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

Inaugural Meeting

Wednesday, June 11, 2003

Vista Ballroom A
Wyndham Washington Hotel
1400 M Street, NW
Washington, DC

IN ATTENDANCE:

Chair

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IN ATTENDANCE:

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (9:05 a.m.)

DR. ZERHOUNI: Well, if we can all be seated, we can start the proceedings. As you've guessed already, I am not Secretary Thompson. I'm Elias Zerhouni. I'm the Director of the National Institutes of Health, and I was asked actually to stand for the Secretary of Health, who really is sorry not to have been able to be here this morning to open the proceedings of this very important committee, the Secretary's Advisory Committee on Genetics, Health and Society.

Actually, I was very pleased when the Secretary asked me to stand in for him to launch the work of this committee. Last year, in the summer, we were reviewing committees and it was very clear to me at the time that the scope of the charter of this committee needed to be enlarged. Due to the progress in genomics and what was happening in the field of genetic research and the development of genetic technologies, we all thought that the Secretary needed a much broader scope of advice, and we're very pleased to have Dr. McCabe serve again as our chair and we're looking forward to your contributions in that regard.

On behalf of the Secretary, I want you to know that he supports genetic research and clearly embraces the plan that NIH has developed, in particular focused on the Human Genome Project and its consequences. As Francis and I talk about the future, we like to say that, in fact, 2003 is an important year because of the completion, full completion on April 14th of the human genome, 50 years after the discovery of the structure of DNA. My advice to him is to change the calendar for science and start with April 14 being Day 1 A.G., after genome, and anything before that was B.G.

Well, in fact, you are an important committee in this new era, and your advice and direction is going to be extremely critical. There isn't one aspect of what you're touching that will not affect both research and health care in this country for years and years to come. So it's important, I think, to understand and to realize that the Secretary, myself, all of us are really supportive of your efforts and look forward to your contributions.

I think, because of the longstanding commitment of the Secretary as a policy-maker and national leader to ensure that our laws and policies keep pace with scientific developments, it was not a surprise to me, in fact, that the Secretary took a personal interest in restructuring and rechartering this committee and expanding its charter once we advised him that it would be a good thing to do at this time. NIH is honored to be able to support the committee, to in fact assist the committee and be the lead agency in support of the activities of this committee. I know that the staff at NIH is really excited about being part of this and supportive of this.

So again, on behalf of NIH, on behalf of Secretary Thompson, I want to express our appreciation to each of you. Clearly, your work is not entirely related to just the Department of Health and Human Services or its agencies. You have to look at the broad scope of implications of the development of policies and issues in this area.

So again, I want to express my special appreciation to you, Dr. McCabe. It's clear that you've been a leader before and you'll be a leader again, and I know, based on all of the work that has been done already, there is a base here to build on and that the committee is going to be able to do so.

I don't want to make a long speech about the varied applications that are going to define the way we perform medicine that are arising from the Human Genome Project, but more importantly it's not just the Human Genome Project that we need to consider. It's all of the diagnostic technologies that are related to the downstream technologies that are emerging from rapid DNA sequencing, from DNA arrays, from proteomics. All of those technologies have an impact, I think, in our era.

There's no doubt that the issue of genetic discrimination is an important issue. As you know, the

President has called for federal legislation to prevent the misuse of genetic information in health insurance and employment. We believe this is a core issue for the country. There's no progress possible unless we can provide assurances to individuals that their genetic information will never be misused against them. This is something that I think is making great progress. In Congress there is actually a bipartisan bill that is walking its way through the arcane process of becoming law, and I think the Genetic Information Non-Discrimination Act of 2003 will be a landmark if it goes through.

So clearly, our position is to be very supportive. Francis and the Genome Institute and I and many people have contributed in informing both the Senate and the House of the importance of this bill. It's been a long process, but I think we're there, and your support here would be very important.

So although we've made a lot of advances in terms of technology, as you know, from the very beginning, with the leadership of Dr. Watson, there was a commitment to spend 3 percent of the budget of the Human Genome Project on what we call ELSI issues. This is, in fact, something that needs to be expanded in its scope and depth, and the apex of that I think is your committee.

There's no doubt in our minds that without your work and the detail of the seven specific areas that your charter outlines -- one, the integration of genetic technologies into health care and public health; two, the clinical, ethical, legal, and societal implications of the new medical applications in the emerging technological approaches to clinical testing; three, the opportunities and gaps in research and data collection efforts -- we'd like you to focus on that.

What is missing in the portfolio of activities that we need to focus on today in this country that might actually influence our research portfolio and our stimulating the field towards directions that you may find are not explored at this point? The use of genetics in bioterrorism; the impact of patent policy and licensing practices on access to genetic technologies; the uses of genetic information in education, employment, insurance, including health, disability, long-term care and life; and the law. Obviously, the emerging scientific, ethical, legal, and social issues that are raised by these new technologies.

The public is really, I think, looking forward to an enlightened and informed debate. We sense that. Many, many constituencies will talk to us about their need for guidance and their need for clear policies, and I think it is the time to do so aggressively.

So we're just very confident that your work is going to be, A, very supported; B, very important; and three, needs to be wide-ranging. I think this is probably the challenge that you have to undertake.

I have the pleasure also to swear you in for this new job that you're undertaking for the country. So I'd like to have all the members stand up and be sworn in. Raise your right hand and repeat after me.

(Committee members sworn in.)

DR. ZERHOUNI: Thank you very much. You are now sworn in. To all of you, again thank you for the service you're about to render to the United States government and to the American people, and we look forward to learning of the outcome of your deliberations. Again, I wish you a thought-provoking and productive meeting.

I'll leave you now in the capable hands of our chair, Dr. McCabe.

DR. McCABE: Dr. Zerhouni, thank you very much for opening this first meeting of the Secretary's Advisory Committee on Genetics, Health, and Society.

The public was made aware of this meeting through notices in the Federal Register, as well as through announcements on the Secretary's Advisory Committee on Genetics, Health, and Society, SACGHS, website and listserv. I want to welcome all of the members of the public who are in attendance, all of

you here in the meeting room, those of you viewing the proceedings from the overflow room in the hotel, as well as those of you who may be watching from offices and homes via the webcast.

Members of the public in attendance who wish to address the committee may do so during the two public comment periods. If you do want to make comments and haven't yet signed up, please do so at the registration desk. We do ask that you register for those comments.

We're going to go through a round robin, go around the table also to our representatives of the various agencies, and introduce ourselves. I would ask everyone to try to keep that to one to two minutes of introduction so that we can have time to fit everyone in. I will begin, and then we'll go around in alphabetical order here, and then alphabetical order by the agencies from the ex officios.

So with that, let me begin by introducing myself. I'm Ed McCabe. I'm Physician-in-Chief for the Mattel Children's Hospital at UCLA. I actually began in genetic testing at the age of 15 when I was given the good fortune of working in a pediatric research laboratory at the University of Maryland School of Medicine. My job was to screen urines from Rosewood State Hospital, an institution for the mentally retarded at the time, looking for PKU and other inborn errors of metabolism. Then at the University of Colorado, when I was a little bit more mature as a fellow, I actually learned how to run a biochemical genetics diagnostic lab and began my career as an independent investigator.

In the late '70s, I was involved in the expansion of the Colorado and Mountain State Screening Program. I've done research on newborn screening. I chaired the American Academy of Pediatrics Committee on Genetics, which was very involved in newborn screening, and then began to do research showing that DNA was in those dried blood spots and moving from technologies that we still use that were developed in the '50s and '60s to molecular genetic technology.

When I moved to Baylor College of Medicine, I began to be involved in broader genetics policy and was chair of an advisory committee to the Texas Genetics Network for organization of private and public genetic services in the State of Texas, and also began to work with Tom Caskey on the Human Genome Initiative, first with the DOE and then the NIH.

I continue to be involved with the American Academy of Pediatrics, co-founding the AAP section on genetics and birth defects. I've been president of the American Board of Medical Genetics, president of the American College of Medical Genetics, have served as a genetics consultant to the Clinical Laboratory Improvement Advisory Committee, and chaired the Secretary's Advisory Committee on Genetic Testing under Secretaries Shalala and Thompson.

We have established the UCLA Center on Society, the Individual, and Genetics to look at the tension between the interests of society and the interests of the individual, and I think that it's interesting that it reflects very much the broadening of the scope of this committee.

I'm really honored to be appointed to the Secretary's Advisory Committee on Genetics, Health, and Society and to have the opportunity to provide institutional memory. I think it's important to use that rather than the term "continuity," because we are a new committee, but hopefully we can learn from some of the things that we experienced and began to develop with the Secretary's Advisory Committee on Genetic Testing.

I'm pleased to have been appointed along with two other colleagues who also served on the SACGT, Cynthia Berry and Reed Tuckson. The SACGT was one of the most exciting and fulfilling experiences in my career. I look forward to working with all of you to assist the Department of Health and Human Services and Secretary Thompson to address the issues in our charter. I anticipate that our service on the SACGHS will be an exhilarating experience for all of us.

Thank you very much for your kind comments.

MS. BERRY: Good morning. I'm Cynthia Berry. I am General Counsel and Managing Director of Wexler and Walker Public Policy Associates. It's a government affairs firm in town. I'm an attorney with a trial background and also health policy background, so I care very much about the intersection of medical science and discovery and public policy, as well as the ethical issues involved with that.

I currently serve as co-chair of the Virginia Birth-Related Neurological Injury Compensation Program. That's a mouthful. It's one of only two such programs in the country, and it's quite a challenge. We have a special program and fund set up to care for children who suffer from birth-related injuries due to oxygen deprivation. Instead of going through the tort system, they receive all of their care, all of their help for the rest of their lives, as well as their family, through our program, and that's been quite a challenge. There are actually issues that we face all the time -- health-related, public policy-related, ethical issues -- in that group, and I'm looking forward to working here on the innumerable challenges that we face in this area.

Another part of my background is that I was Washington counsel for the American Medical Association. I also worked on Capitol Hill for Senator John Kyle when he was on the House side, handling health policy issues for him as well. Prior to that, I practiced law in Nashville, Tennessee for several years, did trial work as well as commercial work. Again, just looking forward to working with everybody on this committee and hearing all of the public comments, because no matter what your background is, we may all think we're experts in a particular area but we all have so much to learn. We're plowing new territory.

I look forward to receiving all of that information and soaking it up like -- is it Sponge Bob Square Pants or whatever?

(Laughter.)

MS. BERRY: Thank you very much.

DR. McCABE: Thank you.

DR. HOOK: Good morning. I'm Chris Hook. Professionally I'm a hematologist and medical ethicist at the Mayo Clinic in Rochester, Minnesota. A good portion of my practice in hematology is in the areas of coagulation and non-malignant hematology, so I deal with genetic diseases and maladies on an almost daily basis in that practice. Some of the other specific ethics activities that I do at Mayo include chairing their ethics council, but also I have served in the past for our IRB in the development of its policy regarding genetics research, and one of the outcomes of that process was to be invited to speak to President Clinton's Bioethics Commission, and then also to an NIH group concerning how our institution had dealt with issues of genetics research.

Presently, we're expanding activities to focus not only in genetics research in general but in psychobehavioral genetics research. I'm working with our chair of psychiatry to spearhead an ELSI support committee for that activity.

On a personal level, I have significant concerns about genetic issues, as all of us do. Next week my wife is going to have bilateral prophylactic mastectomies because of a significant family history of breast cancer. My oldest son is on the autism spectrum, and we're learning more and more about the genetic indications of those sorts of disorders. I carry a bicuspid aortic valve and look forward to becoming a cyborg in the next 10 years with a new prosthesis.

So these issues are personal to each and every one of us, and like Cynthia, I'm looking forward with great anticipation to learning from my colleagues on the committee and from our friends and colleagues in the community, to learn of their concerns and how we can serve them. I'm very honored to be here. Thank you.

DR. McCABE: Thank you.

MR. MARGUS: So I have absolutely no institutional memory. I'm the new person. I feel very honored and appreciative of the opportunity to meet everyone here and to serve on this.

Ten years ago this week, two of my sons were diagnosed with a brutal genetic disease called ataxia telangiectasia that combines muscular dystrophy-type symptoms, loss of muscle control with a deficiency and about a 40 percent cancer rate. At the time, I was pretty much a Forrest Gump running a shrimp company and I had no knowledge of microbiology or molecular genetics or how government funds research or how scientists think. But over the last 10 years, a lot has happened in my life.

I'm currently the volunteer president of an organization called the A-T Children's Project that helped to find the gene but also continues to orchestrate research to try to find a treatment for kids. At the same time, I'm currently the CEO of a company called Perlegen Sciences. It started out in Mountain View, California two years ago. It uses high-density oligonucleotide microarrays to hold genome scanning, trying to find the genetic basis of common diseases or drug response.

I've been on several boards but on the board of the Alliance of Genetic Support Groups, which is now called the Genetic Alliance. It's an umbrella organization representing a lot of people with genetic disease. So I've dealt with those issues.

Besides the kids having A-T and having this terrible disease, it turns out that heterozygotes with one mutation like me supposedly have a three- to four-fold risk of cancer. So we don't worry about that day to day. All we care about are our kids, but there are issues related to some insurance discrimination that we've dealt with.

DR. McCABE: Thank you.

DR. TUCKSON: My name is Reed Tuckson. I'm trained as an internist and a general medicine physician. Early in my career I spent a lot of energy and time on being a consultant on sickle cell disease. I served as the administrator for the Mental Retardation Developmental Disabilities Administration for several years in this city, eventually becoming the Commissioner of Public Health in this city for several years; then Senior Vice President of the March of Dimes Birth Defects Foundation, where, among other things, I was responsible for the research agenda for the March of Dimes.

I then had the opportunity to serve time, six years as the President of the Charles Drew University of Medicine and Science in Los Angeles, and again given a good opportunity I think to understand the issues of research and science. I was then able to serve as the Senior Vice President for Professional Standards of the American Medical Association, where I supervised medical education, ethics, public health, research, science and technology. Now I'm serving as the Physician Senior Vice President of UnitedHealth Group, which is a large multifaceted health care organization that touches the lives of about 40 million Americans and is very rich in the use of data in being able to improve the quality of health care for those that we insure and those who we organize health care services on behalf of.

As mentioned earlier, I did enjoy my service as a member of the previous, although non-continuous committee, and I'm happy to be here with my colleagues.

DR. McCABE: Thank you.

MS. ZELLMER: My name is Kim Zellmer, and unfortunately I'm not here because of my scientific expertise. I'm here because I have a daughter who is six and a half who has neuronal ceroid lipofuscinosis. Thankfully for us lay people, they also call it late infantile Batten's disease. My daughter, Maddy, developed normally until about age 3. At age 3, she began having seizures, and that was the first sign that there was any problem. So for the next year and a half, we struggled with trying to get seizures

under control, and when we thought we were winning that battle, unfortunately she began to lose skills. She lost her ability to walk, her ability to talk, she lost her eyesight.

About that time, we finally got the diagnosis, which is obviously a devastating disorder. It's a terminal disorder. Her life expectancy is eight to twelve years old. So I have first-hand knowledge, I guess, of the devastation that genetic disease can cause to a family.

I have a three-and-a-half-year-old daughter, Megan, who is a carrier of the disease but thankfully is not affected. Through Madeleine's disease for the last two years, I have been fortunate enough to meet a lot of families who are struggling with various genetic disorders, who have children affected or who are affected themselves.

When I'm not spending my time being a mother to Madeleine and Megan, I'm an attorney. I work for the Husch and Eppenberger law firm in Kansas City. I do estate planning. I'm also president of Heart of America Batten Disease Support and Research Association. Hopefully I can bring a different perspective to the committee.

DR. McCABE: Thank you.

DR. LEONARD: Hi. I'm Debra Leonard. I direct molecular pathology at the University of Pennsylvania. I'm boarded in molecular genetic pathology, and my practice is really the translation of the Human Genome Project into diagnostic tests, not only genetic tests but also cancer-related testing, infectious disease testing,, identity testing methods. The focus of my career has been basically setting laboratory standards and practices for laboratory testing, including genetic testing. I've been President of the Association for Molecular Pathology and work with the College of American Pathologists on their molecular pathology committee, as well as working with government relations.

I'm also interested in the training of medical students, physicians, physician trainees in genetics and laboratory practices and work with the American Board of Pathology on their molecular genetic pathology committee to set the examinations that will be taken by physicians to be board certified in molecular genetic pathology. My research interests are the impact of gene patents on clinical genetic testing as well as research, and I work on this with Mildred Cho and John Mers, and it's really an honor to be a member of this committee and work with all of you. Thanks.

DR. McCABE: Thank you.

DR. LANDER: I'm Eric Lander. I'm a Professor of Biology at MIT and a member of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. I direct the Whitehead MIT Center for Genome Research, which is one of the centers that's involved in the Human Genome Project and continues to be involved in the successors to the Human Genome Project.

My background is originally as a mathematician, and my scientific interests are human genetics, particularly understanding the genetic basis of the susceptibility to complex disease. I'm very proud of the work of the Human Genome Project over the last 15 years, and my interest in serving on this committee is that I want to be very proud of the work of the Human Genome Project 15 years from now. It will take an awful lot of work here to make sure that that is the case.

DR. McCABE: Thank you.

DR. REEDE: Good morning. Joan Reede. My background is in pediatrics and child psychiatry. I've served in a number of places before coming to Harvard Medical School, where I am now. So I've worked in community health centers, in juvenile prisons, in public schools, and ended up at Harvard Medical School, where I'm now Dean for Diversity and Community Partnership and oversee the Minority Faculty Development Program and the Office for Community Outreach programs, and also run a center of

excellence in minority health and health disparities.

My faculty positions are in medical school, the Harvard School of Public Health, and my focus is really on bridging academic medical centers to communities, and also on the training and education of physicians to deal particularly with issues of minority health, the health of minority populations and disadvantaged communities, with a focus on areas of health policy. I recently stepped off the Secretary's Advisory Committee on Minority Health, and also served on the Board of Governors of the NIH Clinical Center.

DR. McCABE: Thank you.

DR. WILLARD: Good morning. I'm Hunt Willard, Director of the Institute for Genome Sciences and Policy at Duke University and Vice Chancellor for Genome Sciences at Duke and the Duke University Health System. Prior to taking on those jobs, earlier this year I had been Chairman of the Department of Genetics at Case Western Reserve University at Cleveland for the past 11 years during a time at which we attempted to put together, along the lines of the old pathology model, both basic science and clinical genetics activities under the same departmental umbrella and fuse training activities across that spectrum, trying to anticipate precisely the kinds of activities that we're doing on this committee.
In the institute at Duke University, this is a somewhat unusual institute in that it's campus-wide. So although the center of gravity for the institute is decidedly at the medical center and the health system, it in fact bridges across the entire campus. So I'm working within the institute with people from the law school, the business school, the engineering school, the divinity school, the School of the Environment, et cetera, in order to take head-on this charge of figuring out how to translate genome sciences into issues that are relevant to society and the public policy issues that are critical to that effort.

It feels like I'm a lifelong member of the American Society of Human Genetics. I served as its president a few years ago, and I'm pleased to be on this committee as the manifestation of a commitment on many of our parts and now the government's part to make sure that the products of the Human Genome Project and human genetics more generally do indeed translate into the betterment of society and the public good.

DR. McCABE: Thank you.

MS. HARRISON: Good morning. My name is Barbara Harrison. I'm a Certified Genetic Counselor. I work at Howard University. I am the Co-Director of the Genetic Counseling Program there, and so I'm very concerned about the training of competent genetic counselors and have a special interest in training people of color to be involved in genetics both as geneticists and genetic counselors, and just increasing the competency in terms of being able to serve people of color as well.

I'm in the unique position as a genetic counselor of having most of the scientific knowledge, as well as knowing first-hand about the issues that families deal with that have to do with genetic conditions. So I'm hoping to bring that perspective to the committee, and I'm very honored to be here.

DR. McCABE: Thank you.

MS. MASNY: Hi. I'm Agnes Masny. I'm a Nurse Practitioner and a Research Assistant at the Fox Chase Cancer Center in Philadelphia. I work primarily in a family risk assessment program where we service women who are seeking information about genetic testing or, actually, risk reduction measures if, in fact, they are at risk for cancer. As well, I work as an educator and have some funding through the National Cancer Institute in training nurses in this whole area of cancer genetics and the counseling and education that needs to go along with that.

I've had the opportunity to serve on the National Coalition for Health Professional Education in Genetics, and I'm very interested in this area about health professional education. I also work as a project manager

with some network hospitals that belong to our institution in seeing how this whole area of cancer genetics and the risk assessment programs can be actually integrated into community-based settings. So I oversee the program as well as the training of the nurses who are running the program there.

I serve also as the coordinator for the Oncology Nursing Society's Cancer Genetics Special Interest Group, again trying to see the ways that nurses can keep up to date with the cancer genetic information that is emerging. I had the opportunity to give a presentation at the prior Secretary's Advisory Committee meetings on behalf of ONS, so now it's a real honor for me to actually be able to sit on the committee. Thank you.

DR. McCABE: Thank you.

DR. WINN-DEEN: I'm Emily Winn-Deen. My job title is Senior Director for Genomics Business with Roche Molecular Systems. I have a Ph.D. in biochemistry and have spent pretty much my whole working career working in the development of diagnostic test reagents. About the same time that the Human Genome Project began, I started working in the area specifically of DNA diagnostics and over the years have felt that there were a number of different areas that needed focus. Certainly, there was a need for technology development. There's a need to understand the underlying genetic associations with human disease.

But I now feel that beyond those sort of technical issues, we also have a number of public policy issues that we need to deal with in order to really realize the potential of the Human Genome Project to make an impact on health care, and as such I'm currently sitting on the Roche Joint Programs in Applied Genetics Public Policy Committee, and it's a tremendous honor to be sitting on this committee as well.

DR. McCABE: Thank you.

I'm now going to go through the various agencies and departments. I would ask that you focus really on the efforts of your department or agency. You can certainly briefly introduce yourselves, but we're really most interested in how the interests of your group will relate to this committee.

So we'll start with Department of Commerce.

DR. BEMENT: Thank you. I'm Arden Bement, Director of the National Institute of Standards and Technology. My background is in materials engineering, materials science and engineering. I've had appointments in academia at MIT, Purdue University, adjunct appointments at Case Western Reserve, Ohio State University. I had appointments in the Defense Department, the National Science Board, and currently serve in the Department of Commerce.

The National Institute of Standards and Technology is active across a number of fields in biotechnology and tissue regeneration. Our focus is primarily on measurement science and standards, standard reference materials and standard databases. Primarily in genomics and proteomics, we maintain at several universities a protein data bank which is getting more and more hits per month. We set standards for forensics DNA. We have a DNA database which we operate through the National Institutes of Justice.

We're quite active in single molecular measurements, automatic gene sequencing techniques. We have a dental materials center. We're quite active in developing microarrays and studying microphilytics involved with microarrays, automatic gene sequencing chips, gene chips and the use of micropores, both natural and synthetic, for studying DNA and RNA sequencing.

That's not exhaustive. We work closely with the University of Maryland Biological Institute, and also several institutes in the National Institutes of Health, more recently quite active with the newest institute, the National Institute for Bioimaging and Bioengineering.

DR. McCABE: Thank you.

Next we have the Department of Defense.

DR. TURNER: Good morning. My name is Martha Turner and I'm honored to be here representing the Department of Defense. I was asked to represent the Department of Defense in my capacity as the ethics consultant to the Air Force Surgeon General, but in fact I represent all three services here.

The Department of Defense has broad interest in genetics in three main areas: force protection, operational readiness, and health care for all of our beneficiaries. These include the active duty members, their families, and those who have retired. Across all of these, we consider the multiple ethical implications, including access, confidentiality and discrimination, some of the things you've already mentioned.

For force protection, we're looking at survivability in the field, and one example would be early exposure identification and individual protection for the soldiers. For operational readiness, we look at conventional weapons and weapons of bioterrorism and the human response to those weapons. Related to operational readiness, we also have some interest in the forensic application of genetics such as the identification of remains. In health care, we look at drug response, disease-specific prevention, diagnosis and treatment. Across all of these, again, in practice and research and education, we strive for balance of science and ethics.

DR. McCABE: Thank you.

We were just notified that the speakers need to get closer to the microphones because there's some difficulty hearing, and we certainly want the people who are listening to us on the Internet and in the other room to be able to hear. So please do get closer to the microphone.

Next we have Department of Health and Human Services, Administration for Children and Families.

MR. DANNENFELSER: Hi. My name is Martin Dannenfelser. I'm Deputy Assistant Secretary for Policy and External Affairs with the Administration for Children and Families. In first coming to Washington in 1981, I served on Capitol Hill for about 14 years and worked for a member of Congress with a very strong interest in the area of medical ethics and continued involvement in that area in the non-profit world for about six years before coming to HHS about two years ago. We deal with the human services side primarily of the issues at HHS, such things as Head Start, child care, child welfare programs, welfare reform, and so on.

As part of the Secretary's initiative, the one department initiative, I am often the representative from ACF on a variety of task forces dealing with such things as HIV/AIDS, program coordination, biomedical ethics, health disparities, domestic violence, and issues like this here. So I try to bring a perspective of the overall well-being of children and families and how we can make a contribution in this area as well.

DR. McCABE: Thank you.

Next we have the Agency for Healthcare Research and Quality.

DR. FELIX-AARON: Good morning. My name is Kay Felix-Aaron and I serve as the Senior Advisor for Minority Health for the Agency. I am a physician and health services researcher, and my career has been guided by improving access and quality of care for low-income communities.

