- will not pay for that so I think that is a big issue to tackle, of how we are going to -- how this country is going to pay for it. Who are these tests going to go to.

DR. McCABE: Judy, and then Francis.

DR. LEWIS: Along with the issue of access and the issue of diversity, I want to make sure that when we address those that we also look at the problems and avoid problems and deal with issues of stigmatization because I think that can become a piece of it. If certain aspects of the population are either -- get access or do not get access and as conditions are found stigmatization can be a problem.

DR. McCABE: Francis.

DR. COLLINS: Yes. I would be concerned that we as a committee try to pick topics that were particularly well suited to try to address. This committee as I remember the charter has two years to sort of do something and then be evaluated of whether it ought to go

away. It would be nice to demonstrate in that two year period that some specific projects could be pushed forward.

In that regard, I think we should also remember that while we have a lot of clout, we are reporting to the Secretary and the things that we could probably most effectively do are things where the Secretary has the power to change things, which is through the various agencies that are a part of DHHS. So that is a bit of a preamble to say I think and you mentioned it already, Ed, that a really critical topic for this committee to wrestle with pretty soon is the whole topic of rare disorders. Now we heard today what the current CLIA regulations are and they clearly are such that most laboratories that are doing testing for rare disorders are breaking the law and there is a terribly difficult circumstance here that needs to be wrestled with.

Do we want to have an adherence to the current legislation or do we want to have -- and have rare testing go away? Or do we want to come up with some other plan here that allows laboratories to do small volume tests for rare disorders, to do so without having to pretend somehow that it is not really a test that has an impact on clinical management?

I think that is a really critical issue and I think it is one that is perfect for this committee. It was mentioned by the task force as being extremely important and I do not think we will deal with it in our next five months here as we are looking at the high stringency test because I do not think the rare disorders are what we are going to be talking about there. So I personally would put that one very high on the list of the next thing to get to.

DR. McCABE: Yes?

DR. FEIGAL: I am not sure I would characterize the laboratories as breaking the law. I think that the way the law –

DR. COLLINS: I was being provocative.

DR. FEIGAL: I think it is important because it bears on the decisions this group needs to make and the things that we as an agency can change, which is that the Center for Devices and to an extent also the CLIA program was asked to take a risk stratified approach. Both of us have things we exempt and have things that we have discretion about what we can do. And that was intentional and so -- but it is again something that we can adjust, we can change, we can look at how we do that, and I think getting back to your comment about looking at things that are useful to look at, that is something that is useful to look at. But it is one of those areas of trade-offs as well.

DR. McCABE: David Lanier?

DR. LANIER: Yes. I just want to pick up on a comment Francis made that in two years we are going to have to say to the Secretary what was the impact of the recommendations that we made. I think some sense of discussion or at least a discussion of us beginning to think even at the very start about how we will evaluate this, what are the outcomes that we can focus on, does it make any difference in recommendations that we have to make?

DR. McCABE: Okay. So some sort of self-evaluation is always very important. Let me give you the topics I have from the discussion and see if people have heard the same topics.

Oversight. Obviously we are going to spend the next five months on that. It is going to be a big task and we have to count it as one of the things we are going to do.

Education, including counseling and comprehensive education of both professionals and the public. And there, though, we might want to go back and see what has already been done so that that would be where we probably need to think about how we are going to review that and put that all together.

Access to testing. It is a problem throughout American medicine but there are some issues specific to genetics and access, especially because many of these are in that quasi-research service interface where no one wants to pay for them and yet somebody is charging for them so we need to think about that.

Diversity. We have heard some powerful discussions today about diversity and the issues of validity of testing in nonmajority populations and how the testing is influenced and access to testing can be limited because it is useless. Or if it is not limited, it is still useless so we need to think about that.

Stigmatization. A big concern and that is certainly in the materials that were given to us and everybody, including the public from all the polls that have been done, are very concerned about stigmatization.

Rare disorders came up several times. I think it is a serious concern and the graph that pointed out that 50 percent -- when you said halve those bars by 50 percent, but that is a lot of little labs that are in that 50 percent that you would not halve those bars for. I think we have some experience. Being a biochemical geneticist, we went through this with biochemical genetics and it gradually became more mainstream. Maybe we should look at some of the experience in some of the other areas as well.