The Agency for Healthcare Quality and Research, AHQR, is interested in the intersection between health care and genomics, and particularly its application in everyday practice. The agency studies research and practice activities that do a number of things: one, improves quality of care; two, ensures safety and

efficiency in health care. So AHQR studies the experience of Americans with its multiple databases, including the MEPS, Medical Expandable database, its hospital administration database, and its consumer assessment of health plans database.

I think AHRQ can contribute in several ways and it's interested in several ways. One is in the evidence base that supports practice and technology, the use of practice and technology. This information can guide purchasers, providers and consumers. It's also interested in studying and supporting how providers integrate diagnostic and therapeutic technologies in everyday practice. A third area of interest for the agency is in access to care and quality improvement. Thanks.

DR. McCABE: Thank you.

Next is Centers for Disease Control and Prevention.

DR. KHOURY: Good morning. My name is Muin Khoury. I'm the Director of the CDC Office of Genomics and Disease Prevention. I'm a pediatrician by training, medical geneticist, epidemiologist, trained specifically in genetic epidemiology at the time when the field was almost being born or non-existent. I joined the CDC in 1986 and I've been there ever since. I've been fascinated by the work of public health and disease prevention that the CDC does in collaboration with many groups.

CDC, as you may know, is the nation's prevention agency. We do a number of activities in terms of surveillance, investigating health outcomes and disease outbreaks, and having a pulse on the health of the nation with the idea of implementing and evaluating prevention activities that work in real communities.

In 1997, the CDC created the Office of Genomics and Disease Prevention in response to the Human Genome Project to figure out how to integrate advances in genomics into public health research policy and practice. I have been very lucky to be part of the initial creation of this office and be part of the whole movement at CDC.

We have a few priorities I'd like to mention briefly. The first is the evaluation for what genes mean in terms of health and disease in real communities in real time, sort of what do you do with a gene when you find one and how it impacts the health of the public in a real community. We have many challenges there, including the integration of genomics and the acute public health response in terms of epidemics and clusters and generally the health of the public.

We also have a challenge to evaluate, from a population perspective and with prevention in mind, how genetic information can be used to improve health and prevent disease both in terms of screening as well as everyday health care for the purpose of prevention.

Finally, we do spend quite a bit of energy working with our partners in state and local public health in terms of beefing up the public health capacity to respond, developing the workforce, and also funding and sponsoring different public health activities in this regard, and we also work with schools of public health and all the federal agencies that are represented here. I'm glad to be part of this.

DR. McCABE: Thank you.

Food and Drug Administration.

DR. FEIGAL: Good morning. I'm David Feigal. I'm an internist by training. I've been at the Food and Drug Administration for about 11 years in the Center for Drugs, the Center for Biologics, and I'm currently the head of the Center for Devices. I'm here actually representing the entire FDA. The types of products and issues that we have with genetic testing is quite broad-ranging. It includes genetically guided therapies, gene therapies themselves and, as was a particular focus of the previous committee, diagnostic devices.

The consumer protections that we are responsible for is to ensure that investigational use of products are safe, that market approval is based on an evidence standard set in statute that products be safe and effective or equivalent to products that are already marketed, we have the responsibility for inspecting and ensuring manufacturing quality, and monitoring problems in the marketplace in the use of the test or drug, such as adverse experiences. We're part of a system that provides the corrective actions when there are problems, along with the manufacturers, including recalls of products, safety alerts and changes in labeling.

The basic scheme of FDA is risk-based consumer protection, and part of the concerns of the previous committee in the debate has been to think about which are the riskier kinds of information, what are the riskier types of products. It's also a complex area because these are consumer protections that are shared with CMS, which is responsible for administration of the Clinical Laboratories Improvement Act, the CLIA program, which supervises laboratories. Our authorities and responsibilities overlap with states which license laboratories and license health professions.

Let me just conclude by thanking you in advance for all of your efforts. These are difficult issues and we all have a stake in this.

DR. McCABE: Thank you.

The Health Resources and Services Administration?

DR. FEETHAM: I'm Suzanne Feetham and I'm briefly sitting in for Dr. Sam Shekar. I am a nurse with clinical practice with children with birth defects and their families. I was Deputy Director at NINR, the National Institute of Nursing Research, at NIH. My program of research has included studies of families' decision-making in families considering genetic testing when they have susceptibility for cancer, and families of children with genetic conditions. I also have published extensively in genetics education in nursing and families and genetics.

Dr. Shekar is the Associate Administrator for the Bureau for Primary Health Care, and he leads the HRSA Genetic Work Group to provide recommendations to the agency on the activities for the Agency in Genetics. We are the access agency and the programs of HRSA focus on providing health care to underserved and vulnerable populations to move towards eliminating health disparities.

HRSA has recognized the significance of genomics for health and the understanding of mechanisms of disease and prevention. We feel that access and quality of care is affected by the ability of health professionals to apply genetic knowledge to their practice. We partner with several of our other federal agencies -- NIH, AHQR, CDC and others -- and also with professional organizations in the programs that we fund in regards to genetics.

Our genetics cover three key areas. The first is our well-known Maternal Child Health Bureau for the Genetic Services Branch, which provides programs for genetic testing and counseling, information development, and dissemination programs related to hemophilia, screening of newborns for sickle cell anemia, and genetic disorders and follow-up. That bureau also focused on programs in public education.

We also have a major program in our Bureau of Health Professions for the education of health and public health professionals. Since 1996 to '01, the funding in this area has increased five-fold in our recognition of the significance of genetic education to health professionals.

Another area of significance for HRSA is that our National Center for Workforce Analysis conducted a study of the genetic counseling workforce and is currently funding a study that is being done in regards to the genetic workforce in primary care, including nurses and physicians, genetic specialists, in partnership with the Maternal Child Health Bureau and our colleagues at NIH, the Human Genome Institute.

Our agency has significant networks that can facilitate the dissemination of genetic knowledge to help professionals. Our programs of HRSA and our commitment to this area can inform the work of this committee, and we are pleased to be part of this as an ex officio. Thank you.

DR. McCABE: Thank you.

National Institutes of Health?

DR. COLLINS: Good morning. I'm Francis Collins, Director of the National Human Genome Research Institute at the National Institutes of Health. I first want to say what a wonderful group we have here in the mosh pit --

(Laughter.)

DR. COLLINS: -- this very dedicated and talented group of members of this committee that I'm really looking forward to hearing from and working with, because I think we have a very exciting opportunity and a challenging one in front of us, with a whole host of topics that I'm sure we'll be wrestling with in the coming days, weeks and months.

The National Institutes of Health is the government's most major investment in biomedical research, with a budget approaching $30 billion a year, research which is carried out now on a host of fronts, from very basic science-oriented enterprises to very translational research, up to and including clinical trials. So this is a very major area of interest for the NIH, to make sure that all that research ends up being applied in a fashion that has maximal public benefit.

The NIH is constituted of some 27 institutes and centers, of which the Genome Institute is but one. I can tell you that all of the other institutes have considerable areas of interest in the purview of this particular committee and have already provided input to me as the NIH representative that I hope will be valuable in informing the committee of NIH's concerns and hopes.

For myself, I'm a physician. I'm trained as an internist and a medical geneticist. My career has been initially in an academic environment at the University of Michigan but for the last 10 years as an institute director at NIH leading the Human Genome Project, with a particular focus on trying to understand the causes and ultimately the cures of diseases that have genetic components, which is in fact virtually all diseases.

I will tell you one other hat that I wear, which is as the chairperson of the National Coalition for Health Professional Education in Genetics, an organization which currently involves some 120-member organizations which collectively is trying to achieve education of health care professionals in the principles and practice of genetics in anticipation that this is going to be a discipline which spills out, and in fact already is, into the mainstream of medicine and for which all health care providers will need to be prepared.

Finally, I'd just like to say that in terms of input to this committee's deliberations, I hope that I can be of some help by the fact that we do have a wonderful wealth of scholarship in many of the issues that you may want to consider, and that comes from research that's been supported, particularly from the ELSI program, the Ethical, Legal and Social Implications program of the Genome Institute, which has been in place since 1990 and which has investigated in rigorous, scholarly ways many of the topics that I think this committee may wish to deliberate on, and happily that means that we do have some evidence upon which perhaps to base some of our discussions. That ELSI program continues to be a critical part of our hopes for the future, with many areas of research bubbling up on an almost weekly basis as new developments occur in this rapidly advancing field.

So again, I'm delighted to be able to be a part of this as a liaison from NIH and looking forward very much to working with all of you and with the chair, the very capable Ed McCabe. Thank you.

DR. McCABE: Thank you.

Office for Civil Rights?

DR. FROHBOESE: Good morning. My name is Robinsue Frohboese. I'm the Principal Deputy Director of our Office for Civil Rights at HHS. I'm very pleased to be able to join you and to bring the perspectives of the Office for Civil Rights. I'm an attorney and a psychologist and actually have a longstanding interest and history in medical ethics issues dating back, like Marty, to the days that I spent on Capitol Hill in the early 1980s when I worked for the Senate Health Committee and was involved with a number of issues around medical ethics.

In my capacity of representing the Office for Civil Rights, I will be bringing to the committee two key important perspectives. The first perspective has been mentioned by a number of the members, and that is ensuring equal access by vulnerable populations and minority groups, eliminating health disparities, and also ensuring non-discrimination on the basis of race, color, national origin, disability, and age, all of which our office is responsible for in HHS-funded programs.

In addition to the traditional civil rights perspective, our office is also responsible for the new privacy rule under the Health Insurance Portability and Accountability Act, which many of you may know went into effect two months ago in April of this year. There are a number of considerations in protecting the privacy of information, including genetic information, and I will be happy to share our perspectives about the rule and to offer guidance about our interpretation and enforcement activities. Thank you.

DR. McCABE: Thank you.

Department of Justice?

DR. MAJIDI: Good morning. I'm Vahid Majidi. I have my degree in chemistry, and I started my career as a professor at the University of Kentucky. I was there for about eight years, after which I went to Los Alamos National Laboratory. Currently, I'm on detail from Los Alamos, and I'm the Chief Science Advisor at Department of Justice. We have a very broad interest in genetics information as it relates to forensic science, as well as all legal aspects of genetic information, genomic technologies, and genetic materials. Thank you.

DR. McCABE: Thank you.

And next is Department of Labor.

MR. ZURAWSKI: Hi. I'm Paul Zurawski, the Deputy Assistant Secretary at the Employee Benefits Security Administration, the agency at the Department of Labor which has jurisdiction over employer-provided benefit plans, including health care. We currently have the regulatory and enforcement responsibilities of HIPAA, at least in terms of the preexisting condition, portability and non-discrimination provisions as they relate to group health plans. Thanks.

DR. McCABE: Thank you.

Equal Employment Opportunity Commission.

MR. MILLER: Thank you. My name is Paul Miller and I am a Commissioner at the U.S. Equal Employment Opportunity Commission. The EEOC enforces all federal workplace discrimination laws prohibiting discrimination on the basis of race, gender, age, religion, disability, and pregnancy. The EEOC intersects with these issues of genetics in terms of prohibiting and thinking about employment discrimination, particularly genetic discrimination. Most of the bills I think that Dr. McCabe referred to earlier, genetic discrimination bills, foresee an enforcement mechanism through the EEOC, and the

EEOC has also litigated the first case of genetic discrimination against a railroad.

My background, I've served on the working group that drafted the Executive Order on Genetic Discrimination and Privacy. I've previously served as a member of the President's Committee on People with Disabilities and was a White House staffer on disability issues, a lawyer by training. It's a pleasure to be here. Thank you.

DR. McCABE: Thank you.

Also, within DHHS, we have the Centers for Medicare and Medicaid Services.

DR. TUNIS: My name is Sean Tunis. I'm the Chief Medical Officer for Medicare and Medicaid Programs, and also the Director of the Office of Clinical Standards and Quality. The perspectives that I bring and will be listening with are both related to the coverage policy, the reasonable and necessary determinations of new technologies for the Medicare program, reimbursement policy that goes along with that, and also the agency shares oversight of the CLIA program with the FDA. So we have a component of CMS that has that expertise. Actually, the primary person with knowledge of that person, Judy Yost, is not here today but she'll be joining us at future meetings.

I'm also invited to these meetings to make sure David Feigal stays within the boundaries of sense.

(Laughter.)

DR. McCABE: Thank you.

Well, I think that one of the things that we all observed is that the breadth of agencies who are involved with this committee is extremely broad, and I think it represents the interests of both the government and our population more broadly in what has come from genetics and the Human Genome Project. So I think it's really wonderful to have so many representatives of the various government agencies here and involved with this committee.

Most important to this committee's function is really the staff of that committee, and we are incredibly lucky that Sarah Carr, who was the Executive Secretary for the Secretary's Advisory Committee on Genetic Testing, is also the Executive Secretary for this committee. Anything that goes wrong I will take full credit for, but I can tell you I won't have too many things that I have to take credit for because Sarah and her staff do such a wonderful job. So I think we should have Sarah introduce herself, since she's really the key person for the success of this committee.

MS. CARR: Well, thank you, Ed. Again, my name is Sarah Carr, and I'm called the Executive Secretary of this committee, but I'm part of a team at NIH that helps staff you. It includes Lana Skirboll, Amy Patterson, Suzanne Goodwin, and this summer Olivia Hess, our summer intern. The other role I have when I'm sitting here with you is to be the designated federal officer, and I'm supposed to keep you from doing anything wrong, and I have great faith in all of you that I won't have a very hard time making sure that you don't do anything wrong.

So it's a pleasure to be with you, it's a pleasure to see this committee start, and we look forward to staffing you and helping you navigate these challenging waters.

DR. McCABE: With typical modesty, Sarah will not tell you of all the other responsibilities that she has. We are not her only responsibility.

Before we go on, I want to take a moment to review the rest of the agenda with you and explain the principal goals of the meeting. Our main objective is to identify and to prioritize issues that the committee will address and develop as a workplan for addressing these issues. We do have an extremely

broad range of opportunities. Our challenge will be to identify one or two opportunities over this meeting and the next meeting in priority as our initial areas on which we will focus.

The informational presentations that we've scheduled for today and tomorrow morning are preparatory to our priority-setting deliberations. They're intended to provide the committee with a common foundation from which to consider and prioritize these issues. We will have background presentations on key issues from some of the nation's leading experts in their fields. We will hear perspectives from the public, we will review the work of our predecessor, the Secretary's Advisory Committee on Genetic Testing, and finally we will be briefed about what the federal agencies represented on the committee think are their highest priority issues.

So with that, let us move on, and I want to thank all of you for your informational introductions and also with the brevity of those introductions so we could move on with the work at hand.

We now want to talk about the relevant rules of conduct, and we will have presentations from Valerie Hurt from the Office of the General Counsel, Public Health Division, DHHS, on Federal Advisory Committee Act regulation, and also from Holli Beckerman-Jaffe from the Office of the General Counsel, Ethics Division, DHHS, on ethics in government regulations.

MS. HURT: Thank you, Dr. McCabe.

I'm an attorney at the Department of Health and Human Service's General Counsel's Office. I work in the NIH branch. I've been asked to speak to you briefly about the Federal Advisory Committee Act. A lot of you are familiar with it. You've served on federal advisory committees before, so this is really a quick overview.

As Dr. Zerhouni explained, Secretary Thompson convened this committee to seek advice from all of you concerning genetics, health, and society. The purpose of the Federal Advisory Committee Act is to ensure that when the government asks for advice from experts like yourselves, the public has the opportunity to participate. All of FACA's rules stem basically from that concept.

You are an advisory committee; we know that. You come under (C), established or utilized by one of the agencies. There are a few exceptions. I'm not going to go over them.

As I mentioned, Congress enacted the Federal Advisory Committee Act because it believed that it was important for the government to seek advice from outside experts such as yourselves, but it wanted to ensure that when the government did that, there would be uniform standards and practices for obtaining advice and that the public would be kept informed and have the opportunity to participate.

There are a number of laws that govern what you do. I'm not going to go through them. The number-one law is obviously FACA. If you have any questions, you can ask Sarah. I mentioned the primary requirements are that advisory committees should meet in the open. That's why you're all here. That's why the opportunity for people to view it on the Web is available.

The idea is that the government wants to ensure the public has the opportunity to know what you're doing and to participate. Notice of your meetings has to be published in the Federal Register 15 days ahead of when you meet, at least. The reports that you prepare, transcripts of your meetings, minutes, working papers, basically all the information that you receive should be made available to the public as well, and the public has the opportunity to review that material. There are a couple of exceptions having to do with trade secrets, et cetera, but I'm not going to go through that right now.

These are some of the more mundane aspects of the law, but they'll explain a little bit, for those of you who are less familiar with how it works, why certain activities have to happen. A federal official has to be here, minutes have to be kept, financial records must be kept, all federal advisory committees must be

chartered -- you have your charter -- and the membership must be balanced in terms of points of view. Again, that's explained. Congress wanted to ensure that both the public would be informed and it would do what it could do to ensure that the government got good advice.

There are some activities that you may do which may not necessarily be subject to the open meeting requirements, and that's working group activities into relatively narrow contexts. Again, remember the idea was that the public should have the opportunity to know what you're doing and participate. However, the law recognizes that for certain activities, it maybe makes more sense and the interest in ensuring public participation isn't perhaps as strong, and those activities are preparatory work, which means doing an investigation, gathering information, conducting research, maybe drafting some position papers, provided that that drafting, investigation, et cetera, isn't passed on to the advisory committee in a sort of pro forma fashion. If a working group develops a paper or an idea, that really has to be the kind of thing that the committee then deliberates upon fully.

Similarly, administrative work. To the extent that some of your members are going to learn about administrative activities related to what you're doing, that doesn't need to necessarily proceed in the open because the judgment has been made that those kinds of activities aren't the kinds of things that need to necessarily occupy the whole committee and the public access.

Sarah is your designated federal officer. Sarah has a bunch of jobs. She approves or calls the meetings. She approves the agenda. She attends the meetings. She adjourns the meetings. She chairs the meetings when directed by the agency head. I doubt that Dr. McCabe will let that happen. She ensures that the minutes are kept. Also, if you have questions, at least initially about how your operations proceed and what you can do and what you can't, Sarah is here to answer those questions.

As you know, you all serve by appointment and you vote, and you have the full right to participate in the activities of the committee. You're compensated for your time and site visits, et cetera. As I mentioned, if you have questions, refer them to Sarah. Although Holli is going to speak at length to you about this, the other thing to sort of keep in mind is that if you have a conflict of interest or you're concerned about a conflict of interest, you need to be sensitive to that and raise it. You are, when you are here, serving as a special government employee and subject to all the restrictions and obligations of that role.

So as I mentioned, the key point to keep in mind is that the Federal Advisory Committee Act regulates the way you do business, and its primary purpose is to ensure that the public has a meaningful way to participate in what you do.

That's it.

DR. McCABE: Thank you very much.

Our next speaker is Holli Beckerman-Jaffe.

MS. BECKERMAN-JAFFE: Good morning. I'm Holli Beckerman-Jaffe, General Counsel's Office, Ethics Division.

You should have one sheet in your file that says "Ethics Overview for Members of the Advisory Committee." I'll take you through that. Thank you.

The first thing I want to raise is the U.S. Constitution, the emoluments clause. This is something that applies to you 24 hours a day, 7 days a week, as long as your appointment to the committee is active. What the emoluments clause says is that as an SGE, a special government employee, you may not accept a present, emolument, or officer title from a foreign government entity. So some examples of that. You may be asked to go speak by the Canadian government. That would not be considered an officer title because there is no what we refer to as durational quality. So it's a one-time deal. So that's not the

problem.

What the problem would be is that if you accepted compensation for that speech, that would be an emolument and you cannot do that. So it's not just that they ask you to come and speak about your advisory committee work. It's anytime. This rule applies all the time to you. So it applies when you're doing work for your university or your home institutions or your corporations, whatever the case may be. It's only governmental under this, though. If it's a private concern that's foreign, that's fine.

If you hold an honorary position, you're a professor at a university, and that appointment was made prior to your appointment as an SGE, you may keep that position. You can be an adjunct professor to the University of Beijing. That's absolutely fine, as long as you perform no duties for the University of Beijing.

(Laughter.)

MS. BECKERMAN-JAFFE: I know, small consolation. But you can keep the title. That's one more line in your CV. You can keep that.

You're not prohibited from accepting emoluments if your home institution -- a lot of times we have a situation where you're invited to come speak and the foreign government entity is willing to pay your travel to get there and back, which is reasonable since they're asking you to travel. If your university or your corporation has a procedure where they can accept the travel reimbursement, so you'll be traveling on their dime, the university's or the corporation's dime, so you're going over there under -- we call it travel orders in the federal government. I've been in the public sector for so long. It's just a plane ticket, okay? They buy the plane ticket and send you over there.

(Laughter.)

MS. BECKERMAN-JAFFE: That's perfectly acceptable if they have a legitimate accounting. Some universities and corporations, they don't want to deal with it. They're like, "That's your private business, we're not going to tie up our accounting office with that."

DR. LANDER: They'll also cover your hotel and things. They'll reimburse through the university.

MS. BECKERMAN-JAFFE: Right, right. There's actually another exception for that. But, yes, it would include that also. So if you can get travel reimbursement that way, where the foreign government is reimbursing your home institution and not you directly, then that's fine, you can accept that.

Also, if the United States is a member of an international organization, like the World Health Organization, that's not an emoluments problem because we're a member of the World Health Organization. However, that could be a problem under the Foreign Gift and Decorations Act. The Foreign Gift and Decorations Act is an exception to the emoluments clause. The emoluments clause says you can't accept unless Congress consents. Congress consents to some foreign gifts through the Foreign Gift and Decorations Act.

The Foreign Gift and Decorations Act allows you to accept medals, badges, awards, plaques, the stuff you really don't want. You can accept that. Tangible gifts less than $285. Yesterday I reviewed an invitation for one of our IC directors at NIH which said, "We'd be happy if you'd accept our token of thanks of $285." We were like, "Ah, terrific, somebody read the Foreign Gift and Decorations Act." So that was exciting to us. The IC director was kind of insulted that he was only getting $285. We thought it was kind of fun because somebody read the statute. It depends where you're coming from.

Educational scholarships or medical treatment. So if you happen to have a heart attack in the streets of Beijing, don't worry, you can go to a Beijing hospital and accept the medical treatment there because

that's an exception to the emoluments clause under the Foreign Gift and Decorations Act.

DR. LANDER: Can I just probe for a second? If you got an award somewhere -- I'll be specific. With a bunch of people in the Genome Project, we shared some award in Canada from the Gairdner Foundation, but this year they gave it to a bunch more people and they got contributions to the Gairdner from the Canadian government to be able to give it to more people.

MS. BECKERMAN-JAFFE: It depends. When it's something like that where it's a private foundation or institution and they're getting government funding, it depends how much involvement. If the institution itself, if the foundation has a private board and it's not a problem, that's usually not a problem because the institution is independent of the foreign government.

DR. LANDER: So how do we find out when we're confused about this? Because we're probably confused about this already. We just ask Sarah? Sarah knows everything?

MS. BECKERMAN-JAFFE: Ask Sarah and Sarah will call me. Valerie and I are not trying to get out of work. It's just that it's best if Sarah, for institutional knowledge and --

DR. LANDER: Cool.

MS. BECKERMAN-JAFFE: Because a lot of times you have the same questions. So if all the questions come to the same point, she'll consult Valerie or me. We spend a lot of time trying to figure out if a foreign entity truly is a foreign governmental entity.

DR. LANDER: I was at the NCI yesterday, and their interpretation of emoluments said that if one got reimbursed by a private conference that had received government funding, you couldn't take that directly.

MS. BECKERMAN-JAFFE: Could not?

DR. LANDER: Yes. But your interpretation seems different.

MS. BECKERMAN-JAFFE: No, it's possible. I mean, if the private foundation -- it depends on --

DR. LANDER: (Inaudible) runs a scientific conference, it costs $100,000, they put in a grant for $20,000 toward their 100 expenses from their health institute. According to some other part of the federal government, you couldn't get reimbursed because it became contaminated by any touch of government support.

MS. BECKERMAN-JAFFE: Well, since I probably gave the emoluments advice to NCI, I'll say there's a piece of information that we don't know, and what they're saying and what I'm saying is consistent.

(Laughter.)

DR. LANDER: Pay me the pleasure of getting two of these lectures in the same week.

(Laughter.)

MS. BECKERMAN-JAFFE: Well, it's good that you're paying attention. That's good. I'll get back to you.

DR. LANDER: Thank you.

MS. BECKERMAN-JAFFE: The last exception under the Foreign Gift and Decorations Act is travel wholly outside the United States. So if either you paid your way or the university accepted the travel

reimbursement, legitimately accepted the airfare to China, once you're in-country, then under the Foreign Gift and Decorations Act you can accept hotel, meals, lodging, internal transportation. So believe it or not, the Department of Justice has said if you go to Canada on your own dime and then have the foreign government entity fly you from Canada to Europe or Asia, that's fine because that's travel wholly outside the United States and you can accept that. So Canada or Mexico, we give you two options there, two borders. It's possible.

I know. Justice, I'm blaming this on Justice, the Department of Justice. They say that's legitimate. It seems like a way around the statute, but it's wholly outside the United States, and that's the exception.

I believe what that exception truly was trying to get at, if you were in Munich giving a speech and they said, "Hey, there's something really interesting we want you to see in Berlin," and they pay your intra-country travel, that's what I think this is really getting at. I don't think that they really thought about running up to Canada. But that's how the statute reads, and we're going to read the statute very literally.

So there are exceptions. This is very fact specific. I could spend my whole day -- happily, I don't have to, but I could easily spend my whole day doing emoluments and Foreign Gift and Decorations Act questions, because it is sometimes very, very difficult to figure out if an entity is a foreign governmental entity or is just a foreign entity. So if you have questions, and you will have questions, direct them to Sarah and she'll get them out to us, and we'll hopefully get an answer that's consistent with NCI.

The next issue, which is probably your biggest concern, is conflict of interest. This applies, again, 24/7, but only with respect to the stuff that you do as an advisory committee member. So the statute, and this is a criminal statute -- Valerie kept saying public, public, public; I'm going to keep saying criminal, criminal, criminal, okay? This is a criminal statute. People do get prosecuted under this statute.

It prohibits you from participating as an advisory committee member in a particular matter that will have a direct and predictable effect either on your personal interests or your imputed interests. Your imputed financial interests are those of your spouse, dependent child, an organization in which you serve as an officer, director, trustee, or general partner, or an organization with whom you're seeking employment. Those are your imputed interests. That's why you fill out the 450 -- maybe because we're a little bit nosey, but really it's to help you guys. We want to try to help you know what interests you have.

So once a year we ask that you fill out this report, and it makes you think, what do I have in my 401(k) account? Where did I put my kids' college fund money? Where am I investing that money? Am I an officer of that organization or am I just on a committee, or do I just pay membership dues and never go, just get the newsletter and read it occasionally?

So we ask you to go through that exercise so we can help you, so we can advise you what you have, a financial interest with respect to 208, the criminal statute, and also with respect to the regs. The regulation under 2635.502 refers to a covered relationship. You have a covered relationship with an organization where you served as an officer, director, trustee, general partner within the last year, because somebody could make the argument that you left on good terms, you still like these people. You may do something differently in your federal position because you still have a lot of friends and colleagues at the place where you just were an officer, or where your wife or dependent child works. That organization is not your employer but your spouse's employer, and that's half of your household income.

You have a covered relationship with a member of your household. It doesn't have to be a family member. But again, it might matter to you whether or not your roommate is unemployed and therefore is not going to pay half the month's rent. So that's a covered relationship. You have a covered relationship with a person in your household. So there are a lot of covered relationships you have to consider.

So both under the criminal statute and under the regs, you have to be cognizant of who you have a

financial interest with, and that's why you fill out the report.

Now, the criminal statute is broader than the reg. The criminal statute says you can't work on a particular matter. There's two kinds of particular matters, and for your purposes it doesn't matter because we're going to boil this down, but there are two kinds of particular matters. There's matters of general applicability, which refer to policy matters, regulations, kind of broad things, like the tax code. It affects every U.S. citizen. If you're working on the tax code, that would be a matter of general applicability.

If you were working on a specific grant, that's a specific party matter. That's going to affect a very small number of people. There are five people applying for this grant. If you give it to one university, the other four universities will get it. And it doesn't matter if you're impacting this negatively or positively. If you affect your financial interest, either in a positive or negative way, you have violated 208 if you do that in your official capacity.

So we ask you to file the report, we ask you to fill out the foreign entity questionnaire to help you with the emoluments clause. You fill out the 450, financial disclosure. Then we say, okay, you have a financial interest with your spouse's employer, you have a financial interest with Coke because you own Coca-Cola stock, you have a financial interest in Merck because you own Merck stock, you are an officer of the American Medical Association so you have a financial interest with them. You have a covered relationship with an organization that you just resigned, that last year you were serving in.

So we write all this stuff down for you on a list and we say, okay, you cannot work on specific party matters that involve any of these entities. You'll be getting this list. I think most of you have not gotten a list for this meeting because we don't expect anybody -- there won't be any specific party matters being addressed today. But hopefully by the next meeting, we should have that list together.

You also receive a waiver, because under 208 general matters of general applicability apply, but we're going to waive those for you. The statute gives the agency authority to waive matters of general applicability. So we're going to say you can work on a matter of general applicability such as a policy matter that could affect a broad range of people similarly, all members of a class in the same way. That we'll waive. So you'll get a waiver and you'll get a recusal list so you'll know what you can and cannot work on.

Like I said, we're here to help you. We want to answer any questions we can. We'll make these lists as best we can. We'll be reviewing the agenda ahead of time so we can flag stuff specific to the agenda. But yet, this is a personal obligation. You really have to keep up on what you have, and you have to be very cognizant of where the meeting is going and what may come up.

A great example of this is now retired Postmaster General Runyon. My colleague over at the Postal Service went through his financial interests and really scrubbed it. It said airlines; get out of airlines. FedEx, UPS; get out of that. Made him divest of General Motors because they buy General Motors trucks to drive around the mail. A uniform company. We buy uniforms, we buy tons of uniforms; get out of that. Really scrubbed it and told him to get out of everything that could possibly come before you as Postmaster General.

Didn't tell him to sell Coca-Cola. What does Coca-Cola have to do with the Post Office? Well, Coke approached the Post Office and said, "How about if we put a Coke machine in every Post Office?" There are hundreds of thousands of Post Offices across the country. That's a lot of bucks for Coke and for the Postal Service, because they were going to rent them whatever, 3-by-4 feet of space to stick the Coke machine on. He didn't think about his Coca-Cola stock. Nobody told him to think about his Coca-Cola stock. Well, there he is working on Coca-Cola. He violated 208. He was not criminally prosecuted, though they did look at him. But he was civilly prosecuted. He paid, I think, $25,000 or $50,000, and he was forced to resign.

So it happens. Even though the ethics official did the best he could, it's still up to the employee to remember and to know what financial interests you have and to just keep focused on that during these meetings.

DR. WILLARD: This applies only to financial personal interests as opposed to personal interests? Obviously, you just heard that many of us have personal issues related to genetics, health and society. Obviously, it's difficult to step outside that role, and yet that may not have any direct or actual consequences.

MS. BECKERMAN-JAFFE: The statute is very specific on financial interests. So it would be a stock, a company that you're an officer in. If you have a personal interest in what's going on because of a family member or your own health issues, no. It would be financial. It's very specific.

DR. LANDER: And the interest has to be, or the potential benefit that would come to a company in which you have interests, does it have to be specific or could it be completely general? For example, we could say things that would be good or bad for diagnostics companies, pharmaceutical companies. What do you say?

MS. BECKERMAN-JAFFE: To be honest with you, it depends, and this is where we have the waivers when you're talking generally. So if you were talking about a regulation or a policy that would say all pharmaceuticals that will receive grants have to put the grants in one month ahead of time, that's going to treat every pharmaceutical the same exact way, the small ones, the big ones. They're going to be treated similarly. They're just a member of a class.

If that policy only affected pharmaceuticals that produced this drug, and there's only three drugs -- everybody knows that it's going to be Merck, Johnson and Johnson, and Glaxo -- then no. If you have Glaxo stock, then you need to recuse yourself. Recusal is just getting up and walking out of the room. Just don't participate. Get up and walk out of the room.

There has been an opinion where just sitting in the room and not saying anything -- a federal employee cleared his throat. He swears he just had a tickle. Well, the IG thought otherwise. He thought he was sending some kind of message.

Get out of the room. Go get some coffee. Don't stay in the room. That's been interpreted that you're peddling influence.

DR. LANDER: So given the nature of what we're likely to discuss, it might be helpful -- although I appreciate that it remains the individual person's obligation -- to get some guidance on where landmines are. For example, in the diagnostics industry, there's considerable concentration with regard to certain technologies. Does that mean that the one or two or three very big players automatically are presumed to be obvious targets of any particular recommendations? I don't have anything to do with them, but I'm curious whether we might as a committee get a little bit of advance intelligence on what would and wouldn't be likely to fall in it given our specific charge.

MS. BECKERMAN-JAFFE: Well, that's what we help to do with these recusal lists. We will be looking at the agenda and our best guess. We will say that this topic may raise issues that could have a direct and predictable effect on this interest of yours, and we would highlight it. That's what we hope to do. But we don't necessarily know where the conversation is going. I'm not a scientist. Eleventh grade chemistry was as much as I got through. It's been a long time. It's our best guess where this is going to go. You're the experts. You know who the players are in the field. You also need to know your own interests and do the best you can.

I would personally say be very conservative. I don't look good in stripes. I don't want to go to jail. I would just be very far away from a criminal statute. So it's up to you how you want to interpret that.

DR. TUCKSON: So the way that we handle this going forward is that we either ask first Sarah, but do we get your number? Are you the person we call?

DR. McCABE: It's better to go through Sarah to keep this coordinated. Plus, it means that Sarah learns from each of these and can help the next time a similar issue arises.

MS. BECKERMAN-JAFFE: But we find that usually you're not unique, that there's a situation that comes up, and then we do a little research. There are a couple of great websites that list competitors. So if I go onto a website and I see that Johnson and Johnson is involved in something, they'll say "major competitors are," and they'll give me three other companies. Now, I wouldn't have known that, but they're telling me this. So that's going to help me.

A lot of times, by having the questions come to one person, the question is usually applicable to more than one person. So we can help out.

DR. HOOK: I was thinking of mutual funds in a 403(b), where they're constantly changing perhaps their holdings, and you may not know of a company in a med-tech or a science mutual fund. Is it best just to divulge all that --

MS. BECKERMAN-JAFFE: This is a great lead-in. Mutual funds that we refer to as diversified mutual funds, they're like the S&P 500 mutual funds, growth and income, don't worry about those. Those are already waived. You don't have any control. You can't call up Peter Lynch in Fidelity and say, "Hey, Pete, in Magellan, I think you should get rid of all your Coke holdings." That doesn't work. So we're saying you have no control over what's in those huge mutual funds. So we say don't worry about those.

When it's a sector fund, Vanguard Health Sector Fund, something like that, there's up to a $50,000 waiver. So if you have up to $50,000 in that mutual fund, you're okay. If you want to play it really safe, either put in a standing order with your broker or something like that to keep that particular sector fund under $50,000. That's great, because on any particular day, if you're near that, it could fluctuate. If you also just don't even want to think about it at all and divest, of course you're free to do that.

DR. McCABE: Let me give a couple of examples, too, having been through this with the SACGT. If you are invited to speak to a group as a representative of this advisory committee, then you need to check that out with Sarah, and then you're traveling as a special federal employee and all of the rules governing special federal employees are in effect for the time that you are functioning in that way.

If, on the other hand, you are introduced as being a member of this advisory committee along with everything else that you do, so you're not representing this committee but it's just part of the introduction, then you're not acting as a special federal employee. You're not only focusing on the efforts of this committee. So that's important. But if you are invited to speak to a professional organization or any other group on the business of this committee, then you really need to work with Sarah on that because you cannot accept honoraria for that speaking, and if you are giving multiple talks on that day, that day you are a special federal employee, so all other talks are governed.

Similarly, when you're in Washington, we all have other hats that we wear, and some of us come from some distance and so it's good to consolidate trips. You cannot go to the Hill when you're functioning as a special federal employee. You really can't do that on those days. You cannot educate our legislators about any issues because of the rules governing lobbying by federal employees. So one needs to be careful of that.

And also, another example. When I was the chair of the SACGT, I was also president of the American College of Medical Genetics. So the ACMG wanted a report from that committee. I would step down formally and have it recorded in the minutes that I stepped down as the president and was not chairing the meeting of the board at that time. Someone else took over so that I was only functioning as the chair

of the SACGT as I was giving that report.

So one just needs to be cautious about what may be perceived as potential conflicts of interest, and when you are wearing this hat, this is the hat you are wearing and it trumps all others.

DR. TUCKSON: Ed, I don't want to wear us out on these issues, but that last point is important. On a day that we come here for this work, first of all, the workday, is that 9:00 to 5:00, or is that the whole day?

MS. BECKERMAN-JAFFE: With these meetings that are usually two days or three days, what we're saying is if you want to come in -- what's today, Wednesday? -- if you came in on Monday and you don't need to start work until 8:00 this morning, you came in on Monday, Monday afternoon, assuming Monday night's hotel was on your expense, you could lobby Congress on those days. It's the days when you are wearing, as Dr. McCabe says, your Committee hat. So I would say today, up until and through tomorrow, tonight you should not be lobbying. If you want to extend your stay at no cost to the federal government, so you're going to pay your hotel, pay any difference in the airfare and stay on until Friday or Saturday, you can do that with respect to lobbying.

DR. TUCKSON: I don't want to split hairs here, but it's important. It's 5:30, and the meeting is over at 5:00. At 5:30, are you free of that, or is that still the work day?

MS. BECKERMAN-JAFFE: For lobbying purposes, I'd wait until the meeting is adjourned the next day.

DR. TUCKSON: The meeting is adjourned at 5:00 and you want to go to the Hill --

MS. BECKERMAN-JAFFE: But is the meeting going to start again tomorrow morning?

DR. TUCKSON: No.

MS. BECKERMAN-JAFFE: Okay.

DR. TUCKSON: Everything is over. We close gavel tomorrow at 5:00. You want to have a meeting at 5:30. Are you still an employee?

MS. BECKERMAN-JAFFE: You're still an employee, but you're not restricted with respect to lobbying.
DR. TUCKSON: And finally, Ed's comment there is if you do any other meeting, not even lobbying -- I mean, let's say you do anything related to your daily work activities while you're in D.C. during that period of time, are you still considered -- is that prohibited behavior? If you convene a meeting, let's say you want to have a lunch meeting while you're at lunch and you want to do a quick 30-minute meeting with somebody related to your normal activities outside of this function --

MS. BECKERMAN-JAFFE: And it has nothing to do with what the committee is meeting on, completely independent?

DR. TUCKSON: Right.

MS. BECKERMAN-JAFFE: You can.

MS. BERRY: I have a question.

MS. BECKERMAN-JAFFE: Yes?

MS. BERRY: What about answering phone calls and what-not during breaks? Obviously, in my role, I'm getting calls from the Hill all the time. Is that absolutely prohibited? So during a break, I get a

voicemail from somebody and they want me to call them back, it has nothing to do with any of this activity at all.

MS. BECKERMAN-JAFFE: The prohibition is against lobbying, so trying to influence. If it's an informational question, you're probably okay. To be safe, I would say try to just leave a voicemail saying you'll get back to them the next day or have them referred to somebody else. There's always a fine line between giving information and influencing. So one piece of information could be very influential. You could be just trying to answer their question, but you could be starting to influence. The prohibition is against lobbying.

What the prohibition says is that you can't use appropriated funds to lobby Congress. So you'd be using appropriated funds because right now we're paying you for the day, and that's where this comes from. So the safer bet would be saying no, don't take the call back, or call them back and just say "Listen, I need to get back to you tomorrow."

MS. BERRY: And it has to do with the compensation that we get? For example, if you live here and you work here, that doesn't matter?

MS. BECKERMAN-JAFFE: Right, because tomorrow or Friday, for lobbying purposes, lobbying is only during your official duty hours. So on Friday, you're back to being just a U.S. citizen and yes, go pound on every Congressman's door. We still have freedom of speech. I like to say that and I need to say that to myself a few times a day. Nothing is absolute, but we still can speak our minds.

DR. McCABE: And I think it's important also to point out that you are here because of your expertise. So we recognize that these issues will arise because of individuals' expertise and their visibility in their fields.

DR. WILLARD: Many of us are either engaged in or are contemplating research collaborations with private-sector companies. Does that constitute a financial personal interest?

MS. BECKERMAN-JAFFE: If you're a PI on a grant and the grant is a collaboration, yes, you might have. I would list that as a position on your 450, and then that may be considered a financial interest. But that may not mean anything. So you have a financial interest with Merck or with a private concern, but you're not working on any specific party matters that are affecting Merck, so that will not affect you one way or another.

DR. WILLARD: If one were not yet a PI but involved in contemplating pre-discussions with a diagnostic company, and clearly we're discussing issues that are presumably relevant to what may be a small number of diagnostic companies with regard to specific technologies --

MS. BECKERMAN-JAFFE: Unless you're negotiating for employment, and I don't think being a PI constitutes employment, you don't have a financial interest yet. Once you get that grant, then somebody could argue that you're doing something differently here on the Committee because you want to help your collaborator. So it may just be a matter of a recusal. But as Dr. McCabe said, you're expected to have conflicts. That's why you're here, because you're experts in the field and we have you talking on that field, and people typically invest in the things they know about. You know about diagnostic imaging, so you're going to invest in the field. We expect conflicts. That's not unusual, that's not bad. We just need to manage it, that's all.

DR. McCABE: As with all conflicts of interest, it's perception also. So if you are about to become a PI on an industry-funded grant, even if you aren't yet the PI, it might be safest to recuse yourself because there might be a perception if, a month from now, you're identified as having been in negotiations with that group, you might be identified, and it's just safer to declare the conflict of interest.

You did actually get the forms that Holli is talking about. They're in your packets. Not all of you got them, but some of you did. I think it's important because as I was looking over mine, there was one that was inadvertently left off, so I added it by hand and will give it to Sarah, and it's something fairly significant, like I'm the past president of the American College of Medical Genetics at this point in time but just forgot to put it down when I was filling out the form. So it's good to take a look at these and to then, if you have any changes, get them back to Sarah.

MS. BECKERMAN-JAFFE: Three additional quick points.

Just like lobbying, political activity, you are restricted with respect to political activity only when you're here as a committee member. Afterwards, that's the difference. We're called FTEs, full-time equivalents. You're SGEs, special government employees. Most of these rules are the same for SGEs and FTEs, except for political activity and lobbying. You are only restricted when you're actually sitting as a committee member, whereas it's the hatched -- we say I'm hatched all the time. You're only hatched when you're sitting here.

Speaking, teaching, writing documents. If it's teaching, speaking and writing that relates to your official duties, somebody comes and asks you to talk about it, it's probably fine. You just can't get paid. Generally, you can't get compensated because the argument is you've already been paid by the federal government for your federal service, so you shouldn't get paid by somebody else. As great as that was, you were paid, so that should be it. Again, you should funnel that through Sarah, let Sarah know that you have gotten an invitation to speak on this particular matter. You can accept travel reimbursement there, assuming it's within the United States, but you couldn't get an additional honorarium for speaking.

On confidential information -- and this is really for life, and I'd be surprised if this is a surprise to any of you. If it's confidential, it's confidential. Once you leave the committee, it doesn't mean that you can become Deep Throat and leak it all over the place. It's always confidential. Insider trading, it's just common sense stuff. Don't trade on your position here and use any information here, public office or private gain, that could be perceived as public office or private gain.

Any questions?

(No response.)

MS. BECKERMAN-JAFFE: That's ethics in a nutshell.

DR. McCABE: Thank you very much.

MS. BECKERMAN-JAFFE: One other thing. You are required as SGEs to have an hour of training. There's a lot of information in your book, so I'm going to assume you all go home and read it so you've all done your hour of training, okay? You do have an hour requirement annually to train, so read all that material so you've met your hour requirement.

DR. McCABE: Or maybe now about 30 minutes worth.

Well, thank you very much.

Again, we expect that there will be conflicts of interest. It's just important to declare them.

Let's take a 15-minute break. We'll resume at 11:00. We're running about 15 minutes ahead of time, but I see that our first speaker is here, so we're ready to go at 11:00. Thank you.

(Recess.)

DR. McCABE: The purpose of these informational briefings is really to give all of the members of the committee the same background and so that we start our discussion with a common understanding of the issues. Bio sketches are provided for the presenters under Tab 2. I'm not going to give extensive information on each of them, but you should read about them. You'll be quite impressed with their bios.

Our first presentation is existing genetic technologies and their integration into health care and public health. That will be presented by Dr. Wylie Burke, who is Chair of the Department of Medical History and Ethics at the University of Washington in Seattle, and also served as a member of the Secretary's Advisory Committee on Genetic Testing.

DR. BURKE: Thanks very much. I really appreciate the opportunity to be here at your opening meeting. My goal is going to be to take a quick tour through the use of genetics currently in health care and in public health.

I want to start by pointing out that as a general scheme, there are two ways to use genetics to get to health benefit. One is to use genetic testing to identify people that have specific needs, make a genetic diagnosis, identify genetic susceptibility, and ultimately create the opportunity to tailor care to a person based on their genetics.

The other is to develop new treatments based on genetic knowledge; that is, to use the tools of genetics and genomics to understand disease biology and thereby increase our ability to treat a variety of health conditions. These two paths are not mutually exclusive and both might apply in a particular condition, but they are two different pathways with two different implications. Most of what we have now is the use of genetic information.

I seem to be missing a slide. I'm sorry. Let me talk, then, about one of the most dramatic examples of the use of genetic susceptibility to identify people with special needs, and this also refers to the most prevalent use of genetic information in a public health setting, and that is the process of newborn screening using phenylketonuria as an example.

One of the fruits of understanding some genetic diseases -- that is, diseases that are predominantly determined by the genetics of an individual -- was to identify some children who would benefit by the initiation of early treatment, and that led in the '60s to the development of a program of newborn screening staring with phenylketonuria, and we now have an increasing number of conditions being considered for this genetic testing model.

The basic idea is that we identify the individuals very early in life and are able then to provide a specific treatment, in the case of phenylketonuria a phenylalanine-poor diet because these individuals on a genetic basis can't handle much phenylalanine in their diet, and the dramatic benefit of preventing mental retardation. This reflects the potential opportunities that we have at one end of the spectrum of the contribution of genetics to disease; that is, that end of the spectrum where genetics is the predominant contributor.

I show the full spectrum here because increasingly genomics is going to give us tools to move down the pathway and identify genetic factors that contribute to common diseases as one of multiple factors, potentially multiple genetic and multiple environmental factors. That's where diabetes, heart disease, cancer, and most common diseases reside.

Sticking with the genetic end of the spectrum for the moment, we have other examples that are comparable to PKU but where genetic testing is used not in a newborn screening program but in the course of clinical care, and a very clear example is provided by the genetic condition called multiple endocrine neoplasia type 2, or MEN2. This is a condition in which people inherit a very high predisposition to develop medullary thyroid cancer, a particular form of thyroid cancer that is difficult to treat. We now know that this particular condition is inherited as what we call an autosomal dominant

condition, which means the mutation, the gene variant that predisposes to MEN2, can be passed on from parent to child. Each child has a 50 percent chance of inheriting it.

We also fortunately know what gene is involved. So MEN2 is due to mutations in the RET gene. So we have a family like the one shown here, where the grandfather died of medullary thyroid cancer, his son was diagnosed with medullary thyroid cancer, and because genetic testing was available, it was done and we now know him to be RET-mutation-positive, and this creates a new prevention opportunity. We can identify his children, all of whom are at 50 percent risk, determine which of them, if any, inherited the RET mutation, and current standard of practice for this condition would be to offer a prophylactic thyroidectomy in early childhood, thus preventing thyroid cancer.

Now, as we develop this potential for predicting genetic disease risk, we also have a conundrum that I think is with us and will stay with us for some time to come, and that is the conundrum of identifying a person with genetic risk but not having anything to do about it. So with MEN2, we have a clear action we can take in order to prevent disease. With Huntington's disease, we have exactly the same kind of genetic situation, autosomal dominant condition; if a parent has it, children have a 50 percent chance of inheriting it. But Huntington's disease is a neurological degenerative disease that typically starts in the early 40s. There's a progression over a 15- to 20-year period of loss of control over muscle action, involuntary muscle action, and also loss of cognitive ability, progressive dementia.

So it's a very tragic disease. We have the genetic test. We can identify in early adulthood whether or not a person has inherited the Huntington gene, and if a person has a normal lifespan, we can predict a virtually 100 percent chance that they will at some point develop Huntington's disease. We have no treatment. What we see in the clinical setting is that this kind of information is of interest to some individuals but not most. So the majority of people at Huntington's disease risk do not choose to pursue this information.

Now, if you think about the distinction between MEN2 and Huntington's disease, an extremely important one, the same kind of genetic prediction is possible but we have treatment in the one case and not in the other. There is a tradition in medical genetics practice that becomes very clear, and that is the tradition of non-directive counseling, which applies very forcefully in the case of Huntington's disease. The choice to be tested is ultimately the choice of the patient. It is a very personal decision. It is not a medical decision in the way that MEN2 testing is, and we recommend MEN2 testing because of what we can do for benefit. With Huntington's disease, we provide the opportunity and let individuals choose whether they want to pursue that.

The same concept of non-directive counseling applies when we use genetic testing for reproductive decision-making. So this is a family with Duchenne muscular dystrophy. The arrow points to a young boy who has recently been diagnosed to have Duchenne muscular dystrophy. He presented with difficulties walking around the age of 2. The pattern was consistent with muscular dystrophy, and a genetic test can provide a firm confirmation if the genetic test reveals a deletion in the Duchenne muscular dystrophy gene.

It turns out that his mother's brother was also affected. We can be certain that his mother is a carrier of this condition, but what we don't know is whether or not his sister is a carrier. At this point, as a child, that's not a burning issue, but as she becomes an adult it may be very important for her to know whether or not she is a carrier for Duchenne muscular dystrophy, and she might make different decisions about whether or not to have children, whether or not to have prenatal diagnosis if she does decide to have children based on her knowledge about her carrier status.

The same test for Duchenne muscular dystrophy gene that's used diagnostically in her brother would be used to determine whether or not she's a carrier, but the implications of testing are strikingly different. In the one case, it's a pretty straightforward use of a test for diagnosis as we do in all sorts of branches of medicine. In the other, it's like the Huntington's disease question, a highly personal matter whether or not

to pursue the information and whether or not to use the information in reproductive decision-making.