And then I think it was very important, the issue about that we have to keep track of our own activities and we have to be grading ourselves along the way. Remember we want to look for things that are going to be high impact. As Francis has said, we want to look at where the impact can make a difference and not just make statements that are going to sound good but are not really going to affect the service delivery in this area. So I think that we also need to spend some time looking at how we are going to develop that self-evaluation and not just say, oh, we will take a look at ourselves in six months but we probably need to look at it a little more formally and make sure that we are satisfied with how we are approaching these issues. So were there other points that I did not hear? Reed?

DR. TUCKSON: Well, I just wanted to re-raise -- did we -- is it -- I missed a little bit of the discussion. Is it subsumed in some of these the introduction of new clinical -- these tests into clinical practice and that is one of the key things I think that Dr. Satcher mentions, and the question of standards versus guidelines versus regulations and how that works.

Secondly, I wonder if -- have the issues of privacy and confidentiality been sufficiently dealt with in other bodies so as to make it unnecessary for us to revisit any of those in light of the topics you now have on the table?

Finally, I was particularly impressed by your presentation on the new CLIA initiatives and I kept writing down the economics of those new requirements and who is going to bear the price for all those new things. Is that going to be borne -- I do not know whether there is any ability for the Secretary to speak to that question but clearly there is a larger bureaucratic infrastructure that goes along with those wonderful things, or it would seem. Somebody is collecting more data, keeping data, doing things. So anyway, bottom line, I did not know whether we would look at any of the financial issues of the enhanced oversight and, you know, these sort of things and what that means to access.

DR. McCABE: That is very important and I think we could put privacy and confidentiality together with stigmatization. I think those would fit.

DR. TUCKSON: I like that.

DR. McCABE: But I think the economic impact of what we recommend we have to think about.

MR. HILLBACK: I thought that getting things into practice was part of the subcommittee that was -- the oversight subcommittee that is really a part of that whole process. Isn't it?

DR. McCABE: Well, I think it is actually in a couple of different areas. I think it may be in the rare disorders. I think as part of our culture it is to rapidly reduce to practice. And so it comes into a lot of different ways but we want to be sure that we are constantly thinking about that in the various venues that we will be addressing. Yes?

MS. BOLDT: I just want to add in terms of the education that we increase our efforts to educate more genetics professionals. I know I talked about that earlier but I think that should be something we look at, too. More genetic counselors, more geneticists. I think that would help us with our diversity issue and the access to care and everything else.

DR. McCABE: Barbara?

DR. KOENIG: An aspect of regulation I am particularly interested in is the issue of direct marketing to consumers and it seems to me that that is an area where we could have an immediate impact in terms of -- as we are just at the point where many more tests are going to -- that have a broad impact across the population are going to be on the market that that might be something we would want to address.

DR. TUCKSON: I would like to triple underscore that one as being absolutely key and that is something that the Secretary absolutely has jurisdiction over and it is a major league issue.

DR. McCABE: I would argue that maybe that should be considered with the oversight because certainly one of the issues that can be brought up in terms of the type of tests -- it can be perhaps woven in there and we might want to address this more directly but

I -- and I am trying to remember, was the Task Force -- I think it is in the task force book also.

DR. HOLTZMAN: Chapter 3.

DR. McCABE: So perhaps -- again it is in one of the chapters that the subcommittee is going to address but I think that is very important and again it is something -- it is an area where we might be able to have an impact.

DR. KOENIG: So you think it should be part of our December 1st report?

DR. McCABE: Well, let's see if we can -- let's -- why doesn't the subcommittee consider that?

DR. KOENIG: Okay.

DR. McCABE: Let's see if it fits.

DR. PENCHASZADEH: In the group of -- having confidentiality and stigmatization, I think we should mention specifically insurance discrimination because, you know, in my experience it is one of the major barriers for people to have genetic testing because either they have to pay out of pocket, they do not want the insurance company to learn about it, and here I think also there is some role for HHS to take some action.