We now have currently within the past year an example that will be affecting or will come up as a matter of discussion for most pregnant women, and that is testing for the cystic fibrosis carrier state. Cystic fibrosis is an autosomal recessive condition, so this is a condition where parents are healthy but can be carriers of the condition. If two carriers marry, each of their children has a 25 percent chance of inheriting the cystic fibrosis gene variant from each parent, and if they get the CF variant from both parents they will have cystic fibrosis.

It's been recommended by an NIH consensus conference and subsequently by the American College of Obstetrics and Gynecology that all pregnant women be offered this carrier test, and clearly it is important for them to understand, as they consider whether or not to do testing, what the options are. The options are going to be reproductive decision-making options and personal decisions that some people may wish to make and others may simply not wish to pursue.

One of the important implications of CF carrier testing as we now have it is shown on this slide. If two parents are tested and both are found to be carriers for cystic fibrosis, as I mentioned, there's a 25 percent chance with each pregnancy that they'll have a child with cystic fibrosis. If one parent tests positive and the other tests negative, the risk to have a child with cystic fibrosis is very low, by my calculations well under 1 percent, but not zero, and that reflects a very important property of genetic tests, which is they are rarely 100 percent sensitive.

There are actually 900-plus mutations in the CF gene. Current recommendations are to start with the 25-mutation panel. We would probably follow up with additional testing in the apparently unaffected parent in this kind of situation, but there are good reasons to start with a 25-mutation panel, and bottom line, it is impractical to test for all 900, and there may yet be more CF mutations that we haven't yet identified.

The American College of Medical Genetics has recently developed a guideline on CF carrier testing, and they have a number of things to say about the recommended testing strategy. The first, of course, is that they highly recommend pre-conception screening whenever possible. This increases people's options to know about their carrier status before they become pregnant, though they recognize that the reality is that this usually will not happen. They recommend that pre-test education be provided, and actually the American College of Obstetrics and Gynecology has produced a very nice brochure that goes through a variety of details and starts with the important message, "The Choice is Yours," as the title of the brochure, and this includes understanding that this test creates opportunities for reproductive decision-making, including the opportunity for prenatal diagnosis and a potential decision to terminate a pregnancy for parents who choose that option if testing begins in pregnancy.

The American College of Medical Genetics has put great thought into their recommendation and recommends a screening panel of 25 mutations to start with what they call "reflex tests," additional tests to clarify the initial positive result if there is a positive result on that screening panel. This particular issue was at the heart of a news flurry about a month ago, and it really reflects the fact that there are certain variants in the CF gene that are important only if other mutations are present but in and of themselves not terribly important. If you test for too many mutations to begin with, you may get a finding of a mutation that, by itself, is not clinically significant and may generate a whole lot of confusion about what you should do.

Again, I think this reflects the complexity of genetic test information, one that is very characteristic, I would say, of genetic tests generally. Then the recommendations, I think, would be obvious for careful post-test counseling if test results are positive for both or even just one parent.

Let me now turn to another genetic disease and talk about genomics beginning to give us new opportunities for therapy. Here is another X-linked recessive disease that is following exactly the same inheritance pattern as Duchenne muscular dystrophy. The mom's a carrier. Her son is affected. Her

daughter may be a carrier. There are the same kinds of carrier testing issues that arise with Duchenne muscular dystrophy.

But with hemophilia, we've been studying this, we the scientific world, since the mid-century and have had very important breakthroughs in understanding this disease that illustrate how useful it is to understand disease biology. First of all, in 1952 there was a differentiation of Factor VIII from Factor IX, and it turns out that those factors, which are factors in blood clotting, represent or are related to two forms of hemophilia. So the classic hemophilia is a deficiency of Factor VIII, and people have bleeding problems because they don't have Factor VIII and don't clot normally. Factor IX produces a separate, different kind of hemophilia.

But once we knew that about hemophilia, we could begin to think about the logical thing, which is factor replacement. If you know what factor a person is missing, you can potentially replace that factor. Starting in the 1950s, there was a lot of experimentation with plasma product supplementation and initial, at least marginal, successes that caused people to keep going forward. In 1965, there was a breakthrough. The technique of cryoprecipitate, which was basically a method of precipitating large amounts of serum in order to concentrate large amounts of factor, resulted in the ability to treat people with hemophilia in a meaningful fashion. Enough Factor VIII could be given that people's bleeding problems could truly be treated.

Now, this needed to be done on a repeated basis. Gathering enough serum in order to create the cryoprecipitate of Factor VIII that was needed was a significant task, but this was a dramatic breakthrough. If you read memoirs of families, this was a major turning point, an important and wonderful turning point in the history of hemophilia. But it did have unintended consequences, and I think it's important for us to think about technological development in the context of this story.

The unintended consequence here is the story of hemophilia and AIDS. The first case was reported in the early '80s. Most exposures occurred between 1983 and 1986 because, starting in 1986, methods to treat blood products in order to minimize, to basically kill HIV virus, were initiated at that point, and the blood supply gradually improved in safety. But as a result of that period of time, a large cohort of people with hemophilia became HIV infected. About 40 percent of hemophiliacs receiving blood products, about 80 percent of those with severe disease, developed AIDS. The consequences of that are still being felt amongst the hemophilia community and amongst families in which people had hemophilia.

Now, genomics has led the way to moving beyond that. So we now have recombinant Factor VIII, Factor VIII made in vitro with DNA recombinant techniques. It's normal, pure Factor VIII. It's a much safer way to make Factor VIII than to concentrate it down from serum. In fact, now methods for making Factor VIII that require no serum at all are being developed. This is now the standard of care in the United States, so this represents a way in which genomics has provided a new and much better treatment and solved a problem.

There are some issues. The cost is $72,000 or more per year. Even in this country with good health insurance, people with hemophilia can run out of their health benefits paying for treatment. It's not an option in most of the world, so 80 percent of hemophiliacs do not benefit from this therapy.

What's coming next? This is obviously not an existing therapy but it's one in clinical trials, so I wanted to mention it, gene therapy for hemophilia. Here's a study that was reported in 2001 in the New England Journal, and this was one in which fibroblasts taken from the skin are used as the method for implanting a normal gene to produce Factor VIII and then implanting those cells back in and actually having normal production of Factor VIII -- again, still under study. One might hope that this is ultimately going to be the solution because even with recombinant Factor VIII, you need repeated treatments. What we really hope, of course, is that this will ultimately be an effective and safe and even relatively inexpensive treatment, although I think getting to that point is way in the future, but there's hope.

Let me return to the spectrum of genetic contribution to disease and now talk about the other important new wave in the use of genetic information in clinical settings, and that is the use of genetic information to predict risk for common disease. So if we move to the middle of this spectrum, we know that genetic factors are tremendously important in the development of cancer, heart disease, and a variety of other common diseases, and increasingly we're able to find gene variants in many diseases that identify people at increased risk. The question is how do we use that information effectively in clinical care.

I want to talk about the challenge involved just briefly, using the example of venous thrombosis or blood clots, a very common medical problem. There are a variety of gene variants. I've listed only a few, including the two most common, on this slide. Factor V Leiden occurs in 1 to 5 percent of the population. A variant of prothrombin occurs in 1 to 2 percent of the population. There are a variety of much rarer genetic factors that contribute to increased risk for blood clots.

There are a variety of potential interventions for people who have an increased risk of venous thrombosis. One might use anticoagulant treatment, either use it more long-term after a blood clot than with the average patient, use it episodically at times when people are at particularly increased risk -- surgery, pregnancy -- use it preventively in people who haven't had a clot yet but you know they have a genetic factor, instruct people also in the avoidance of other risk factors where that's possible. In particular, hormones, oral contraceptives, and hormone treatment therapy might best be avoided in someone who has a predisposition.

So you can see, although this isn't as dramatic as the MEN2 story, there is a very comparable picture here of the possibility of identifying people at risk and then doing something to help them, to minimize the risk. Now, the problem is that approaching blood clots with anticoagulation therapy, you take on a major risk of therapy. So current estimates are that people on anticoagulation therapy have a risk of major bleeding events of about 3 percent per year, and 20 percent of those major bleeding events may be fatal. So we are talking about non-trivial risks.

Now, there might be other ways to approach this -- reduce the anticoagulation. Then we have to see if we get the same effect. The point is we've got a very major risk with the therapy, and we need to make sure that we're really helping people if we use these therapies differently in someone at increased risk.

So when we're talking about predictive genetic testing for common diseases, in order to assure benefit, we're going to have to ask rigorously a series of questions. What test? That is, exactly who is it that we want to identify? What treatment are we then going to apply? At what level of risk is that treatment reasonable to apply?

One of the interesting things about venous thrombosis risk is that the people that are at highest risk are not the people with a single genetic factor but the people with multiple genetic factors. So, for example, here's a study of relatives of people with blood clots. There were people with blood clots who were found to have a genetic predisposition, and their relatives were studied. The initial patients had either prothrombin variant or Factor V Leiden.

What this study did was estimate the relative risk of blood clot in their relatives, calling the relative risk 1, or the neutral risk for those relatives who had no genetic factor. There was an increased risk if a relative had Factor V Leiden. There was an increased risk if a relative had prothrombin of about two-fold; less than that, three-fold, for Factor V Leiden. But the relatives that really had the big risk were the relatives that had both Factor V Leiden and prothrombin variant. They had a greater than six-fold risk. Maybe those are the ones who are going to benefit from an aggressive preventive therapy with anticoagulation therapy.

Similarly, Factor V Leiden, as I mentioned, has a prevalence of about 1 to 5 percent in the general population. That's people who are heterozygous for Factor V Leiden, have one copy. Their relative risk of blood clots compared to the average is somewhere in the range of three- to seven-fold. But if you're

homozygous, and that's not a very common state, but if you're homozygous your risk is 80-fold. So I think it's quite clear that we would like to find people who are homozygous for Factor V Leiden and treat them with anticoagulation, because even the risks of anticoagulation are outweighed by the very high risk of clots. It's not as clear that we want to do that with people who are heterozygous.

Because there are a variety of unintended harms, or potential I should say for unintended harms for genetic information, there's been a lot of talk about stigmatization and discrimination, but I would argue also that unnecessary or unproven therapy would also be a very significant risk of identifying someone at risk without a clear path for what to do with that risk.

I want to finish this discussion of risk with a brief mention of Apo E4 testing, which is a means to predict Alzheimer's disease, just to make the point that we have, in the genetic risk factor category, an entity that's comparable to the Huntington's disease testing for high risk. That is, we have a factor that is Apo E, and specifically measurement for Apo E4, a variant of the Apo lipoprotein E gene that identifies people at an increased risk of Alzheimer's disease. With two copies, your risk is five times higher, and your Alzheimer's disease, if it occurs, occurs earlier, 10 years earlier than average. With one copy of Apo E, you have a more moderate increased risk. But there is no treatment available.

Actually, three separate expert panels have come to the conclusion that with this indeterminate raised risk but not certainty about risk and the lack of treatment, this is really not a wise predictive test to be using.

So what we can say is that there are a range of ethical concerns in predictive genetic testing that I think should influence how we approach clinical practice guidelines. I've categorized tests into four boxes for the purpose of discussion. If you've got a highly predictive test and you have an effective treatment -- the PKU example, the MEN2 example -- what you really want to do is assure access. We really do want to recommend testing and we want to make sure people have testing.

If you have a highly predictive test but there is no specific treatment -- the Huntington's disease example -- there we're very concerned with adequate counseling, protecting individual autonomy, making sure that people make their own decisions based on full knowledge and their own preferences.

If you have a test that is somewhat predictive but not absolutely predictive and yet there is a treatment, and I would argue the Factor V Leiden example falls into that category, what we have is something we have commonly in medicine, which is a careful weighing of risks and benefits and coming to a careful judgment about who it is we want to identify and what treatment we want to give them, and I think that's going to be a very important topic in clinical practice guideline development over the next 10 and 20 years.

If you've got a low predictive test and no treatment, I think it's hard to justify the test, and we should identify and be clear about those tests so that we don't use them. I should say I put Apo E4 testing in that category. The minute we've got a treatment, it changes. So the issue with Apo E4 in that category is that currently we don't have a treatment to avoid risk.

I'm just going to talk very briefly about what's coming down the pike. Pharmacogenetic testing is clearly coming down the pike, and I've got an example here. This is where we identify gene variants that predict people to have a higher risk of adverse consequences to a therapy, or possibly we may have genetic tests to predict people who are responders or non-responders. CYP2C9 has two variants, the 2 and the 3 variant, that predict people who are going to have an increased risk of anticoagulation. I should say this observation does add complexity to the Factor V Leiden example, because it's possible that you're more interested in finding people with Factor V Leiden and treating them if they're not CYP29*2*3, whereas if they are CYP29*2*3, they're going to have increased risk for anticoagulation, makes you a little more cautious.

So that gives us a window, I think, into genetic profiling and its potential value in sorting out what is the

best action for individual patients.

Clearly, we're going to see a lot of tests, there are already a lot of potential tests under study, and we're going to see a lot of potential use of this kind of information in clinical practice. Again, we'll have to think very carefully about risks and benefits.

I have a couple of examples just to say that we know that genome-based therapies are coming. There are two examples that I found. Others are in study. This is going to be the next wave. So Gleevec has been a major drug developer for the treatment particularly of chronic myelogenous leukemia. It looks like it will now have action and value for other cancers as well.

I just want to point out this is a selective inhibitor of a particular enzyme, a particular tyrosine kinase. The point here is that the genetic research was crucial in identifying this specific kinase, starting with patients who had a particular chromosomal abnormality, and then subsequently working with mouse models of disease to clarify the importance of this particular enzyme and therefore the key value of finding a drug that would inhibit this enzyme.

I think this is at least one model of how genomic therapies will help us, genome research will help us with new therapies.

The other is just a fascinating example that I discovered recently, and that is that there is a novel genetic therapy for a particular eye infection, a cytomegalovirus infection of the eye which is a particularly important complication in HIV infection. In this particular therapy, an antisense oligonucleotide, so basically a transcript, an RNA transcript inhibits the messenger RNA that is a crucial piece of the production of an essential protein for this virus. This virus makes a messenger RNA, that RNA codes for an essential protein, and this particular nucleotide fragment binds to the messenger RNA and blocks it and thereby blocks the production of protein.

So this is a very interesting way, I think, in which an understanding of genomics leads to a novel therapy. I'm sure we're going to hear lots more about this kind of trend as time goes on.

I'm just going to finish by saying I think we have three central questions in the era of genomic health care. The first and most unique to genetics is the question of when does the harm of a genetic label outweigh its benefit? This is going to be an important question with all uses of genetic information, particularly for prediction.

Then the second set of questions is who decides when new technologies have sufficient safety and efficacy for use, and on what basis? What are the criteria for saying we're now ready to use a genetic test or a genome-based therapy? These are not questions that are different from other health care technology, but we certainly will need the right kind of expertise at the table as those decisions are made.

Then finally, how do we ensure fair access as we develop those therapies?

Thank you.

DR. McCABE: Thank you.

(Applause.)

DR. McCABE: We'll have discussion of this, along with the next paper, at the end of this session.

Our next talk is emerging genetic technologies and their medical and public health applications by Dr. Nicholas Dracopoli, who is Vice President of Clinical Discovery Technology, Pharmaceutical Research Institute, Bristol-Myers Squibb.

DR. DRACOPOLI: Thank you.

Firstly, I'd like to thank the Committee for the invitation to present. It's an honor to be here today and to see many old colleagues on the Committee and in some of the surrounding groups.

What I'd like to do today is really to focus my talk on the perspective, at least from a pharmaceutical company, on the development and impact of pharmacogenomic methods and applications and the profound impact that those are starting to have and I think will progressively have over a period of time.

The questions I'm really going to focus on, and this is really a technology-driven approach, is what genetic technologies are appearing on the horizon that we're using in the discovery areas right now, and how these are going to be transitioned from a discovery environment into a clinical lab testing environment, and to just discuss some of the issues that are going to be raised by the development and integration of these technologies for the delivery of therapeutics. Then also, finally, to just have some suggestions on the need for public policies that need to be in place to facilitate the development of pharmacogenomic approaches for drug development.

Firstly, a definition. What is pharmacogenomics? We view it as a very broad definition, but it's the use of markers of biological variation, and that can be at really any level -- DNA, RNA, or a protein -- to predict a patient response to pharmaceuticals, and that can both be to predict drug efficacy as well as also predicting adverse events. Secondly, also molecular pathology in terms of more effective definition of disease so that we can identify disease subtypes that can then be treated more effectively and uniformly with the knowledge of that underlying disease heterogeneity.

In a sort of cartoon for pharmacogenomics, the idea is that you can basically pre-identify individuals before the selection of therapy. So you can reduce the risk of adverse events, as well as increasing the proportion of patients who would benefit from a therapy. So the profiling method -- here we describe it as a microarray, but it could be any profiling method, whether it's proteomics or even high-field nuclear magnetic resonance for looking at metabolites, or SNP gene testing -- is to take a heterogeneous group of patients who in this cartoon have a 60 percent benefit of therapy, pre-screen them into two groups, and then you can enrich one group who you would treat with a higher efficacy, and similarly identify a group of patients who are least likely to respond who you could then select for alternative therapy.

Now, the need for this really varies according to the type of indication that you're trying to treat. For example, if there isn't a simple means of measuring the response of your drug before you treat a patient, then this test could be really useful. So in areas of oncology, for example, understanding the particular subtype of a tumor and identifying the individuals most likely to respond is something we have no way of doing right now. We treat a patient and we see their response, and then we put them onto a second round of different therapy or a third line of therapy, depending on how they progress with the disease.

But if you're looking at, say, for example, drugs for reducing lipid, drugs for reducing blood pressure, we have a fairly immediate output for whether the drug is working or not working. So you could argue that it's much less important to develop tests in those areas where there is an immediate output.

So why do we need pharmacogenomics? Well, the bottom line is that in many of our therapeutic areas, the efficacy of our drugs is very low. My background is primarily in the oncology area where this is particularly the case. We're seeing now, for example, at the recent ASCO meeting huge excitement about new drugs for colorectal cancer, which realistically have a 10, 15, maybe 20 percent response rate and are extending life only a matter of months, and these incremental changes, while huge, are sufficient to have headlines in major papers across the world.

So I think there really is a huge area of opportunity for increasing the efficacy of our compounds, and I think the underlying scientific reality is that these diseases are highly heterogeneous and it's very unlikely that individual therapeutics are going to broadly impact all types of a particular cancer. So we need to be

able to identify the molecular pathology underlying these diseases in order to increase the efficacy of our compounds.

To look at cancer for a moment in particular, we're taking a sort of technological perspective. We need to look at two types of underlying causes of variation in response to a drug. These are both driven through the host or these are the inherited factors that essentially are determining the individual's response to the drug, or pharmacokinetic differences, and then also looking at the tumor, looking at the genetic changes that are occurring within the unstable tumor to look for predictive markers and patterns through profiling approaches that then can predict individual response.

These two different methods require totally different technological approaches. So, for example, looking at germline variants, as was mentioned earlier, looking at things like the P450 genes, they are known genetic variants and can be tested for by a relatively simple genotyping test for single nucleotide polymorphisms, and we're developing public databases that are basically helping us to understand how these genetic variants impact an individual's response to the drug and the pharmacokinetic differences, and we now have examples in the clinic where drugs are being dosed based upon genotyping or drug metabolism or drug transport genes. Mercaptopurine treatment for childhood leukemia is one good example.

I think one of the areas of really promising research that we've seen over the last couple of years has been in profiling approaches of tumors where we're now starting to correlate individual gene expression profiles in tumors to drug outcome. So the hope is that we can use these approaches, both with broad-based expression profiling methods as well as analysis of known mutations, to class groups of otherwise homogeneous cancer patients into multiple classes and then ask if those individual classes have different responses to different therapeutics. I think this is an area that we're now starting to see and will soon, I think, have a significant impact on the clinic.

To look at the range of technologies that we're looking at, they really fall into three major categories. This is, again, looking at protein or DNA or RNA. I think the important thing in looking at these technologies is from a pragmatic and cost-driven perspective. The RNA-based approach or transcriptional profiling is still the only approach that allows us essentially to look at all of the known messages, or nearly all of the known messages, in any particular sample.

If we look at proteomic-based screening of plasma, then we can look at complex mixes of up to 100,000 proteins. But a single mass spectrometry experiment can only resolve 2,000, maybe 3,000 complex protein mixes. So in order to be able to scan a proteome, we have to look at a large number of experiments essentially driven by liquid chromatography or other affinity-based methods to break up the proteome into fragments and then look at it in groups of 2,000, 3,000, 4,000 proteins at a time. So here, these experiments are often hypothesis driven, and we have to select particular types of protein, particular targets to look at in these experiments.

In the genotyping world, we now, through one of the great benefits -- one of the immediate benefits of the Genome Project has been the discovery of massive numbers of SNPs. There are now more than 2 million SNPs, I think, in the public domain.

DR. LANDER: Four million.

DR. DRACOPOLI: Four million. Sorry. I don't want to underestimate.

DR. LANDER: That was last week.

DR. DRACOPOLI: Last week, right. There will be 6 million next week.

So more than 4 million SNPs in the public domain. Here, the issue is not so much the discovery and

knowledge of the SNPs; it's the ability to type them. The cost to type them is going down exponentially. But still, in order to type that many numbers of SNPs, we have to take approaches towards pooling DNA from cases and controls and comparing them. But the cost of doing massive genome-wide screening at the level of resolution that we need to do for effective association studies is still too high, and it's certainly too high to be applied to individual patients.

So I think the transcriptional profiling approach, in essence, is still the only approach we can look at that looks at basically all, or nearly all, of the known messages in a particular sample.

In order to be able to profile things effectively and actually have an interpretable result, we have to assume that the patterns that you're seeing within biological samples are not random and that there are a relatively limited number of patterns that you can find. So in this sense, this is a diagram that's sort of known as the circuit diagram for cancer, and I think the key thing why I often use this slide is that little yellow box in the middle of the nucleus there, which may be a little hard to read. It says "Changes in Gene Expression."

In essence, what this diagram is implying is that whatever changes are occurring in a tumor cell, whether it's changes in signal transduction, changes in regulation of apoptosis, changes in the regulation of the cell cycle, ultimately they will have at the end of that pathway an impact, and there are a relatively small number of pathways, and those changes, where they occur, whether it's in Ras signalling, whether it's in the cell cycle, control through mutations in the cell cycle or in other pathways there, there will be a limited number of events and pathways that are changed, and when they're changed, they will give us a consistent pattern that we can detect in cells that are taken from patients at the time of the biopsy.

So the profiling approach -- and this is true whether it's SNPs or DNA or a protein-based approach, even a metabolite screening-based approach -- is essentially to look for patterns. It's a massive pattern recognition problem. So in this cartoon you basically have grouped two sets of samples which are sensitive or resistant to a drug in this case, but you could use any other biological endpoint in which you're interested, and then in this case basically it's genes, but it could be proteins or SNPs. So in essence here, you essentially have a random pattern of expression, and if you then imagine bringing in another tumor or another column, there's nothing predictive. There's no pattern that's suggestive of sensitivity or resistance. So, in essence, there's no marker.

So what we do in a profiling experiment is instead of having 12 lines here, you've got 30,000 lines if you're looking at an RNA profiling experiment, or thousands or tens of thousands of SNPs. You can imagine looking at that. You're essentially looking for a pattern where you then, through mining the information, look for sets of genes whose expression is most correlated to the particular biological endpoint you're looking for. So here in this example, you can see that there's a group of genes which are typically overexpressed in the sensitive cells and underexpressed in the resistant, and vice-versa above.

So you can imagine that if you now sample another tumor, line it up against here, you can predict does it line up with the left or does it line up with the right. If you do this often enough and you have enough samples, you can eventually get to a point where you have some statistical predictability based on these types of analyses. Clearly, there are numerous examples in the literature now where it is clearly showing that the fate of a tumor seems to be, in essence, hard-wired relatively early in the tumor evolution, and at the time of biopsy, at the time the patient presents with a malignancy we can actually take these cells, analyze them and get this sort of data that will help us really direct therapy much more effectively than we do right now.

The difficulty, in order to bring this dream to practice, is going from profiles to assays. The technologies we have available to us now are largely being driven by and developed for the discovery market. They're focused on delivery of very large numbers of markers on relatively small numbers of samples. Chips, bead-based arrays, proteomics screening are all basically focused on looking at many, many different analytes or markers on relatively small numbers of samples in terms of a discovery process. What we

need to be able to do is to convert those profiles and the markers within those profiles that give us a prediction of a clinical output to assays that can be delivered in a clear, certified clinical laboratory environment.

There are two ways that this is really happening, in essence. There is going to be the evolution of these very large chip-based approaches, discovery tools, to focused arrays that can be delivered in the clinic, and also the development of specific clinical assays that are focused not necessarily on the very large numbers of analytes but to deliver these in the clinic. This is still the major technology issue, how we take these profiles, how we take these proteomic scans, some of which have been done here at the FDA and the NCI, how can we bring those to large numbers of patients in the clinic.

In a drug discovery perspective for finding markers, we basically go through a filtration process in preclinical and Phase I, looking essentially at a full array of all expressed genes to the point where we can prospectively identify sets of markers in our Phase II studies. The goal is that when we move forward into Phase III, we can have sets of markers that can be prospectively tested in Phase III studies to determine the correlation of the marker to the outcome. The hope is that in the end you will have a relatively small number of markers that can be converted into clinical assays. The numbers of markers that we need, the numbers of analytes that we need to test are going to be really critical in the choice of technology that's going to be used to deliver this.

Currently, if you look for example at Herceptin or Genentech's Susceptin, there you are measuring the expression of the HER2 protein in order to decide whether to basically add Herceptin to the standard chemotherapy regime you would use for those breast cancers. You're measuring a single analyte. In essence, you're measuring the status of the drug target. But now with these profiling methods, we are developing 50 maybe -- some reports in the New England Journal of Medicine have said you need as many as 70 markers to have the full sensitivity. Others have said many smaller numbers.

The difficulty is how do we deliver these assays to standard immunohistochemistry-based approaches on tissue sections, and how do we basically bring these quantitative measures across multi analytes into practical application?

To give you one example from our own labs, these are in vitro prediction results, but this is drug response to Taxol. You can see two groups. The one on the left -- I think I'm getting this right -- is responsive, and the one on the right is resistant. You can see very, very different clearly predictive patterns that we can use, and then actually a quantitative measure of the expression. So if the genes on the left have relatively low expression, the genes on the right are highly expressed. It gives you a strong prediction of the likely response of those cells, and vice-versa for the opposite response. These examples now are becoming more and more common throughout the literature and being able to use this information.

Another way of using this information that doesn't involve bringing forward a test for efficacy or adverse events to the clinic is use of this data actually in the drug development process for decisions made during development. One of the key decisions is actually defining dose. Typically, an oncology drug is developed so that the dose that you move into a Phase II study is, in essence, the maximum tolerated dose. We usually don't know the biological effect of that dose or of lower doses at the time we take that drug into Phase II in the clinic.

The hope is by using these profiling approaches that we can identify markers that have a dose-dependent change relating to gene expression. They tell us, then, if we can analyze biopsy material, if the drug is hitting the target, and what level of drug you need to hit the target. If we can then basically correlate the impact on the target in surrogate tissues to efficacy results, we can then maybe bring forward drugs at a much lower dose than the maximum tolerated dose but a dose that is defined by biological efficacy rather than the adverse event or the toxicity profile. That, hopefully, given that many compounds fail because of these excessive toxicities, this may be a way that we can enrich the numbers of compounds we bring

forward out of the early clinical experiments.

So the status of diagnostic testing right now is the paradigm of the Herceptin model, where you have a single-analyte test. The diagnostic test is actually the status of the drug target itself. It's used for a single indication and uses existing paraffin formalin-fixed immunohistochemistry technology. The technology is going to evolve to microarray or multi-analyte-based tests where the diagnostic test is not necessarily the status of the drug target but it could include it. So, for example, imagine the EGF receptor, anti-EGF receptor compounds. Even though there's no good correlation, the EGF receptor expression and drug response, understanding what's happening in that pathway may be key to predicting the response of those compounds. These tests could potentially be used for multiple indications, but they will require new diagnostic technologies and the routine preservation of RNA and nucleic acids, which is not standard clinical practice.

This will eventually lead to a reclassification of disease. It won't replace what we do now. Currently, at least in oncology, we classify disease by the tissue of origin. It's a lung cancer with a certain stage and grade, and then we treat based on the stage and grade of that disease. Here we will add on to that standard staging and grading molecular profiling information. It can be specific mutations of known oncogenes or known tumor suppressor genes. It can also be profiles, which will basically group patients into different classes. So we will build molecular pathology on top of the existing clinical and pathological information with these diseases.

So to specifically answer those four questions that were addressed at the beginning, what are the genetic technologies for health care and public health that are on the horizon? I think clearly we need to look at the biological paradigm of going from DNA to protein, and I think now adding metabolite analysis in there. I apologize to Eric for underestimating the number of SNPs, but that changes constantly.

The genotyping tools that are available --

DR. LANDER: You overestimated the number of genes.

(Laughter.)

DR. DRACOPOLI: Okay.

DR. LANDER: That only emphasizes that it's a moving target.

DR. DRACOPOLI: It's a moving target. But I'm within orders of magnitude, except for the SNPs, where I'm out by a factor of 2.

So the now 4 million known SNPs, the technology really has to evolve in the discovery labs to be able to screen subsets of those to the level that we are able to do effective association studies and then identify subsets of those that have clinical impact and clinical predictive power that can then be delivered in a different platform. The transcriptional profiling approach has now become very mature. It's widely used, it's highly standardized, highly reproducible, and we're seeing significant approaches to developing subset tools using this approach for specific clinical answers.

Again, for proteomics, we can look at complex protein mixtures, but we still cannot look at them in a universal way. They have to be subdivided.

Then finally, I thought I'd mention RNA interference as a new target that will eventually, I suspect, have clinical applications. But it was an enormously important tool for identifying and validating drug targets, but of longer-term impact.

What is the impact of these technologies on health care and accessibility and affordability? I think

clearly that probably the most important thing is better definition of disease causation, which will lead to better therapeutics. We've already seen that in some cases. Gleevec was mentioned earlier. I think that's a wonderful example of basically understanding a type of leukemia that has a single type of mutation that's causative in the majority of those cases. Here there was a targeted therapeutic approach, and we're going to see more and more of that as we understand the mutations and pathologies underlying different diseases and the evolution of targeted therapeutics.

But targeted therapeutics implies that we have to know what the target is. So those are going to evolve with specific tests that we have to be able to bring forward in the market.

The molecular definition is easy. It's going to have impact on the pharmaceutical industry and more broadly in the sense of market segmentation. This is clearly an issue, but I suspect it's an issue that is rather overplayed.

The industry already sells drugs into a market that is already medically segmented. We sell antihypertensives, antilipids basically to all comers who have a high lipid profile, high blood pressure. They work 40, 50, 60 percent of the time. Those patients in whom those drugs don't work stop taking them after a while. In essence, by definition, the market is already segmented. It wouldn't really hurt in some sense to be able to identify up front those individuals, but I don't think that's the key issue.

The key issue is to be able to identify up front the choice of therapy where it's really going to have an impact. Failure to treat a cancer patient with the optimal therapy is first-line. It results in a more systemic, more aggressive, more drug-resistant disease. There is an enormous impact if we don't get it right the first time. There's less of an impact if we give somebody a statin whose lipid levels don't go down. The drugs are essentially broadly safe, recent withdrawal of one drug not withstanding. But there isn't a huge adverse event. You measure the response and you can see if the drug works.

But clearly in oncology, this is an enormous unmet need and can have enormous and immediate impact on treatment of cancer.

We will identify new indications. This is the other side of the coin for market segmentation. We can basically, by understanding molecular pathology and common events across different types of tumors, we will be able to develop a drug, a drug will emerge into the market as a third-line indication for a relatively rare type of tumor and then will spread to more common tumors that have similar underlying molecular pathologies. Again, Gleevec is a good example. It was brought on the market for CML but clearly has application in a relatively rare gastrointestinal stromal tumor or gist tumor, which is a totally different type of tumor, has a mutation in a different but very related tyrosine kinase gene, and you can now see how that drug is moving from the original indication to a broader indication, and will probably be able to move to other indications where having mutations and tumors driven by those particular tyrosine kinases.

So there are swings and roundabouts. You have segmented markets, but also possibilities for new indications.

Finally, increased efficacy will be enormously important. As we go forward, it's very difficult to bring drugs forward that only have a 10 or 15 percent efficacy. It's enormously easier to run clinical trials and demonstrate efficacy if you have a higher rate of efficacy. We can do smaller studies, and it will be much easier to get approval. So we hope in some sense that a real balance in increased efficacy will result in lower attrition during our compounds developments.

Finally, better diagnostics that we will create, subsets of common diseases which will be shown to be non-responsive to existing therapies. That's an issue that we have right now. Those patients are being treated with those drugs, but it will help us identify areas of unmet need.

I'm going to move on quickly because I'm running out of time.

The new issues. I think we really need regulatory guidance for pharmacogenomic development. These are coming I think from the agency, and basically I think the key issues are going to be how do we co-develop diagnostics and drugs or biologics and basically coordinate the regulation and delivery of those compounds to the market, and those tests. We're going to need new technology to deliver these tests. Discovery tools will evolve, but the key issue is going to be developing and standardizing multiple analyte tests, which is something that we don't do effectively in the clinic yet.

I think a key important issue is related to education and the resistance and fear of genetic testing. The most important thing we can do is protect privacy of genetic information, treat it like other medical information, and this is really key. We get patients refusing to join into pharmacogenomic studies because of fear of genetic information and genetic privacy, and I think that clearly is something that is of enormous importance.

Developing clear guidelines, and we're seeing those coming from the FDA later this year. I think an enormous contribution could be the public funding and support for pharmacogenomic research in terms of databases and tissue banks using appropriately anonymized and appropriate informed consent to support studies in these areas. Supported public-private consortia, the SNP consortium, the Mouse Genome Sequencing Consortium are examples. I think the ongoing International Genomics Consortium for Cancer Transcriptional Profiling is another area which is really meritorious of public support.

Again, the continued support of public education about genomic sciences.

I'm sorry if I ran over a few minutes.

DR. McCABE: Thank you very much.

(Applause.)

DR. McCABE: Could we have both of our speakers join us at the table here, please? We'll have some discussion.

Any questions from Committee members?

DR. LANDER: First, let me thank both of the speakers for tremendously lucid presentations covering a very wide range.

In terms of precedent here, we sometimes talk about how genetic information is no different than other medical information and all that, and maybe with respect to privacy all that was true. But listening to you guys, there's just no way that's true with respect to interpretation of genetic information. The privacy issues, sure. But the interpretation seems to me unlike anything that I've ever seen.

We have massive numbers of bits of data, very small numbers of studies for each particular type of application. We have zillions of combinations of all the different loci you're talking about and what to make of them, and it's not like testing a drug where you run one big clinical trial to basically answer one yes/no question, or a small number of yes/no questions.

You're asking a zillion possible questions, and you're interpreting very complex patterns, and there are many ways to interpret them. You're in a situation where, at least people who work directly in the field -- or I'll speak for myself, working directly in the field. I don't know what to believe. I read the papers and it takes me a very long time to first decide is Apo E and Alzheimer's right, and then what actually is the relative risk. These things come and go because people are attempting to find things on the cutting edge, which is very important.

We've got to be able to say things that could be wrong and might be flukes and all that. Yet, we could have a world where all this gets translated instantly into direct-to-consumer products.

Is there any precedent that we can appeal to where, in medicine, anything this complex, where you've got to worry about that the scientists can't necessarily understand it yet? Well, they understand it; they just don't know what to believe. The practitioners, I think I've got to argue that most medical doctors are going to have a hard time being able to keep up with tests on 10 to the 4th different possibilities, even the very best of them. The consumer, I think, not wishing to be in any way paternalistic and wanting everybody to have access to everything, it simply isn't realistic to expect most people to be able to evaluate the claims.

So all of that makes me ask: Can't we appeal somewhere to find that this isn't as novel as I think and this is routine and it's been solved somehow, or not?

DR. McCABE: Do either of you have a comment on that?

DR. BURKE: Well, I'll make a brief comment. I'm not sure I can address everything.

I think the kind of complexity that comes with RNA expression profiling data, for example, does seem fairly unique. It's certainly fair to say that over the past 50 or 75 years in medicine, there's been a constant and steady onslaught of new technologies and medicine has had to figure them out, and maybe that's comparable.

But I think the important message in your comment is really how important it is for us to be thoughtful about when we're still in the research phase and when we're ready to move into clinical prime time, and even not very complex examples provide really powerful lessons. What's been happening over the past year, for example, in our knowledge of estrogen therapy, there's a moral there, because for 15 or 20 years, hormone replacement therapy was being proposed to reduce heart disease, maybe even reduce Alzheimer's disease risk on the basis of some observational data, and it turns out that on both fronts estrogen may increase risk rather than decrease risk when it finally comes to the data.

So I think those lessons should be taken to heart as we think about the need for robust clinical research where there's a good clinical hypothesis but caution about when it's ready to move into clinical care.

DR. LANDER: I'm all in favor of caution, but are you saying more that we have to have a clear and sharp distinction between lots of interesting research results and some bright line as to what is accepted clinical wisdom that has had some level of proof? I'm not saying how that happens in any regulatory fashion or whatever, but that somehow, in practice, the medical community has to come around and say this has crossed the threshold where we believe this result means something, and if we don't do that, we will simply have complete chaos in terms of information.

DR. BURKE: My guess is there's never going to be a bright line. In fact, genetic testing would suggest to us that we're going to have situations where a genetic test makes a lot of sense for a small subset of families with particular unique characteristics, but isn't ready to span. So I think there's going to be an evolution. We know this and can do this, and don't know that and can't do that.

DR. LANDER: I don't mean a bright line as to whether we do or don't do. What I mean is does there have to be some way where the community comes together and attempts to agree on a consensus of what we think we know about something? Which may be that we don't know, but it still might be tremendously helpful for the general public to have a way to go to someplace, whether it's just a website or a regulation, and find out that we actually don't know diddly about X despite all these exciting headlines, or the general consensus is that this does have some predictive value despite the fact that there's nothing you can do about it.

DR. McCABE: And the problem is, too, that it may have predictive value when you're looking at a patient with symptoms. It may have a very predictive value if you're using it for population-based screening. So I think we also have to educate ourselves and the public and develop educational tools to allow people to understand those differences.

DR. DRACOPOLI: Just to get at your question, I think it's very clear that clinical trials are designed and focused on getting a yes/no answer about efficacy within certain parameters relating to safety. They are not designed, empowered, to do genomic analysis. So the sample sizes you often have are usually too small to get the level of sensitivity and specificity we would like with these assays. So I think what you will see happening is these being applied retrospectively in postmarketing, in Phase IV, that you will see things emerging onto the market without tests, some of them with maybe hints of tests.

Gleevec is a relatively unique example in the sense that there are not that many oncology mutations that are present in 90 percent of all that type of tumor. So what you will see, in essence, is basically I think a much greater amount of work in Phase IV, in postmarketing analysis, collection of samples, to get the sorts of numbers you need in order to drive tests with a level of sensitivity and specificity that people will believe. But ultimately I think every test is going to have to meet very, very strict criteria, although who sets that criteria, I don't know, sensitivity and specificity.

DR. LANDER: I'm pleased to hear you say it, because we all struggle with these things. I'm curious about what the thinking in pharma is today about if one does these sorts of things in Phase IV, papers will come out in some interesting journal or something. But what's the thinking in pharma as to whether or not you kind of let those things randomly drive the clinical usages of the drug or whether you really try to go for a label around those sorts of tests? I realize these are complicated issues.

DR. DRACOPOLI: Let me give you an aspirational and pragmatic answer. The aspirational answer is we're trying to make better drugs.

DR. LANDER: Indeed.

DR. DRACOPOLI: Certainly in oncology, and you could argue in many other therapeutic areas, whether it's infectious disease and you're looking at pathogen identification or oncology. Understanding the disease, subdividing the patients to drive efficacy is going to be really key, and that's the way forward. The industry cannot continue to bring drugs forward into the marketplace that only work 10 or 15 percent of the time.

The pragmatic answer is that if the industry doesn't do it, it will be done to it. There is already in the market opportunities for third parties to be running pharmacogenomic tests independent of the drug maker. The drug companies spend a huge amount of money basically doing life-cycle management to try to drive their products as effectively as they can. But if they're not doing pharmacogenomics, they're essentially handing over information into the public domain that will basically drive the use of their compounds broadly across the market.

So I think that the pragmatic answer is that the companies have to do it. I mean, there is no choice, and it is also good clinical medical practice to do this. I'm not sure about the right way to phrase it, but there is always the perception that I get asked, why do you as a scientist and a drug company want to segment your market? Is that not in your interest to do so? But I think when you look at it scientifically, it's very much in the company's interest to do so, with the goal of bringing better, more effective drugs to the market.

DR. LANDER: I'm not surprised to hear you say it, but it's great to hear you say it. That's good.

DR. McCABE: I have two other people, Reed and Emily, and then I think we're going to take our lunch break, and we can pursue some of the discussions at the roundtable.

DR. TUCKSON: I really appreciate the line of questioning that Eric has just engaged in, and I think it certainly makes me anxious to hear from, at some point soon, our FDA and other colleagues about where is the current state of rules, regulation, rationality in what looks like chaos. It looks to me that given the incentives of the marketplace, Eric, I fear that without some rational controls here, we are going to see a whole bunch of people marketing diagnostic tests and therapeutic interventions directly to the public without the kinds of controls and guidance that are necessary.

On the other hand, let me hasten to say I would be obviously sensitive to not stifling innovation in the scientific community, bringing better drugs to all of us. Since that work has been done, let me ask you this, and this is probably to you, Nick, more. I am worried about what the costs are going to be. It is hard to ignore the juxtaposition of our conversation with the conversations in Congress at this very moment around trying to figure out how the heck we're going to get some basic drugs to seniors, lots of people dying who can't afford diddly squat.

If you have a smaller market and, as you've said, better drugs targeted to the right people, it would seem worrisome that the base around which you're going to spread your development costs are smaller. We have to be worried, and maybe we can be less worried because all these 4 million SNPs in the public domain means that your research effort is being aided by Collins, et al., and therefore, since the public and the government have funded your research, you'll decrease the costs on the back end. Can we hope for that?

DR. DRACOPOLI: Yes. Let me try and answer that. Clearly, the Genome Project has changed the way drug companies do their research and apply that work to drug development. I would argue that was one of the intended fruits of the Genome Project, to do that. The pragmatic approach is -- the biggest problem for the industry right now is the paucity of compounds we're bringing forward into the marketplace. The attrition rates in preclinical, early clinical development are getting worse, and I believe -- and this is the scientist in me, maybe not the economist -- that the use of pharmacogenomics can really help that.

We have modeled across an oncology portfolio, and the conclusion we generally came to was that reducing the attrition rate, where roughly 10 percent of the compounds we take into Phase I will eventually make it to market, which really drives costs -- that's what drives the $800 million cost you see from the Tufts study per compound. It's not $800 million per compound. It's that compound plus all the nine others that failed that we're developing.

If you can reduce the attrition rate even marginally so we don't have to have 60 compounds in early development to have 30 compounds in early clinical development, to have five or six compounds in full development, to make one launch a year, if you can thin down that whole pipeline, you would totally and utterly change the whole economic picture for development.

So I think in an area like oncology, where you have such low efficacy of your compounds, there really is room for improvement in the sense that you reduce attrition, we get to the point of bringing forward drugs that have maybe 30, 40, or better, hopefully, efficacy rates. It's a lot easier to run the trials. We can run smaller trials. We can do those compounds more quickly. So I think in oncology, I think there is a good answer to your question.

DR. TUCKSON: So we get lower-cost drugs.

DR. DRACOPOLI: I would hope so. I would hope you would get more of them. I don't know. I'm not sure that I'm the right person to be asking about cost. But what I would hope from a research perspective is that we could bring more forward from the $2 billion that BMS invests every year in drug development, that we could maybe get more launches out of that, and that should ultimately impact cost.

DR. McCABE: Chris, very brief follow-up.

DR. HOOK: That is a major concern, though, because if you look at Gleevec, which went from research to marketing in a relatively rapid fashion, it still costs the basic patient $2,300 a month. That's the base price that they can get for the standard dose, and that makes it inaccessible to a number of patients, unfortunately.

DR. DRACOPOLI: Absolutely, yes.

DR. WINN-DEEN: I wanted to ask a follow-on question for both the speakers in the morning, and that is that it's clear that in the new drug development process, the whole genomics concepts are starting to get incorporated. But what do we do about all the drugs that are already out there on the market which didn't have this sort of parallel track marker development along with the drug development? I think the example that Wylie gave for Factor II, Factor V, and warfarin is a really good example. Here we know the underlying genetics, we know that 2C9 genotype affects how you should dose warfarin, and even so we're really not making use of that information in standard clinical practice.

So what do you guys see as the barriers to really getting things that are even reasonably well clinically validated out into standard-of-care clinical practice?

DR. BURKE: I'll just address this and reflect back to the point that Eric raised earlier. Clearly, to use 2C9 data in clinical practice, we need some outcome data. So we need some clinical trials, and that gets back to the point of what do we need to do. I think we need to develop some methods to bring the right people together to think wisely about where clinical trials are now merited and worth doing, which I would argue they are with 2C9. We really need to know what's the gain from 2C9. Do we in fact, as predicted, see less bleeding complications when we profile people with 2C9? And what happens to the people who are found to have the low-risk genotype? Can we save some money by backing off on the surveillance of those patients, or should we not? Those are the kinds of outcome data we need.

DR. WINN-DEEN: So whose role is it to do those studies?

DR. BURKE: I think that's the interesting question. The interesting question is who is going to fund those studies. You can't fund a clinical trial on everything. And it speaks to, I think, the larger question, which is what are the criteria? It's not really what are the clinical practice guidelines for a particular genetic test, but rather what are the criteria by which we should determine when a test is ready to use? For that particular test, it seems to me, and that's the opinion I'd throw out to a group discussion, that we need some clinical outcome data, and I think it's that discussion of what kind of data do we need, followed by how can we most cost effectively get that data, obviously, as well as who will fund it.

DR. McCABE: Nick, do you have a comment?

DR. DRACOPOLI: Yes. I would say you could look at two things. There are a couple of examples you could look at. In the public sector, I think what's being done with TPMT through Dick Weinshilboum and the group at St. Jude's is an example, and I think there are others involved as well. We're taking an existing generic but important therapeutic for ALL, which basically has a severe impact on roughly 1 in 300 kids who are homozygous for a mutation of TPMT. That genetic testing is now standardly used at medical centers using that therapy, and that was a public effort which was driven by real medical need for an important drug that had high efficacy.

The other examples you can look at are several examples where you can look at small genomic biotech companies who are now running clinical studies of marketed therapeutics. Those therapeutics that are in that list right now are largely currently patented, relatively high-priced therapeutics. But clearly, their goal is that they see a market opportunity for developing tests that are independent of the manufacturer. The issue is, as we mentioned earlier, how good those tests are. But I think there clearly is for many compounds where there is an opportunity for diagnostic companies to actually run those clinical studies that were never run before.

For new compounds, I think you're going to see more and more Phase III, Phase IV. We're pushing towards this. But for the existing compounds, I think it's a combination probably of smaller genomic-driven biotech companies running independent studies and publicly-sponsored research-driven work.

DR. McCABE: Thank you. I'm going to cut off the discussion so we can have some lunch.

Lunch is available in the hotel. There's the restaurant, the American Harvest, in the upper mezzanine. For members, ex officios, and presenters for both the morning and the afternoon session, there's an area set aside. Also, another place in the hotel is the Federal Bar, which serves lunch and appetizers, and there are nearby restaurants. You can get a list from the registration desk.

We'll be back at 1:15. Thank you.

(Whereupon, at 12:32 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)

AFTERNOON SESSION (1:27 p.m.)

DR. McCABE: Welcome back from lunch.

This afternoon we will continue with discussion of a variety of different topics. The first will be the financing of genetic technologies in the U.S. health care system, and the presenter will be Dr. Jack Rowe, who is Chair and CEO of Aetna HealthCare.

DR. ROWE: Well, thank you, Dr. McCabe, and thank you for including me. I'm delighted to be here representing Aetna and the health insurance industry. I must say also, as someone whose entire career has been in academic medicine up until three years ago, I'm delighted to be paired -- in fact, I even showed my wife that I was paired in the schedule here with Francis Collins and Claire Fraser, who, along with her partner, Craig Venter, have made such historic contributions to human biology and health. It's quite exciting for me.

I'd like to propose the proposition, at least, that the impact of the contributions of our colleagues in development of genetic tests is going to be influenced by the effectiveness of a partnership between three groups. One group is the producers of the tests and the biology behind it. A second group is the users or the consumers of the tests. The third group, whether one likes it or not, are people such as me who, in fact, decide whether to pay for the tests. I think that that's an important trio and that we have to work effectively together in order to realize the promise of genetics in enhancing the health status of individuals and populations.

I'm going to focus on genetic testing, although there are certainly other aspects of genetics that we could discuss here. Four of the usual and customary requirements for an effective screening test are here. The tests we're talking about are, of course, very sensitive and, in the main, very specific. So the question is are they cost effective and are they safe?

The cost effectiveness, from an insurance point of view for genetic testing, is determined by the degree of risk in the population that is tested. I think this is very important for us all to understand and agree upon. There are much data in the literature with respect to this, but let me just cite two examples of slightly different types. The first is a study by Eccles in the British Journal of Cancer, 1998, looking at the cost for detection of an abnormality in the BRCA1 gene, and looking at the cost if you were screening a general population, $170,000. If you screened only women who were under 40 years old, $1,700; and only women with a strong family history, less than $500. So obviously, the issue here is to apply these

tests, if possible, to individuals who you can identify as being at risk.

Another way to look at the cost effectiveness of a genetic test is to look at its application once a test is conducted and the result is known. With respect to that, Vasen and colleagues in Cancer, 1998, reported this result in individuals who had the test and had a positive result for the familial form of colonic cancer. In that case, a group of 25 individuals were followed up routinely with passive clinical evaluations and no colonoscopies, and another group of individuals had frequent colonoscopies at one-year intervals in this case, although follow-up studies have been done every six months.

If you look at the cost of taking care of an average case of colon cancer that developed in these populations, you see that the individuals who were followed up more regularly, despite the extra cost of the colonoscopies, actually resulted in 27 percent lower cost. So that is the business case for quality, if you will, in not only doing tests but following them up with aggressive monitoring of individuals.