DR. COLLINS: Actually the department has a position on this and it would be very useful, I think, for this committee to endorse that and in the political arena, there are pretty good pieces of legislation that are floating around Congress. Some of them better than others but they have not sort of made it across the finish line. One hopes that that will happen this year but who knows. So certainly I agree with you this is a topic that this committee could usefully weigh in although obviously we cannot pass laws and what really needs to be done is to pass a law.

DR. McCABE: So, Sarah, perhaps you could get us the Department's position on that.

MS. CARR: There is a briefing -- issue brief in this volume that kind of gives the background on that but we can get you more on it.

DR. McCABE: So let me run through the list again and see --

MS. DAVIDSON: I just wanted to weigh in and I agree with Francis because there is a lot of talk and no action on the issue of privacy right now and I think it could have great power if this group could endorse the Secretary's position.

DR. McCABE: Okay. Let me go through what I have as a list again and see if we have left out any of the real big ones. It is not an immutable list. We can certainly add and subtract, and genetics is a dynamic field so we should feel free to do that.

First of all, I think Sarah and I need to begin to think about how we are going to keep

a tally of what we are going to do and present that to the committee on a regular basis so you can be sure that -- and that we can evaluate ourselves and be sure we are moving in the right direction.

In terms of the topics: oversight; education; access to testing; diversity; stigmatization along with insurance discrimination, privacy, confidentiality and all of those other things that come under that; the rare disorders issue; the introduction into clinical practice and how that is accomplished. I think there may be some of that that is done in the oversight but it is a bigger topic. The economics of -- and first when Reed said it, I was thinking of the economics of testing. He was talking about the economics of oversight. But we need to think about the economic dimension in just about everything we do. And then direct marketing and whether that can be woven into the oversight or not or only a piece of it. We need to look at that but we will leave that to the subcommittee to determine whether that is something we can do right up front or if we do it after the first five months. Other big things that we have missed?

Okay. If not, then I think that we have certainly accomplished quite a bit on the first day. I want to thank all of the presenters, the commentators, and certainly the committee members, and our liaison members. Is there any housekeeping stuff, Sarah?

MS. CARR: No, I do not think so. We will be posting -- because I think we have to reassess the meeting schedule so we will post -- when we get a final date on our web site. I wanted to say Francis' slides are going to be on your web site soon.

DR. COLLINS: That is what I hear.

MS. CARR: And we will make a link on our's to your's so if they do not get it through you, they will get it through our's.

MS. BEARDSLEY: Sarah?

MS. CARR: Oh. There is a car going back to the hotel at 5:00.

Ms. BEARDSLEY: Sarah, is there a transcript or minutes of this meeting?

MS. CARR: Yes.

MS. BEARDSLEY: That will be available?

MS. CARR: Yes.

MS. BEARDSLEY: Because I think it would be helpful at least to the subgroup.

MS. CARR: Right.

MS. BEARDSLEY: How do we get that?

MS. CARR: I will send it. I will send you a copy.

MR. HILLBACK: Do we have all the e-mail addresses for everybody?

MS. CARR: I could do that. You mean like a list?

MR. HILLBACK: Yes.

MS. CARR: Yes.

MR. HILLBACK: So we can start reacting and getting in touch with each other.

MS. CARR: You could always do "reply all" to the things I send you but I will do it the other way, too.

MR. HILLBACK: That would be great.

MS. CARR: Okay.

DR. LEWIS: And so you said that we are going -- the meeting date is September 1st and 2nd.

DR. McCABE: It may not work and I think we need to also -- we are probably going to have to do it by e-mail.

MS. CARR: In terms of finalizing the date.

MR. HILLBACK: I guess, I would like to propose if there is any way we can do it to have two full meetings before we have to send a report to --

MS. CARR: Right.

DR. McCABE: No. We have got that message. We are feeling that pressure and we would very much like to do that. It is just trying to figure out how to do that because the summer is busy and then it seems like September and October, all weeks are busy for people as well. But Sarah will be working on that to see what we can do.

Okay. Well, thank you very much. See you at the next meeting whenever.

(Whereupon, at 4:46 p.m., the proceedings were adjourned.)

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