I was very interested in this. This is something this audience may not be too used to thinking about, but this is a note from a sell-side analyst at Lehman Brothers on Wall Street. When we came up with our guidelines for the use of genetic testing, we thought we were going to get killed by Wall Street, and instead Mr. Raskin came out with this quote the next morning: "It becomes clear that as health plans become more proactive with respect to disease prevention, genetic testing will begin to assume a more central role from both a clinical and a cost-containment perspective," and I think that is very, very good news. I think that is, in fact, currently the prevalent view on Wall Street.

Now, is it safe? I'm sure you all feel that these tests are safe, but a lot of people don't think these tests are safe. They're safe from the point of view that doing the test doesn't hurt anybody. But the fact is that people fear these tests. They fear that if they have these tests, that they will be subjected to discrimination in the workplace and discrimination in trying to get insurance. There are a fair number of individuals who have, in fact, gone to health care providers anonymously or under aliases to have tests because they are concerned about the issue of privacy.

Fortunately, this is not the prevalent finding. In fact, I'll show you some results from a Harris poll indicating how people nationally feel about genetic tests, and then I'll look at some of the regulatory and legislative issues and the myths that are relevant to the issue of privacy and safety for individuals.

Harris did a poll last year of 1,100 adults nationally, and what they found was that over 80 percent felt that genetic testing was a good thing. They found that the more familiar people were with genetic testing, the more likely they were to say that they would have it. In fact -- and I don't know if this is good or bad -- half said that they'd be interested in having a test for a very serious disease even if there was no known treatment or way to prevent the disease, which is interesting.

So while there is a lot of concern from the privacy fundamentalists about safety issues and privacy issues, and those are important concerns and I'll address them in a minute, I think we should be aware that most people, in fact, are not in that camp. Forty percent of people said that they thought health insurers should have the information as well as their doctor, and we believe that to be the case, and I can give you an example of why.

Now, as far as the states are concerned, all but two states, Idaho and North Dakota, have passed some form of genetic non-discrimination testing legislation. The Partnership for Prevention has just put out a very nice pamphlet that you may all have seen about state programs in genetic testing, and I would recommend that to you. Perhaps, Sarah, the Committee would appreciate getting copies of that. It's a very useful, well-done piece from a good organization.

So all but two states have passed laws. The laws impact individual and/or group insurance and specify broadly that health plans may not do one or more of the following things. Don't establish rules for eligibility based on genetic information; don't require genetic tests; use genetic information for risk

selection or risk classification purposes; and don't disclose information without informed consent.

Now, it's interesting that most of the regulators that we contacted didn't know why the laws were passed. In other words, they knew that the laws were passed but they couldn't exactly tell us what the problem was that the law was designed to correct. There was concern about privacy and a fear about it, but there hadn't been examples in the states of some behaviors, egregious or otherwise, that the law was in response to. In fact, I'll show you some data on this in a minute, but I think this is a situation where the lawmakers are ahead of the law breakers. In fact, there's been an epidemic of these laws, and that's fine, except it creates a problem for insurance companies because if you're an insurance company like Aetna, we sell insurance and serve members in 50 states, and now we have to comply with 48 different laws, soon to be 50. No two of them are exactly the same.

So we would be much better off with a national standard so that people in the same company who happened to work in different factories in different states were being dealt with the same way. So we're looking to a national standard, and there are two bills in Congress. The first is from Congresswoman Louise Slaughter, who I think is in Rochester, New York, and she's offered H.R. 1910, which prohibits the same things that the state laws generally do and does allow a private right of action, which would mean that there would be an uncapped potential liability for insurance companies, and individuals could go to the courts if they had a dispute.

On the other side, in the Senate, there is a Snowe/Jeffords/Gregg bill, which I guess qualifies as a tripartisan bill --

(Laughter.)

DR. ROWE: -- which has been passed. It passed out of the Health, Employment, Labor, and Pensions Committee on May 20th. We support this bill strongly, and it has the same prohibitions but it basically gives people relief out of ERISA rather than on individual state court levels, and it's a very similar discussion as to the current medical malpractice discussion that is ongoing around the country. We would hope that this bill might get --

DR. LANDER: Could you just elaborate on relief through ERISA?

DR. ROWE: Yes. ERISA is a national -- it's the Employment, Retirement, Income Security Act, or something like that, and what it does is it basically preempts state regulations. So you're forced to go to a federal court, not an individual state court where there's a lot of variability, and there are some limits, I believe, to the awards that could be given, equitable relief, et cetera, instead of permitting the private right of action for an individual to go to an individual state court. That's my understanding. I'm not an attorney, but many insurance issues are covered under ERISA rather than under individual state mandates. States are preempted by ERISA for many insurance issues. So I think that's the distinction, and this would give a national standard dealt with in state court -- in federal court, not in state court.

DR. LANDER: So this would remove any private rights of action currently available under state laws?

DR. ROWE: Well, I'm not an attorney, so I'm not prepared to provide an opinion with respect to that, but informally I might think that would be the case.

DR. LANDER: That would be interesting to find out.

DR. ROWE: Yes. This is the same provision that's in many of the medical malpractice so-called reform bills that are discussed as well.

DR. McCABE: We will have a presentation by Congressional staff tomorrow, so we can get that clarified at that time.

DR. ROWE: Okay, great. Thank you.

MR. MILLER: If I may just jump in, there is a private right of action in the Snowe bill, and enforcement through --

DR. ROWE: Through ERISA rather than at the state level, I guess. What it does is it permits a private right of action but not at the state level, at the federal level.

MR. MILLER: In federal court.

DR. ROWE: Right.

MS. BERRY: I could be wrong, and we'll find out more tomorrow, but I think that the compromise that was reached between Senator Gregg and Senator Kennedy might have removed the private right of action provision that was initially in the Snowe bill, but the Snowe bill was how it started out. I may be wrong, but we'll get clarification tomorrow. That's my understanding.

DR. COLLINS: I just want to point out the bill is in the briefing book, and if you turn to the second page, there's a summary of what happened under enforcement that goes through the penalties and the remedies in enough detail that I think you can figure out what the compromise was. I don't think we should spend a lot of time on it now because we'll talk about it more tomorrow, but it is right there if you want to go and look at it.

DR. McCABE: Is there a comment from someone in the audience? Please come to the microphone.

DR. BARASH: It's my understanding that one of the issues in regards to this legislation is that ERISA exempts self-insured employers, and there are quite a lot of self-insured employers.

DR. McCABE: Please identify yourself, please, for the record.

DR. BARASH: For the record, Carol Barash, Genetics/Ethics Policy Consulting in Boston, Massachusetts.

DR. McCABE: Thank you.

DR. ROWE: I have a number of comments about this which you'll all be happy to hear I'm not going to offer at this point.

(Laughter.)

DR. ROWE: But that is correct. If you're a self-insured employer, and that of course makes a huge difference to large employers who are self-insured because there are some states in which there are many mandates, and the self-insured employer is not currently subject to those state mandates, whereas a small company that can't afford to be self-insured and is fully insured is subject to the mandates which we think increases the cost of insurance, which makes it worse just for those employers who can least afford it. So this is the issue about state mandates and ERISA.

You should also be aware that 62 percent of my customers are self-insured, and 65 percent of UnitedHealth Group's customers are self-insured, where Dr. Tuckson works. Is that right, roughly? I think 60 percent of CIGNA's customers are self-insured. So self-insured is a really big part of the commercial health insurance business in the United States, and therefore these ERISA preemptions of state mandates are very, very significant issues, whichever side of the issue you're on.

Moving along with respect to the fear factor, in addition to the issues about the legislation, I think it's

worth talking with you a little bit about the myth versus reality in the genetics of health insurance. I mentioned to you that the lawmakers are ahead of the lawbreakers, which is ideal. There was a study by two folks at Wake Forrest, Hall and Rich, that was published in 2000, and they evaluated the history to see whether they could collect examples of group insurance cases where individuals were discriminated against based on genetic testing. They were unable to find one case.

There have been, to my knowledge, no published cases of group insurance where individuals have been discriminated against. For those of us in the insurance industry, this makes perfect sense for a number of reasons. Number one is most of our customers are self-insured, as I said. Number two, the average age of our customers is 32, at least at Aetna. We have our customers for an average of two to four years, and then they leave and go to someone else. Ninety percent of our customers are gone within seven to ten years. The near-term expenses are the dominant focus. It feels like it's the next quarter or the next week, but it's never more than the next year. The major determinants of expense are demographic ones and not really related to issues of genetic tests.

Now, another myth is that health insurance coverage decisions are arbitrary, and I can tell you what we do. Dr. Tuckson can tell you what they do at United, which is a leading company in our industry. My guess is that there are more similarities than differences about the approach. But we have what we think is a comprehensive process for making these decisions. It's based upon current peer-reviewed literature. It's based upon recommendations, standards and guidelines of the relevant professional colleges.

So we start with professional sources, whether it's the IOM or the published literature or the American College of whatever, Obstetrics and Gynecology, Genetics, whatever the relevant group is; and then we go to a national expert review group and we pull together people such as some of them in this room, and we ask them what they think we should do. Then we go to participant providers in our network who, in fact, see Aetna members and are paid by Aetna, and we develop a policy with their assistance and disseminate the guidelines.

If you go to the Aetna website and you go to the Coverage Policy Bulletins, which are on the Aetna websites, there are hundreds of these, and for each test -- hemochromatosis, familial colonic polyposis, whatever it is -- it will tell you what our policy is, it will give you the references, and it will tell you why we made this policy, and when. This is available to the public and you can access these coverage policy bulletins. So we try to have as much transparency as possible.

Now, our coverage policy principles with regard to genetics basically indicate that we want to pay for these tests for individuals who are at risk, back to the breast cancer example. We want to pay for tests in which there is information that affects the course of treatment, and this is often very difficult. If somebody says "I want to be tested for Alzheimer's disease," and they have no symptoms, and we are not aware of any treatment that has been generally agreed upon to be effective in the preclinical phase of Alzheimer's disease, and there may be a study showing that people with Apo E4 may respond to this or that but there's not enough literature to meet the test of generally accepted at this point in our minds, then we would say no.

That person might say, well, for family planning reasons, financial planning reasons, professional planning reasons, life planning reasons, I want to know whether I have the likelihood of getting this, and we would say those are all valid reasons, but we don't think your health insurance should pay for that test. We think you should pay for that test if this is a legal or family planning or financial planning issue rather than a health issue, per se. Obviously, you get those kinds of things in other diseases for which there's no treatment.

Huntington's, on the other hand, as somebody said, I'm going to decide whether to have a baby and I want to know if I have Huntington's disease, then that's a different story. That would change something clinically and something different would be done clinically, and therefore we would pay for that kind of test.

We also are interested in care services and treatment for our members, rather than people who are not our members but who are related to our members, such as siblings, twins, et cetera.

So several months ago we offered a set of guidelines. We didn't offer this so much as groundbreaking but we saw confusion, all of these different state regulations. There was a lot of sense that insurance companies didn't want to pay for genetic tests. We didn't think that was the case. We think most of us are paying for these tests. So we offered some guidelines, and I'll give you Aetna's guidelines. I'm happy to tell you that since we offered these, these have been discussed and, in fact, a set of guidelines have been adopted by the American Association of Health Plans which are very similar to these. They're not identical but they're very similar. So the industry has now followed with a set of guidelines.
I'll show you ours, and I have copies if anyone wants copies of the Aetna guidelines. We feel that there are things that health insurers should do and things that they should not do. All the state laws are pretty much the things you should not do, thou must not. So we have thou shall as well as thou shall not.

With respect to thou shall, we believe that we should cover genetic testing in individuals shown to be at risk where the results may affect the course of treatment of the insured. That's critical and central to our position. Second, we should cover genetic testing for a family member where the family member is not otherwise insured and results may affect the course of treatment of an at-risk insured. So if there is a mother who is not an Aetna customer but knowing her genotype with respect to a certain situation will be important to how we treat a child who is an Aetna member, we would pay for that test.

Three, we would cover consultation with qualified counselors and physicians and facilitate the appropriate interpretation of genetic testing results. I think this is one of the most important things we've had to say. No genetic testing without genetic counseling. In fact, we believe that often the genetic counseling should occur before the test. In fact, sometimes the right thing is not to have the test, and we think it's very important for insurance companies to pay for counseling as well as pay for testing.

We support physician education in the appropriate interpretation and use of genetic tests, including guidance in the selection of medications -- i.e., pharmacogenetics. This, I think, is really important too. This a lot of people think is a throwaway. "Of course, physician education. They always say that." But the fact is if there were one thing the federal government could do, it would be to really get a push behind physician education in the appropriate use of genetic tests and genetic counseling, and we are strongly in support of that and looking to work with foundations and others to try to help in that regard. And we believe that we should work with physicians to promote confidentiality and to use the information for the maximum benefit of the member.

I mentioned, I think, that we should have the data as well as the doctors. Let me tell you for a second why I think that is. We have a lot of disease management programs, and we enroll people at risk for disease or at risk for complications of a present disease, such as diabetes or chronic heart failure, in these management programs. There are cases in which we can't enroll people unless we know the results of the test.

For instance, let's say that you have the gene for colonic carcinoma. You should probably have a colonoscopy every six months, let's say. I'm making that up, but I've heard that recommendation. Now, we wouldn't ordinarily pay for that. We would only pay for X number of years depending on your age, or not at all depending on your age. But how do we know that we should pay for it unless we know that you have the gene? So we have to have the result.

Now, it's true, we don't have a lot of people asking to have six-month colonoscopies, so there's not a lot of abuse here.

(Laughter.)

DR. ROWE: But nonetheless, you get the idea that if we have the information, we can identify people.

Then if information comes up about treatment or preclinical stages of diseases and we have the information, we can contact the 400,000 doctors in the Aetna network and say we know that you have a patient in your practice who has this, and are you aware of this treatment? Because, in fact, early treatment is a good thing. It's good medicine, it's good business. So we believe it's important for us to have access to this information.

Thou shalt not.

DR. WILLARD: Let me jump in before you move on.

DR. ROWE: Yes, please.

DR. WILLARD: What do you mean by "at risk"? Is it two-fold elevated over the population? Is it greater than 25 percent?

DR. ROWE: I think it depends on the cost of the treatment, probably. If the test is $1 million, you don't want to do a lot of people. If it's very inexpensive -- I think it sort of depends on the effectiveness of the treatment or the change that would be available. I don't think there's a simple rule. If you're an obstetrician and a patient comes in and you go through the usual sort of software package that obstetricians have, which you may even be for all I know, and you calculate did your mother have it, and your sister, and your twin sister, and your grandmother, and you get a probability, and if it's more than 30 percent likelihood that you have the BRCA gene, the recommendation is that you're at risk and should have the test.

Well, somebody made up 30 percent. I mean, they just picked it out of the sky, some group of experts. It could have been 50 percent. It could have been 10 percent. So we generally go by what the profession says. If the American College of whatever says they think people with X percent, then that's what we would use. We're not trying to set our own limit, and Reed can tell you how he thinks it's approached at United at this point. But it does vary from group to group. Thank you.

DR. WILLARD: Thank you.

DR. ROWE: These are the things you should not do, and these are basically the same things as are in the state laws. Establish rules for eligibility; require that tests use the test results for risk selection or risk classification; and disclose the results without authorization.

Let me end with a little commercial. This is actually our award-winning website. There are awards for websites. This one won a Webbie. I have trouble keeping Tonys and Emmys straight, and now we have Webbies. This is available to the public. We own a website called IntelliHealth, which is populated and edited by colleagues at Harvard Medical School, and there's a genetic testing set here of several pages, 10,000 words -- Do I need a genetic test? What is genetic testing? -- and we have different modules for different diseases that we're putting on this, so one or two at a time, and it's going well, so everybody who has used it is very enthusiastic about it. I think this is helpful to physicians as well as informing lay individuals.

Again, thank you very, very much for inviting me to participate in this. I think it's an exceptionally important group and I think you have a lot to offer.

DR. McCABE: Thank you very much, Dr. Rowe.

(Applause.)

DR. McCABE: We'll move on, and we'll have a chance to talk with all of our speakers at the roundtable this afternoon. Let's move on now to Dr. Francis Collins, future directions in genetic and genomic

research, Director of the National Human Genome Research Institute, and it's great to have you joining us in the mosh pit, Francis.

DR. COLLINS: Nice to be down here.

Good afternoon, everyone. I'm delighted to have a chance to speak to this distinguished group in this inaugural meeting of this new Committee that I believe has a very important mandate and clearly a lot of work to do.

In figuring out what to say to you, I thought I would focus particularly, because I think that was the charge, on some predictions about where genetic and genomic research is going. While you're all ruffling through your papers, let me tell you that I don't have a handout in front of you, but you will find in your briefing books a copy of a paper published in April in Nature under the "Genetic and Genomic Research" tab which I'm going to go over, albeit somewhat lightly because of the time, which will point out a series of areas where we believe the highest priorities now can rest in terms of where genetic and genomic research will be going next. Then I will at the end come up with some suggestions perhaps of particular areas that I think are ripe for further exploration by a group such as this.

So just by way of context to remind you that genetics didn't come around yesterday, we are actually standing on the shoulders of people all the way back to Mendel, and of course many things that followed on after that, the discovery of the DNA double helix, already having been mentioned, exactly 50 years ago. Of course, building upon that was the discovery of recombinant DNA, and then in the 1980s many other additional technologies coming along, leading to the initiation of the Human Genome Project in 1990.

A whole host of things happened that I'm not going to go over in any detail at all, only to remind you that the Genome Project was about a lot more than just getting those 3 billion letters of the human DNA in place. It was also about model organisms, it was about technologies, it was about map development, and it was about ethical, legal, and social issues. The ELSI program, the HGP, founded in 1990, represents the largest investment in bioethics on any topic, and as I said this morning, I hope that research will turn out to be very valuable to this Committee as input into some of the areas that you decide to focus on.

The second component of the genome enterprise over the last 13 years is depicted here, decorated by a number of publications of increasing complexity, including a draft sequence of the human genome in February of 2001, and the finished version of the human genome sequence having been announced just about six weeks ago. But I want to point you also to those three little words down in the right margin there, those three little words that say "To Be Continued," because I think that's what I'd like to now pay some attention to in the rest of this presentation, because I think it would be important for this Committee not only to think about our current situation but what's coming next.

So what is next? Well, in this article which you have, we depicted this future that we're aiming to try to develop as a metaphorical building, a building resting upon the foundation of the Human Genome Project, as you see here, and consisting of three floors of this rather Frank Lloyd Wright-inspired-looking edifice here. One floor is genomics to biology, another floor is genomics to health, and the third is genomics to society. That, by the way, looks an awful lot like the three designations of this Committee, the Secretary's Advisory Committee on Genetics, Health, and Society. What about that?

You will notice also that this building is held together by a series of vertical cross-cutting elements that touch on all the floors and are going to be necessary if this building is going to come to pass and be structurally sound. By the way, notice that the door is open here, which is inviting you to come in and work on any of these floors that you'd like to, and also that the data that will be generated by this enterprise will be accessible to anybody without passwords or other restrictions on access.

But this is a pretty bold notion, that we would try to do this. So what exactly is going to be going on on

these various floors? The process by which we develop this set of grand challenges that are described in that particular article involved input from more than 600 scientists and ethicists and public policy experts over the course of almost two years, and out of that, after many iterations, came this series of grand challenges which are aimed to be perhaps a little on the audacious side in that they are, many of them, things which we do not currently see a direct and time-limited pathway to achieving, but they are things which, if they could be accomplished, would make a profound impact on research and on the practice of medicine.

So in that regard -- we have some very interesting biology here in this room. I won't even tell you what's crawling across the rug over here.

(Laughter.)

DR. COLLINS: It's a model organism, I can tell you that.

(Laughter.)

DR. COLLINS: It probably has more genes than I do. The smaller they are, the more genes they have. That seems to be the rule.

(Laughter.)

DR. COLLINS: Well, here we are. Let me try to get back on track here.

(Laughter.)

DR. COLLINS: Are you all getting scared over here?

(Laughter.)

DR. COLLINS: Some of the things that are being focused on with regard to the basic science component of this, the genomics to biology, include the following. We need to understand that 0.1 percent of the genome differs between individuals, because that carries within it the clues to common diseases like diabetes and heart disease and mental illness and hypertension and on down a very long list. It carries within it the clues to differences in drug responsiveness. Many of the things that Wylie and Nick were talking about this morning could be understood in a much more effective way if we had that complete structure, not only of all the SNPs in the genome, as Nick was talking about, but also how they correlate with their neighbors into something we call haplotypes. I'll come back to that in just a moment.

We need a lot more sequence data. Having the sequence of some organisms only gets us more hungry for more, and now that we have the sequence of the human and an advance draft of the mouse and a pretty good draft of the rat, and increasingly other organisms coming through the pipeline like the chicken and the zebra fish and the chimpanzee and a host of others, the information we learn by looking into this comparison between genomes is profoundly interesting and really does give us in many ways our best handle on understanding function.

In order to achieve that, we believe that we have to drive the cost of sequencing ever downward. It currently would cost me about $50 million to sequence one of your genomes to a high degree of accuracy, and we clearly can't afford to keep doing it at that rate. So the technology not only for sequencing, which is highlighted here, but for many other applications, like genotyping and looking at gene expression, has to come down in cost, and we will only see that happen if we invest in it.

But imagine how things would change if we could today sequence the genome for $1,000. Imagine how that would change the way we practice medicine. You'd be very tempted, with appropriate restrictions on

access to who gets to peak at it, to just get the sequence done once and for all and keep it as part of your medical record, and not have to go back and do specific genetic tests on the germline DNA for particular applications. You'd just have it all there, and as new information came along you could quickly in silico determine the consequences and the possible interventions for that individual.

Obviously, comparative genomics, looking at lots of genomes, is giving us a very good window into function, but we need a lot more, other windows, in order to understand that. We now think that about 5 percent of the human genome shows evidence of strong conservation by the evolutionary mechanism, and yet for most of that, about two-thirds of it, we don't know what it does, and we need to figure that out in a robust way that combines experimental and computational approaches.

Clearly, the focus on the proteins that are encoded by the genes is a highly appropriate one, although in many ways the technology is what's rate-limiting at the moment. But we are going to need to push on that and are pushing on that in order to understand how the proteins interact with each other to construct themselves into pathways and networks that carry out function, and how that goes wrong in the case of disease.

And, perhaps, if we do everything right, beginning with simple cells and moving into more complicated ones, we might be able to model a cell in some considerable detail on the computer, making predictions about biology without having to do a wet-bench experiment, or at least making hypotheses that could be confirmed at the bench.

So here are some of the more basic biology things. You may then wonder, well, what's that got to do with this Committee's enterprise? Well, I think a lot, because built upon this will be the clinical and the non-medical implications that this Committee will be wrestling with.

But let me move to that second floor, genomics to health. If we have a good handle on variation --

MR. MARGUS: Can I ask you a question about your previous slide?

DR. COLLINS: Sure.

MR. MARGUS: What is the time frame for those things?

DR. COLLINS: Well, they're different for each one. A thousand-dollar genome is probably the one on here that has perhaps been talked about the most in terms of what is the timetable for that. In order to get there, we really are going to have to jump curbs from our existing approach, which largely depends upon Sanger dideoxy sequencing and/or other enterprises, and obviously your company is engaged in one that people are watching closely. Single-molecule sequencing is a very important new approach that many people are counting on, as well. So perhaps we might get to that in, say, 2015 if all goes well, maybe even sooner if things go really well.

Defining the structure of human variation by this haplotype map, we aim to have that done in the course of the next couple of years; and sequencing lots of additional genomes, it depends on what you define as lots, but we'd expect to have another 30 to 50 gigabases of DNA sequence in public databases in the course of the next three or four years, or we're not doing a very good job with the possibilities that are there.

All functional elements of the genome. Well, you know, it depends on how rigorous you want to be about all, and how much you have to know about their function. That's a bit of a squishy definition. This blueprint that you can read about in the Nature article is not as focused on timetables as our prior five-year plans were for the Genome Project, because in many ways we're in a different circumstance. The Genome Project had a set of deliverables which were supposed to be produced by 2005. They all got delivered, and now we are in a circumstance of looking at a much broader array of opportunities going

well beyond what was contemplated for the Genome Project, per se.

I think as we move along, some of these goals are going to need to be tied to more specific timetables. Right now, they're sort of put out there as challenges to the scientific community, saying can you do this? If you can, the consequences will be substantial. There is more information in the article than I have time to put on the slides, and some of it does get more specific about the timetables. It's not as squishy as it may sound from what I just answered in response to your question. But I do think this is a circumstance where we're trying not to be overly restrictive in terms of only putting forward things that could be done, say, in the next five years. There are certainly things here that reach well beyond that.

Genomics to health. Here is perhaps the one that I want to dwell on the most because it is perhaps the most relevant to where the future of genetics is going in terms of its medical applications, to actually identify the genetic and the environmental risk factors for all common diseases, and to do so with those things being studied in concert as opposed to separately, because obviously a lot of the important revelations about common disease are going to come from an understanding of how heredity and environmental triggers interact with each. I'll come back to that in just a moment.

We also need to push forward on some of the things that were discussed in some ways this morning, sentinel systems that would allow you to detect disease before symptoms have appeared, and also ways, as Nick described, using things like microarrays, to take a disease where currently you lump what is probably several different conditions together under one label and you distinguish them by a careful understanding of the differences in their molecular taxonomy.

An area that I think many of us are quite excited about but which is really quite a paradigm shift for academic researchers would be to put into their hands the kind of capabilities which are the mainstream of the pharmaceutical industry by allowing academic investigators access to high-throughput screening of small molecule libraries to identify compounds that act as agonists or antagonists for particular pathways of biological interest. Those, of course, also could become the first steps towards drug development, and that kind of greater partnership between academia and the private sector, in many people's view, would be a very valuable direction to go in.

One that I think we ought to think carefully about here this afternoon is the need, if all of this is going to come to pass, to have really large human cohorts in order to try to understand genotype/phenotype and environment correlations. I think we've learned over the course of the past several years that those kinds of studies really need to be set up in a fashion that's unbiased. They need to be large, otherwise one tends to draw conclusions that don't end up getting replicated because you're looking at relatively modest contributions from any particular gene variant that's involved in a disease.

And yet, many people perceive there to be barriers to this kind of large-scale cohort study, and I want to come back to that in a moment.

Also in this genomics to health floor, clearly we need not to limit our studies on genomics to any particular population, and certainly it would be a mistake to focus, for instance, on the majority population in a particular area. We need to understand whether health disparities have a contribution from heredity, as well as from other areas which are probably more likely to be involved in most instances, such as socioeconomic status, access to health care, and cultural and dietary practices. But we'll never really know unless we in fact carry out those studies in a rigorous way.

And perhaps you will say this is a bit idealistic, but I don't think so. The ability to use genomics to unravel the causes and potential treatments for conditions such as malaria excite many of us, that here's a science that does have an opportunity not only to touch upon people in the developed world but also to go after diseases that have been largely neglected with a new focus built upon the field of genomics.

So let me just say another word here about how we're going to get to this point, because that obviously

would change many of the issues that we would be deliberating about around this table. Frankly, most of us are carrying risks for future illness somewhere in our DNA, and at the moment we don't have the ability to know very precisely what those are except in instances, some of which Wylie described very eloquently, where we already are beginning to get a handle on those conditions. But for the most part, we don't. How are we going to get there, and how soon will we get there?

Well, what do we need here? We need this catalog of human variation, and yes, we have 4 million SNPs, and yes, by August we'll have 6 million SNPs, and we need to put those into a map that organizes that variation across the chromosome, so-called haplotypes, because that will be a wonderful shortcut to using that catalog to identify the variants that are associated with common diseases. We need better technology, as Nick pointed out, in order to apply that in a cost-effective way to make associations of particular variants in a particular gene with a disease risk or with drug responsiveness.

And, I would argue, we also need advanced methods for collecting environmental exposure data. If we're really going to understand how those genetic susceptibilities interact with the environment, we need to measure the environment, and that is at the present time something which I think there is a fair amount of expertise, but it's not widely shared with geneticists, and vice-versa. We've got to get these fields together in terms of those who understand heredity and those who are focused on the environment and convince them that they're not actually working at two different purposes. We're working at the same purpose.

Then, if that's going to happen, and here is a case where I think many of us are looking in some optimistic way for perhaps a really new and bold enterprise to emerge, we really need in this country a large cohort study of perhaps half a million individuals who are carefully followed over the course of several years for whom a consent has been obtained in a fashion that is able to stand up to all possible standards. They will be involved in an ongoing way in such a study, if it could be mounted, so that it's not a one-time analysis.

The incidence of various diseases would be noted over the course of that timetable, very careful records of diet and other environmental influences could be kept, and extensive DNA genotyping as well. If you go through the expectation, that would finally give you an opportunity in an unbiased way to determine what the effect is of a particular variant on disease risk and how that interacts with the environment.

It is fine to do a lot of disease-specific case/control studies, and we're all doing lots of those as well, but they're often chosen in a fashion that they emphasize the more severe end of the spectrum of the disease, and therefore they may tend to overestimate the genetic contribution. If we're ever going to sort that out for common diseases, this kind of a large-scale cohort, as is currently being contemplated in the U.K. with their BioBank program, as Iceland is doing in terms of the whole country in collaboration with a company called Decode, as the Japanese are just beginning to mount with their own BioBank program which is about to get underway, but here in the U.S. we do not have such a plan.

If we're serious about health disparities, for instance, we need to have a plan that involves adequate sampling of some of the minority populations in this country. Otherwise, we will end up again not quite clear on what's happening there. So that's a need, I think, that we need to address very soon.

If we do this all right, both in terms of understanding how to measure genotypes, how to collect environmental data, and how to carry out large-scale studies, there's no reason we can't identify the major contributing genes for the common diseases that fill up our clinics and hospitals in the next five to ten years. That really would, then, position us to be able to offer people the opportunity of a multiplex kind of test to discover what one's individual susceptibilities for future illness might be, focusing of course on those conditions, as Wylie made the point very clearly, for which some intervention is available, because I think those are the ones that people are going to be most interested in. Of course, that will be a subset of the total for which such testing can be accomplished.

That will then put us finally in the circumstance of being able to move into the lower part of this diagram, which is a time description which we hope to traverse from top to bottom for disease after disease over the course of the next couple of decades, and ultimately, of course, get us down here to the point of being able to offer therapies for conditions that we currently don't have very good solutions for. Again, I think Wylie did a wonderful job using the example of hemophilia, showing how many of these various arrows can be traversed, but they do take time and we can't expect that they're going to happen overnight, and the relative speed with which an effective therapy arrives is probably the least predictable of all.

So, I've now touched upon those first two floors. What about genomics to society? What did we put in that particular part of the building? Well, several bullets are here described, and they're ones that have already been brought up, most of them during the course of just this first half-day of discussion of this Committee.

Clearly, there continues to be concern about genetic discrimination and genetic privacy. We have major issues, and Lawrence Sung will be talking about them later on this afternoon, about intellectual property, and we should I think move beyond the debates about genes and whether they should be patented because, frankly, that horse is very far out of the barn, and in fact pay more attention to some of the other entities for which that has not yet been settled, such as haplotypes, such as expression data, such as protein crystal structures, all of which are also contemplated as being intellectual properties in a way that may or may not be good for the public in the long term.

Very much I think on many people's screen and high on the list of things that we need to pay a lot of attention to as we focus on the study of variation is how that study might reflect usefully on the topic of race and ethnicity, recognizing that this is not a simple issue and that it is not so straightforward to simply say that race has absolutely no biological basis, as has been I think occasionally said in too strong a fashion. Race is basically a reflection in a very fuzzy way of ancestral geographic origin. Ancestral geographic origin is a reflection in a fuzzy way of genetic variation. They're not completely disconnected, but they're very fuzzily related to each other.

Now, how do we formulate that message in a fashion that is benevolent and actually provides a useful commentary on a dialogue which has often been contentious?

As we understand this variable part of the genome and apply it for medical purposes, it will clearly also be applied for non-medical purposes. We are going to uncover in the next decade or so variations in the genome that play a role in such things as intelligence and sexual orientation, and there will be such discoveries that actually, after people test them, are validated, unlike the ones that have been reported in those areas for the most part up until now. How are we going to fold that into our social discourse and our understanding of ourselves and our fellow human beings?

In that regard, are there boundaries that we don't want to cross in terms of the applications of genomics in the non-medical arena? And if so, who establishes them and who enforces them?

So those are some of the things that we think are most deserving of intense attention in the coming years. Again, this is not my list so far. This is basically the list that this group of 600 advisors came up with and which we formulated into this prospectus for the future. But now, in a somewhat more directed way, and again without being able to completely defend this, because I think there are so many different topics that might have been proposed, let me just mention a few areas that arise from this list that might be appropriate for focus by this Committee, recognizing that tomorrow is largely going to be the point at which that discussion goes forward.

I can't help but put genetic discrimination first. I celebrate the accomplishments of the Senate HELP Committee and I'm delighted by comments from Dr. Rowe that the industry is supporting this bill, and my hope is that the House of Representatives will act quickly on the same kind of bipartisan basis to achieve what we've waited for now for seven years; that is, effective federal legislation that will outlaw

the use of predictive genetic information in health insurance and in the workplace. So we need to achieve that. We're not quite there. It's a great moment that it's finally made it through a Senate Committee in a bipartisan fashion, but there are several steps still to go.

Let me then be bold enough to say that while the complications in terms of adverse selection issues are much more complicated than these other types of insurance, and I think that has kept people from wanting to even engage on them up until now because of the need to focus on health insurance in the workplace, perhaps it is time to think are there options, at least for some floor, some minimal level of care that could be, in fact, considered in terms of life insurance disability and long-term care insurance where, again, somebody with a high risk based upon genetic information would not be completely screened out or to the degree that it became unaffordable.

Basically, there hasn't been a lot of discussion about that in this country. There's been a fair amount of discussion about life insurance issues in the United Kingdom, in part because they're not as worried about health insurance because that's covered. But perhaps it might become time to begin to consider that.

Of course, there are other areas of genetic discrimination that have not, I think, received as much attention which are not part of the insurance issues, but the notion that your genetic information might be used against you in other considerations, such as an adoption proceeding or in ability to gain an education or the military, and there are dots here because there are others you can think about as well. So that was bullet number 1.

Bullet number 2, and it has already also come up, we do not at the present time have an effective system for overseeing genetic tests to ensure that clinical validity, and hopefully clinical utility, but at least clinical validity has been established prior to marketing. The current system, as we all were part of the SACGT's discussions, does not allow confidence that a test has achieved that kind of status before it becomes marketed to practitioners, and sometimes even to the public. I think that is an issue which we continually are concerned about and need to return to as part of this Committee's discussions.

A special concern in that regard is the proliferation, mostly on the World Wide Web, of direct-to-consumer marketing of genetic tests, some of which, I must say, are of deeply questionable validity and for which at the present time there seems to be no particular oversight whatsoever. I show you as an example this one from the Web. This is a company that is offering to concerned parents genetic testing for the millennium, as it says here. I'll quote from their Website: "Are you concerned about your children's future? Does your child have the genetic trait that leads to disruptive and addictive personalities?" I'm not quite sure how the parent was supposed to know if the child had that genetic trait. Maybe they had a bad day in school. "DNA testing can help you understand and manage a child's behavior before it gets out of control."

You go down here and it tells you how to take a foam-tipped applicator and rub the inside of the left cheek 25 times, send your DNA sample off, have it tested in some way, and then notice if, in fact, the test comes back indicating some alarm. They will then sell you some neutriceuticals at a considerable price that will perhaps protect your child from a terrible outcome.

This is junk science, and it is not the only example that one can find out there on the Internet of similar such things that are happening in greater and greater profusion, and they run the risk, I think, of perhaps fouling the nest here in terms of convincing the public that genetics is junk science in general. If we don't have the ability to restrict in some way the marketing of such information, we may later find out that the public has concluded that this whole field is not something to be trusted.

Just two more areas that I might suggest based upon the predictions of the future enterprises that the genome enterprise might be engaging in. I must say, when I speak to researchers who are most interested in seeing the medical advances occur in terms of connecting up genetic variation and environmental

exposure with disease risk, they are deeply concerned that our current system, with a very uneven focus on protection of human subjects, is making it increasingly difficult for clinical investigators to do research.

Now, I grant you, I think those protections need to be there, and they need to be very rigorous and extremely well thought through, and we have representation here from Dr. Carome from the Office of Human Research Protections. But I think the conclusion of many clinical investigators is that somehow we've built a network that is so complex and so restrictive and so difficult to deal with that it's beginning to get very hard to do research. The public has an interest in the research getting done as well, and perhaps we need to reconsider whether we've got the balance right here or whether there are actions that could be taken that would make it more feasible to undertake large-scale studies of the sort that we really need if we're ever going to sort all of this out.

I don't know that this is an easy question to deal with, but I think it is number one on the minds of many investigators. I just came back from the Cold Spring Harbor genome meeting, where most of the world's major investigators in genomics were gathered, and this was much the discussion at the meeting, both during the meeting and in the hallways afterwards.

My fourth bullet here -- and again, I could go on with a much longer list -- relates very much to other things that have been brought up. Again, I was very impressed with Dr. Rowe's presentation about what Aetna is doing here in terms of making sure that genetic services are offered and are connected up with adequate counseling. That's a wonderful step in the right direction. I'm a little less optimistic that that's going to be happening in quite such a broad way as one would like. There are workforce issues here in terms of who is going to be providing the expertise that's needed in order to interpret all of this information and provide the kind of counseling that the public is going to need.

There are chronic access issues about who actually is able to get the information, and related to that are cross-cultural issues. Are we really prepared to deal with the very different ways in which different people may assess the information and need to have it explained? And reimbursement. Who is actually going to pay for all of this? Where is that going to come from? Those are clearly issues that have to be solved in the next few years or this revolution in availability of genetic information, which I think everybody agrees is coming, may encounter a major problem in health care economics.

So those are a few ideas of areas that might be attended to. Again, I look forward to this Committee's deliberations, and I count on them turning out well, and for that particular optimism I refer to a particular verse from Proverbs, which says "Plans fail for lack of counsel, but with many advisors, they succeed." We seem to have many advisors and expert ones around this table, so we shall count on success.

Thank you very much.

(Applause.)

DR. McCABE: Thank you.

Our next speaker is Dr. Claire Fraser. Her topic is issues in the use of genetic technologies in bioterrorism. Dr. Fraser is President and Director of TIGR, the Institute for Genomic Research.

DR. FRASER: Thank you very much. It's really a pleasure to be here. I was delighted to receive the invitation to speak with you today.

This was not my topic. This was one that was assigned to me, and I think it would perhaps be equally well-framed if the title of my presentation was issues in the use of genetic technologies and infectious disease, because I think that the challenges before us, the opportunities that come from having the availability of these new genetic technologies, are very much the same; and I think, as we've seen from

the recent outbreak of SARS, that on balance the challenges we face from natural outbreaks of disease are hopefully going to be far greater -- not hopefully, but will likely be far greater than any that we will face in terms of any deliberate acts of bioterrorism.

But nonetheless, I've put together this talk with the bioterrorism aspect as a framework, and let me begin by just quickly reviewing what I think our current vulnerabilities are. This is, again, across the board in dealing with infectious agents in general.

With only a few exceptions, we really don't have adequate systems for rapidly and accurately detecting and recognizing a specific infectious agent, again whether it be deliberately released or a natural outbreak. We clearly have a fundamental lack of basic knowledge regarding the pathogenesis of most infectious disease agents, perhaps more so with biowarfare agents because the number of investigators that have studied these is much less. As a corollary, I would make the point that we also have a fundamental lack of basic knowledge of host response following exposure to infectious agents, and the two of these really go hand in hand. We have the tools now at our disposal to begin to think about tackling these issues.

We don't have adequate forensic methods for the purposes of attribution, and you'll hear certainly much more about this from Bruce Budowle in the next talk, whether we're talking about forensics having to do with human DNA or microbial DNA, as we're now starting to think about more that the issues are very much the same. I think there's good agreement that our arsenal of available vaccines, antimicrobials and antivirals could certainly stand to be beefed up.

Given that as a background, it's not surprising that when the microbial genomics efforts began in the mid-1990s, some of the most important first organisms to be tackled with these approaches were those that cause human disease, and I don't think it's any exaggeration to say now that essentially all of the major human pathogens have genome sequences available, and in many cases for some of these more important organisms we now have sequences available for multiple isolates. As I'll talk about a bit later, that's turned out to be extremely valuable.

The point of all of this was to hopefully use this information to accelerate the development of new and better diagnostics, drugs and vaccines for treating infectious disease. But specifically in terms of bioterror agents, several years ago there was a concerted effort among a number of federal funding agencies to put these organisms on the list for genome sequence analysis. The smallpox genome sequence was completed some time ago, in the early 1990s, but since then we've now tackled essentially all of these agents under Category A and Category B. These are the lists put out from the CDC, and these tend to be the more esoteric infectious agents, ones that don't often come into typical conversation about infectious disease.

I think that Francis made the point that the more sequence we have, the more we seem to want, because the real power from having this information comes from the ability to do comparative genomics. In the microbial arena, some of the most interesting and most informative comparisons so far have come from looking at differences between species. Sometimes these are distantly related, other times more closely related. I think one of the big surprises in the microbial area to come from this analysis was the observation that the process of lateral gene transfer, exchange of DNA in the environment, seems to be playing a much bigger role in generating genetic diversity among microbial species and pathogens in particular -- this is an important area of this -- than we had previously appreciated.

So it says that these genomes are not static and it suggests mechanisms whereby new isolates with different properties, increased virulence, for example, antibiotic resistance may arise. Just to give you one very quick example of the kind of insights that you can get, at TIGR we've been working on a number of organisms in the Bacillus anthracis, Bacillus cereus, Bacillus thuringiensis group. This is a very closely related group of microorganisms. Anthracis you all know about. I don't need to tell you why that's so well known. Bacillus cereus is an organism found in the soil. It's an opportunistic

pathogen in a small number of immunocompromised patients, but in most cases it just goes about its business in the soil. Bacillus thuringiensis is an insect pathogen. Those of you who put BT on your lawn to kill Japanese beetle grubs, BT comes from Bacillus thuringiensis. It's a toxin that interferes with insect feeding.

So we've been working on genome projects on this group of organisms, and I bring this up because what this information can provide when you take a comparative look at it is insights as to how some of these organisms have evolved. In particular, there was an issue of Nature just a couple of weeks ago with two reports on the complete genome sequence from Bacillus anthracis. This is work from TIGR by Tim Read; Bacillus cereus, work from a group that integrated genomics.

The take-home message here is that, as had been thought prior to having complete genome sequence information, these two organisms are extremely similar, especially if we're thinking about these as two different bacterial species. Their genome size is very much the same, just over 5 million base pairs. Many of the predicted proteins in one have best hits in the other, and vice versa, and we see a great deal of gene syntony. That is conservation of gene order in very large clusters when we do whole-genome comparisons.

This has confirmed that, in fact, these two organisms are very closely related and most likely shared a common ancestor. One of the questions is are there additional virulence factors in Bacillus anthracis that we don't know about? Can we get insights from taking a comparative approach? One approach that was taken -- and this is work that was done previously. There was a major transcriptional regulator. This is a master switch, if you will, in this group of organisms that, when activated, turns on a whole cascade of events, with the end result being increase in expression of a number of virulence factors. It's thought that this is a key trigger in activating the virulence pathways in thuringiensis, in cereus, and Bacillus anthracis.

One of the things that you can do when you have whole-genome sequence information is scan the genome for the known binding sites for this transcriptional regulator that occur upstream of genes. In doing this, we were able to identify a much larger number of these genes in both the cereus and the anthracis genome. Given what we know about this transcriptional regulator being important in virulence, we can then assume as a new starting point for follow-on investigation that the genes that have been identified, the additional genes that are preceded by this binding motif here may also be involved in virulence.

When we put together a list of what those are, we see a much larger number of potential virulence factors than had previously been appreciated, and interestingly those on the chromosome are essentially shared entirely between Bacillus anthracis and its much less virulent relative, Bacillus cereus. So this gives us a way now to begin to focus in on a subset of genes and ask what role do these play in virulence and begin to help put the relationship between these organisms in better perspective.

Continuing with our anthracis work, we've also, I think, done a great deal in the past few years looking at differences between various isolates of Bacillus anthracis, hoping to better understand the known differences that have previously been described in phenotype. There are some isolates of Bacillus anthracis that are almost avirulent, and others, like the Ames strain that was sent through the U.S. mail, that are highly virulent. We'd like to understand what those differences are and ultimately use that information in the design of novel vaccines, novel drugs, et cetera.

It just so happens that in 2001, at the time of the anthrax letter attacks, TIGR was working on finishing the genome sequence of Bacillus anthracis, and we decided that we would ask the question could we use comparative genome analysis and leverage the genome data that already existed to try to get additional insight about the attack strain that had been sent through the U.S. mail. At the time of the attack, the VNTR analysis done in Paul Keim's lab at Northern Arizona University had shown that the bioterror isolate was the Ames strain, but there was not much that could be said beyond that.

This is a summary, if you will, of the history or what we think the history of the Ames isolate is. It originally came from a dead cow in Texas in 1981, was sent to Fort Dietrich, and from there it was distributed to labs around the world. We received our isolate for genome analysis from Horton Down in the U.K. To make a very long story short, what we did in terms of comparative genomics was get access to the isolate that came from the CSF of the first patient to die of inhalation anthrax in Florida, and by doing a high-draft sequence coverage of this Florida isolate, we compared it with the reference Ames strain that we were working on and, in fact, found a number of additional polymorphic loci between the two strains. These were then used by Paul Keim, who was a key collaborator on this project, to further extend his genotyping assays.

The outcome of this was that we were able, using this new information, to further distinguish a small number of Ames isolates, all shown here in blue, that had previously been indistinguishable based on existing genotyping information back in October of 2001. We were very encouraged by these results, and we have been funded now by the National Institute of Allergy and Infectious Diseases to take this a bit further and to look more broadly within the Bacillus anthracis project to develop new tools to analyze these closely related genomes to look at these clonal isolates, and at the same time to develop new methods for automated SNP discovery and to further explore B. anthracis as a model system for comparative genomics.

Shown here on this slide is a family tree, if you will, of Bacillus anthracis. This is also work from Paul Keim's lab, genotyping assays looking at many hundreds of isolates that had been collected around the world. It's suggested that there are two major groups of Bacillus anthracis, A and B, and within each of these groups there are a number of subgroups, and we have looked, at least we've started to look very broadly across this phylogenetic tree looking at isolates with different geographic distributions, with differences in phenotype.

This is still work in progress, but with the available sequencing capabilities that we have, we're able to generate data very, very rapidly. I think one of the most exciting and completely unexpected results from this work is the discovery of an entirely new taxonomic group of Bacillus anthracis that Paul Keim has designated as Group C. This was originally isolated from Louisiana several years ago. There are two strains that exist of this new Group C. They contain one of the key plasmids that encode the important virulence genes but not the other.

You might say, well, so what? What's the importance of one more group of Bacillus anthracis isolates? I think it becomes important when you put this information in phylogenetic context. Here is the new Group C that has been identified. These are the existing Groups A and B that we are working on. It turns out that this Group C Bacillus anthracis looks to be much more closely related to Bacillus cereus, that we think may have been an ancestor of Bacillus anthracis. So it looks as if, as part of doing this work, we're beginning to perhaps get better insight as to where these more highly virulent isolates of Bacillus anthracis might have come from. So this is work in progress and we're going to be continuing with this over the next 18 months or so.

The ultimate goal is to develop a comprehensive database of Bacillus anthracis isolates, and I'm not going to say too much about databases. You'll hear much more about this from Bruce Budowle. We're taking a number of approaches, and I think it's important not to just limit this activity to Bacillus anthracis. I think that this is the kind of information that could be critically important for all major human pathogens, because if this kind of information existed for the family of corona viruses, for example, we would have been able to ask when the SARS outbreak first occurred where did this come from, where was this last seen geographically, what does this most closely resemble in terms of other corona virus isolates, and I think we would have been much further ahead than we were, although I have to say the speed at which the developments in tackling the SARS analysis have taken place have really been very laudable.

So the bottom line is that I think if we have a better understanding of DNA variation among various bacterial isolates and strains, it will be important for a number of reasons, both in terms of

epidemiological studies and microbial forensics. It's not out of the question to think that if we have this information and we can do additional follow-up work, that we may be able to predict clinical outcomes based on having genotype information.

In the case of bioterrorism events, this kind of information would certainly increase our ability to rapidly detect genetically modified strains, and for a lot of work that's currently going on in terms of vaccine development, development of novel therapeutics, this is critically important information. You don't want to be developing a new vaccine against a protein that's not widely distributed among natural isolates of an infectious agent. So we really want to know what the variability is, and as we've seen already from some key examples, the variability can be quite profound. So it would be nice to have that information up front.

Bottom line is I think that over the next several years we'll begin to see this information applied in new ways. This is perhaps a bit of an exaggeration of where we are today in terms of our ability to make identifications, but I think with genome sequence information, microarray technology, proteomics technologies, et cetera, it's not out of the question to think that at some point in the future we will be able to much more rapidly collect this kind of information about a particular isolate, and that will give us a tremendous advantage over where we are currently.

Again, I remind you that this is not about bioterrorism. I think more importantly it's about anticipating, understanding natural outbreaks of disease. I think this Newsday headline is very, very topical, that the worst bioterrorist may be nature itself. We've seen too many examples of that recently. What could be added now to this slide of a number of emerging and reemerging diseases over the past 20 years or so is West Nile, SARS, and perhaps even the most recent reports of the outbreak of Monkey pox in the Midwest.

So let me conclude, then, by just briefly talking about how microbial genomics approaches have had an impact already on our understanding and treatment of infectious disease. One of the real hopes in undertaking a lot of these studies initially was that this kind of information would greatly accelerate the discovery of new antimicrobials and would provide new targets for antimicrobial development over the current three pathways that are targeted with all existing antibiotics, those being DNA synthesis, protein synthesis, and cell wall biosynthesis.

Many academic investors, many biotech companies, many large pharma companies have certainly used genomics information to begin to identify new sets of targets, taking very different approaches, some of which are summarized on this slide. I heard Gail Cassell speak about a year ago. Gail used to be head of infectious disease research for Eli Lilly, and she said microbial genomics has more than delivered on its promise to identify new targets. In fact, the pharmaceutical company now has probably close to 200 new targets for follow-up. Not all of these make good targets, and the next step is, in a large number of new targets, identifying those which make the best targets.

But I find it ironic that in this era where there are potential new avenues of investigation for development of new antimicrobials, that a large number of pharmaceutical companies are shutting down their infectious disease research programs. This is extremely troubling, because I think there is very much a consensus that our current arsenal of antibiotics is not sufficient. With one exception, there hasn't been a new class of antibiotics developed in 30 years, and many of those that are out there, we see many, many examples, ever increasing, of antibiotic resistance. There have been too many reports over the past few years of Vancomycin-resistant Staph. aureus, Vancomycin being considered the last line of defense.

So I think that this is a critically important issue. I think that we collectively are poised to begin to try to exploit some of this information, but unfortunately the economics of the bottom line are just not making that a reality, and I find that very disturbing.

The other area where we've seen some notable successes using genomics data is in the area of vaccine

research. Whether it be for infectious disease or bioterrorism, the goal is to develop new vaccines to protect all groups of civilians, and there are two needs here, to develop better vaccines against microbes for which vaccines currently exist -- I think the example with the smallpox vaccine is a great one -- and also the opportunity exists to develop new vaccines against pathogens for which none currently exist, and the list there is quite long.

This is just one example of how this kind of information can accelerate vaccine development. This is work that I know well because it came from TIGR, in collaboration with a group at Chiron Corporation, but there have been many reports published since this first appeared in March 2000 in Science using a similar approach to vaccine development based on having genome sequence information available.

In a very short period of time now, we can generate the complete sequence of a pathogen genome of interest. Back when we were doing this, three to twelve months. We can now say this is, depending upon the center you're looking at, three to twelve days or three to twelve hours, depending upon who is doing the work. In a very short period of time, this information can be mined using a number of available algorithms to look for potential new vaccine targets.

In the case of Neisseria meningitides here, 570 putative secreted or surface proteins were identified. These were all expressed recombinantly in E. coli, used to immunize mice. The sera were collected and screened in a number of assays. In this very large-scale triage process, seven proteins emerged with very high titers. In all of the assays, and these were finally assessed for their sequence variability, something that pathogens seem to be able to do well is generate sequence variability in their cell surface proteins.

To make a long story short, two of these proteins out of this screening are now in Phase I clinical trials, and our Chiron colleagues have told us that having this information and taking this new approach accelerated this part of the vaccine development process by about three to four years, so that's very encouraging. But again, we're also finding ourselves in the situation with vaccine development of perhaps not having sufficient incentive for large pharma to develop vaccines.

Finally, with the availability of the human genome sequence, we can think about tackling infectious disease as well from the point of view of the host. I think some of the most exciting work that will come in this arena in the next few years will be further exploring both innate and adaptive immunity, and we should probably add to this slide host susceptibility to disease, because there certainly have been a number of reports already that have suggested that, in fact, there is individual variation. So when we're talking about SNPs and variation and susceptibility to disease, it's important to include susceptibility to infectious disease in that group as well.

This is work from David Relman's lab. I think this represents some of the most exciting potential application of human genome sequence information to infectious disease. What this is, is information from a microarray analysis of human lymphocytes following exposure to a number of pathogens or microbial components known to induce an immune response. It's too early to know whether we'll ever be able to generate signature expression patterns that will be able to say that an organism has been exposed to a specific agent, but it certainly looks from this information that we can say that an organism has been exposed to an infectious agent in general.

One of the hopes with this kind of approach and technology is that with the development of these kinds of assays, it may in fact be possible to get a readout like this before symptoms ever appear. So when we're thinking about the bioterrorism scenario, it would be wonderful to think about being able to screen large numbers of patients who were potentially exposed and get an answer before symptoms develop, because sometimes that can be too late.

Final slide here is that as we continue to make progress in the area of microbial genomics, and there has been a focus on biowarfare pathogens more recently, there have been some renewed discussions about whether some of this information should be kept out of the public domain, the fear being that somehow

perhaps we may be providing information on new virulence genes, mechanisms of pathogenesis that may facilitate engineering of a superpathogen, if you will. There are a number of discussions ongoing. This is not a dead issue by any means.

My own opinion is that the more open these databases are, the better, because without this kind of information, we're not going to see the follow-up work taking place that we've already had a glimpse of already. But these are terribly complex issues. It's not so simple to say we need to have this information out there to accelerate research. I think the real difficulty comes in not being able to adequately assess the risk or the potential risk of this information for those who might want to use it for malicious intent. So this is a somewhat recent development but one that we're going to be following very closely.

Let me just conclude by acknowledging my colleagues at TIGR and a number of important outside collaborators who have played key roles in our microbial efforts over the past several years. Thanks.

(Applause.)

DR. McCABE: Thank you.

We're going to alter the schedule a little bit. Francis, if you could join us down here -- well, I guess you can take questions up there as well. If you can join us at the table, Dr. Fraser, because Dr. Rowe has to leave at 3:00. So we'll do some Q&A now until 3:00 and then take our break. Dr. Budowle has agreed to take the break out of sequence.

Questions for any of these three speakers?

DR. WILLARD: Francis, can you say a little about --

DR. McCABE: Can you get closer to the mike, please? Thank you.

DR. WILLARD: Can you say a little more about the thinking about this half-million patient cohort from the perspective of the depth and the type of clinical information that one would want to have? Obviously, one doesn't want to get partway down this process and then find out that, oops, we should have been collecting other kinds. And yet, we have this wonderful, wonderful in quotes, track record of people keeping dietary questionnaires, and it's just not a terribly robust or reliable set of data, and yet that's what I thought I heard you arguing for.

DR. COLLINS: Well, this is still a sort of very early stage of any discussions on such a project, and I can't say at the present time there's even a groundswell of enthusiasm for doing such a project. I happen to be pretty positive about it because I think without it we're going to be kicking ourselves in six or seven years wondering why it was we didn't think about setting up a study that would give us an unbiased view of genotype/phenotype correlations.

But there's a whole long list of critical questions that would have to be answered. What is the right number of subjects to enroll in order to get sufficient power to make those assessments for common illnesses? You can go through the mathematics. If you draw much below half a million, you're not going to have enough incident cases, even of reasonably common disorders, to be able to draw strong conclusions about the relationship of a particular allele to the onset of disease, and particularly so if you want to intersect that with environmental data.

You're asking a very good question: What kind of environmental data should one collect, and how sophisticated can we afford to make that in terms of the cost of the enterprise? Dietary questionnaires would be a small part of this. Obviously, you want to know about more than that. You want to know about exercise, you want to know about smoking, you want to know about alcohol, you want to know about work, you want to know about stress, and there are certainly people who have studied those kinds

of issues to a considerable extent, but it's certainly never been contemplated to apply something on quite this scale.

We certainly talked with our colleagues at the CDC about this. Obviously, the NHANES experience is one to look at in terms of an enterprise that's tried to do some of those same things. But I think before one would even think about starting a project of this sort, you would have a couple or three years of a very careful planning process to try to pick the brains of everybody who has useful ideas to contribute about how to design such a study, as is currently ongoing in the U.K. with their BioBank project.

DR. McCABE: Because we don't have much time, I've got Reed, Chris, and Debra, and that will be it before the break. So please try to keep your questions and your responses brief.

DR. TUCKSON: After the wonderful, vigorous ethics discussion at the very beginning, I would have liked to have asked Jack more questions that would have elucidated the comments he made, which I thought were terrific. But I'll have to pass on that part.

DR. ROWE: I'll take advantage of this, because I wanted to follow up on something that Francis said which is very important to me and to Aetna, and I think to all of us, and that is with respect to the issue of racial and ethnic disparities. Unfortunately, there appear to be data to indicate that certain racial groups, particularly African Americans -- and I haven't seen the primary data here, but this was reported to me -- are much less likely to be willing to have genetic tests and much more concerned about issues of discrimination, which is understandable.

But if that's the case and if that plays out with respect to the clinical application of genetic tests, this is just going to further aggravate the racial and ethnic disparities we have with respect to being able to provide people with access to appropriate care, et cetera. So this is, unfortunately, in the wrong direction and is an issue that I think would be particularly important with respect to the education of physicians so that they will be aware that there may be some reluctance and particularly motivated to make sure that the patients who fit into those important populations did have the opportunity to have tests that would be appropriate for diseases that they were at risk for.

DR. TUCKSON: What I'll do is just ask Francis, and maybe we can come back to it for a deeper discussion.

I want to have a little bit of assurance on your research agenda. It is a very big agenda. You talk about diabetes, cardiovascular disease, cancer, psychiatric disease, arthritis, asthma, and right now we've got basic research in all those areas. We've got therapeutic interventions being developed in each of those areas, and diagnostics. We've got a health services research agenda to worry about. We've got a CDC preventive agenda to worry about in all those, and it sounds sort of like there is, although listening carefully I don't think this is what you called it, another set of research agenda.

We've got to feel confident at some point that somebody in this government is coordinating all of these things so that things are not additive but they're synergistic, prioritized, and some sense of sequentiality, that one thing is related to another and to another. Unfortunately, as a member of this Committee and really a member of the public, we don't hear that articulated. So it sounds like these are mutually competitive agendas, and I hope at some point we will have time as a Committee to delve into that.

DR. COLLINS: I would like to reassure you that that is not what this document aims to try to put forward. Clearly, the ambitious nature of the milestones that are described there would never come to pass without the participation of lots of other entities, just well beyond the Genomics Institute at NIH. If you look in some of the language that's in that document, it repeatedly talks about this is only going to happen with partnerships, partnerships with other NIH institutes that have specific interests in particular diseases, like diabetes or heart disease.

We see genomics as providing some tools, and that's certainly what my institute hopes we can do. But the application of those to specific diseases goes well beyond anything that we could contemplate or should contemplate doing by ourselves. Similarly, as in the example of this large-scale cohort study, the kind of collaboration between NIH and CDC that would be necessary to make this happen, and in fact other agencies within the department as well that have already been represented in this group, like HRSA, for instance.

So I would like to be somewhat reassuring that although it may seem as if all of these various plans are occurring in silos, my own experience after 10 years of being here is that that really is often not the case. In fact, it's usually not the case. One does identify ways in which agencies have shared missions, and we work on them together and not in isolation from each other.

DR. McCABE: Thank you.

DR. HOOK: This is a question for Dr. Collins, but it follows up on what Dr. Rowe has just mentioned, and that is the issues of racial disparities and racial attitude toward genetic testing. In the 500,000 epidemiologic project you're discussing, how much of that is planned to include adequate numbers of minority individuals? How do we ensure that they will participate? Are we going to have to expand it to make sure that those data are appropriate for all the different populations we represent?

DR. COLLINS: That would be absolutely critical because, as I outlined it again, please don't assume that this sort of idea that I floated in front of you this afternoon is one that's already been fleshed out in a lot of detail. It certainly has not. But for this to be a defensible project, it would have to be set up in a fashion that sampled adequate numbers of minority populations to be able to draw meaningful conclusions, and certainly that would have to include in this country African Americans and Latinos and Native Americans, and perhaps others as well, in the same way that the NHANES effort that CDC has done, which I mentioned as a possible pilot, has done that same sort of oversampling in terms of relative numbers in order to be able to draw conclusions that are meaningful across populations.

All of that would then have to deal with the issue already pointed out about reticence, and even suspicion on the part of some members of some populations about research in general, and particularly genetic research given the history of sickle cell disease and carrier testing for that, which is still resonating in many people's minds and which was a very unfortunate experience back in the 1970s.

DR. LEONARD: I don't mean to beat a dead horse, but this large patient cohort with genotype/phenotype correlation is, I think, essential to achieving that correlation between genetic variation and all these different diseases that we talk about. If that is not in place somehow, then I think all the benefits that you're talking about are not going to happen. So this is already happening in the private sector, and my fear is that there will be -- or my concern is that there will be privatization of this type of information as private cohorts are created, cohorts of patients.

Is there any way that policies or recommendations can assist in moving this project forward in a public manner so that it doesn't get privatized, as we've seen with other things?

DR. COLLINS: I don't in any way think that it's a bad idea that there are private-sector investments going on in cohorts of this sort. I think they are, in general, not going to be like what I'm describing, which is a large-scale, covering all disease kind of enterprise. They will be cohorts focused on specific diseases for specific drug response clinical trials.

DR. LEONARD: No, there are private ones that are just "send in your buccal swab and your medical information" that exist now.

DR. COLLINS: Okay. But to what extent are those aiming to accomplish this kind of large-scale genotype/phenotype correlation, collecting all of the kinds of additional data I mentioned? I would be

doubtful that there's something quite on that scale that would make business sense in terms of being able to accomplish what we're talking about here.

Never mind. Just the same, I think it's critical to have a public effort of this sort if you're really going to be able to have the kind of input that we would all want to see in the design of the study, if you're going to get public participation on the scale that's expected here. I mean, I would hope that participation in a study of this sort would be seen as sort of a badge of a U.S. citizen of a particular dedicated sort, that I'm part of the United States National Study of Health and I'm going to be enrolled in this study for the next 10 years and undergo questionnaires and some additional medical testing that otherwise I wouldn't because I want to do something to help understand why some people are healthy and some people are not, and maybe this will be a contribution I can make to my family, to my community, to my country.

DR. LEONARD: We need to do it.

DR. McCABE: With that as a comment, you can sign up for Francis' study. There's a sheet at the registration table.

(Laughter.)

DR. McCABE: For all ex officios and Committee members, please come to the front of the room before you take your break. We're going to have an official photograph.

(Recess.)

DR. McCABE: We're going to go ahead and get started. Our next speaker is Bruce Budowle, who will speak on issues in the use of genetic technologies in forensics. Dr. Budowle is from the Forensic Science Laboratory, Federal Bureau of Investigation.

DR. BUDOWLE: Thank you, Ed, and thanks for inviting me to speak today. Just first a word from my sponsor. It's not a Webbie but it is an icon. I was asked to talk about genetic technologies and issues in forensics. I didn't plan to talk about microbial forensics. I thought of focusing on humans. But there is a large field of initiatives in microbial forensics on much of the issues that Claire talked about, and I'd stress the same things about databases. Many of the people with purse strings today think that sequencing one organism is all you need to do and that's sufficient for information. That would be a bad decision to make both for forensics and understanding diversity for the significance and weight of an observation, as well as for therapeutics, drugs, and so forth.

The other main issue to be concerned about is big discussions in security and dissemination of information, where there are some very diametrically opposed viewpoints on information. It gives bad people tools to make bad weapons, versus information helps good people make good tools to fight disease.

I thought I'd start off with the questions that were posed to me so my talk would address the questions that I think Sarah sent me on what are the technologies and the purposes, samples being collected, the kinds of people we're collecting samples from, expanding the breadth of individuals that we might be collecting samples from, are those samples available for other things, privacy issues, legal/social issues, and databases.

So first, we ought to understand what forensics is about and have a case, and I could have put up a violent rape case or whatever, but this makes the point just as well, where we have an individual that's been murdered obviously by a sharp object, and we have to now resolve who was the perpetrator of the crime by being able to identify one individual at the exclusion of all the others in this population here. We're going to use tools, genetic tools and other kinds of tools -- a fingerprint can be a tool, whatever it may be -- to identify who could have done it and who could not have been the perpetrators of the crime.

That's our ultimate goal.

So forensic science is basically just science with legal matters. We're going to use science and technologies to be witnesses to help us resolve an event. It may not be the absolute identifier, it may not be the smoking gun. It's just a tool that can be used in addition with other evidence to help, and it plays a special role. But we like it because it is objective. We can make a test and we can interpret the evidence. But I wanted to stress that it's for identity purposes. It does not prove guilt or innocence for human identification. It only identifies an individual or a group of individuals that might be the source, as well as identifies those who may not be the source of the particular material found at the crime scene.

There can be situations where a sample is found and it has no bearing on a crime. For instance, you could have an estranged husband and wife, the wife kills the husband -- which would probably be justifiable in most cases -- and you find a small blood spot in the house. Well, the wife also resides in the house, and having a small blood spot in the house that matches her does not necessarily mean that she killed him or not. I should have said allegedly killed her husband.

There are many kinds of applications for human identity tests, and I've listed them here so I won't go through them. But realize that it's used more than just in criminal cases. It's used in paternity testing, historical investigations, evolutionary studies, for the military, mass disasters, mixed-up samples in hospitals. These are just some numbers to give you an idea, and these may be a little dated because it's probably a little higher now, but there's about 250,000 paternity tests done each year in the United States, about 20,000 criminal cases that are analyzed per year. So it's well ingrained and routinely done. Probably this field has embraced and applied molecular biology tools more so than any other field to date and has had success in resolving cases.

The advantage of using DNA over the prior systems, the protein systems, is that you can look at a large variety of tissues that might be found at a crime scene such as a hair sample. If we look in this room, we'll find hairs from a number of individuals that have been naturally shed, some of us unfortunately more so than others. Right, Ed?

(Laughter.)

DR. BUDOWLE: He wasn't listening, so --

DR. McCABE: I just have less to shed.

DR. BUDOWLE: That's one way of looking at it, yes.

(Laughter.)

DR. BUDOWLE: Makes you a better perpetrator.

DR. McCABE: Yes.

(Laughter.)

DR. BUDOWLE: A single hair could not be typed for the typical isoenzymes or serological proteins, but if there's any nuclear or mitochondrial DNA residing in that hair, it could be exploited and typed.

There are many methods that have been used, and the predominant methods of today are looking at microsatellites, repetitive elements, not a lot of information that can be gained from them on a personal level but only for identity purposes. Mitochondrial DNA for those very challenged samples such as old bones, teeth, a hair shaft; and then there's work also using Y markers for special kinds of cases, not for routine, such as a violent crime where there's very little male DNA in a large background of female DNA,

which would be difficult to type by standard systems; then with some of the mass disasters and other issues arising, SNPs have been applied looking at specific sites in the nuclear DNA and mitochondrial DNA.

The kinds of evidence you see, I'm going to run through these quickly so you get an appreciation. It could be anything from stained clothing to bodies being recovered in Kosovo, and we all know the World Trade Center, predators on children. This is a case where DNA was used to identify three missing girls in Virginia, recently resolved. Using the data to solve older cases by database work; we'll talk about that in a minute. Vehicular manslaughter cases being tied up. People being exonerated who have been falsely associated with the evidence or with the case and having now the tools to be able to get better resolution. You can have a man being freed by implicating his brother because he has a similar DNA type.

One of the things that makes it valuable is that it's hard to get statements out of some witnesses. Witnesses don't want to testify. So when you can have scientific evidence, that can help resolve some of the information that's provided. Some witnesses aren't considered credible by some people. A prostitute who is testifying may not have the same credibility to a fact-finder that would be the President of the United States in another kind of DNA case, would not have the same credibility as maybe some other witnesses may have. So again, this has value in that sense.

Victims. This was a woman I talked to who actually was abducted from her home and raped, and then sent back and said if you say anything I'll kill you, and for many years she had this tremendous fear of even going outside, always looking around that somebody was going to attack her, because this person was still out there. Recently they actually identified him with the database, and that brings a different kind of security to the individual subsequently, even though it was years later.

Then there are the parents of victims who are still on vigil looking for the killer of their daughter, for instance. So you can see a wide range of applications and uses that affects society. Paternity testing, as I mentioned. Lineages; this is the lineage study of Thomas Jefferson and Sally Hemmings, an offspring. I might mention that it's the lineage of Thomas Jefferson. It doesn't prove it's Thomas Jefferson because it was a Y marker. It could be any male relative that would be in that lineage.

It can also be used with animals, tying things together in cases. This is a well-known case with Snowball the cat, where the perpetrator was identified, had a jacket, and there were white cat hairs on it, and the victim had a cat. They did some STR typing on the hairs, and the cat matched them up, and that was entered into court to help them assist in determining the course of the case.

It can also be used in poaching, smuggling, population management, all these applications, and also botanicals might be typed to help resolve a case. This was a well-known interesting case in the early '90s where a woman was found buried next to a Paloverde tree out in Arizona, and the suspect had a truck, and in the bay of his truck were Paloverde pods, seed pods. They did a rapid DNA test on it and they matched and went into court. They said it was unique because they typed 18 other trees and they were all different, so it could only have come from that tree. There was a little debate on that and may still be a debate on that. There was a number entered in, but it wasn't uniqueness.

Now that you have an appreciation for some of the ways it can be applied, we use databases to help solve cases by giving us investigative leads, and the idea of a database is to put in your information, to retrieve it to, as I said, get an investigative lead. So a crime is committed, you have no suspect. If you can go to a data bank of convicted felons with the idea of recidivism being that some people commit crimes over and over again, he may be in the database and you can catch him before he does it again.

The database is called CODIS for Combined DNA Index System, and it's a hierarchical database on three levels, from local to state to federal, and it has a number of files in it today, from convicted offenders files, people convicted of certain crimes based on the state's legislation and federal, and each state has

slightly different legislation of what samples they can take or who they can take them from. There's a forensic file of case samples from unsolved cases. Now we have a missing persons file and a human remains, which are the same file; relatives of missing persons, which is a special file; a file for using population statistics, why we need databases of anonymous individuals; and I mentioned suspect files, although there is no legislation and the FBI does not have a suspect file of DNA profiles. Some states do have what we'll call shadow databases, and that might raise some concern on privacy, so I bring that up.

There are a number of databases planned around the world. Many countries have implemented them, quite different rules and regulations depending on them. The British, for instance, have probably the most open rule. Just about anybody walking with a tire iron in their hand can be taken a sample from, versus some others where it must be very serious crimes and only for a limited amount of time, to everything in between.

Although there are different policies from all the states and countries, there's sufficient common base on the genetic markers such that we can communicate from state to state. Within the United States, it's all the same. But from country to country if there's any kind of international incident that has to be done.

Now, of course, with success, the first thing that happens is you've got to expand the crimes that you're looking at. Initially it was violent crimes in the United States because we were interested in what we call quality of crime, the worst types of crimes, the ones that affect individuals, rape and sexual assault being the highest level. What's been found since then is that a lot of cases where they've been convicted of rape or murder, a good percentage of them actually were convicted of burglary or other things earlier. So it now expands to all sorts of felonies and maybe other kinds of crimes as well.

Now there are some states, Virginia and New York in particular, that are considering all arrested individuals. I don't know where they're going to get the money to do this, but that's going to be a large database. It can include indicted persons. Terrorism-related offenses are now being part of this system here. There have been studies through the National Institute of Justice, but it does bring up an issue of individuals' rights in society, and there's a real balance here of who should be tested and why. I mean, I personally don't want to be tested. Probably one of the first famous cases in DNA is two teenage girls are murdered, there was sexual assault. It was in England. They go around and collect up 5,000 people, and they do it voluntarily. But, of course, if you don't volunteer, then you're a suspect. So there is this peer pressure and it does create a problem that I hope does not become the norm for the United States. But that's an issue you have to think about when you're applying these.

Now, when you have the data, you're going to have all these samples, and I mentioned these things, but I'll mention the relatives of missing persons. Those are in there voluntarily for one purpose only, and that's to compare for when you find the remains of some putative missing person. Well, it is a missing person but putative to the family members. They cannot be searched against any other data files, and they can be removed upon request.

The interesting one is that you have unidentified human remains that are found because you just found remains, and currently they can be searched against the criminals' samples and the convicted offender files, and that becomes interesting because it could be the brother of somebody in there, as well as you could search a crime where the brother committed it but he's not in the database and look for partial homology because of the relatedness of the individuals, or a parent or whatever, so you have to think about these things.

I mentioned the suspects issue, and the last I'll mention is the DNA samples. Currently, we collect the blood or a buccal swab, extract the DNA or maintain the sample, and that's stored. The reason it's stored is for really good reasons. It's a quality control factor. Let me take a step back. In forensics, when you make a case and you're going to err, you'd like to err on the side of a false exclusion as opposed to a false inclusion, because you'd rather let a guilty man go free than convict anybody who is innocent.

In a database, you want to err the other way. You'd rather have a false inclusion than a false exclusion, because if you falsely exclude, you don't make the match and you don't solve the crime, you don't get that person off the street. If you falsely include them, since you have the original samples remaining in the data set, you can go back and confirm it and resolve those kinds of mismatches. That's a real value in the system.

The second is that as technologies change, although we don't foresee this technology changing for a long time for a lot of other reasons, stability being one of them, and cost being another, you would want to go back and re-do those samples so that as you're typing new cases you have the same individuals typed for the current set of genetic markers. If you throw away the samples, you may never get them again. So there's some really legitimate reason for it, but using it for any other purpose is a serious concern, and I can talk about that as you want.

So questions you might ask are can the suspects in that shadow suspect database who have been exonerated, because if they'd been convicted they're in another database now, can they be searched against other cases on a future date, whether that's a legitimate thing to do? I mentioned some of these other ones.

Because of the tools now, we can look back at older cases, and because of the lag time because of resources to analyze cases, some crimes fall under statute of limitations. So now there are some very clever ways that have been constructed -- I don't want to say contrived because that sounds nefarious -- constructed dealing with an unknown perpetrator, and I think this first case was in Wisconsin of creating a John Doe warrant. In other words, I don't have a name but I do have a profile that represents a person, and that now no longer allows you to be stuck under that statute of limitations. So you have to think about other issues that arise when you have the tools to analyze things.

You could also extend the statute of limitations, you could eliminate the statute of limitations, and various jurisdictions are considering these.

Now, for privacy concerns, there are issues that have been addressed about limited access based on the law and for identification purposes only. So this is not that someone can go out and say I'd like to get a bone marrow repository enhanced by all these convicted felons. That's not the purpose. But I do think one or two states do have this humanitarian clause, but most of them do not.

So what is the federal law? The federal law dates back to 1994. It authorized the National DNA Index and put certain requirements in there for this index, and participation, who can actually create a file and who can access those files. So the records are of persons convicted of crimes, recovered from crime scenes, the unidentified human remains I mentioned and so forth, and the people for the index shall only include information on quality assurance and proficiency testing. There is no other kind of identifiers in this information. It's all coded, so when you look into it you'd have to go back to the state itself or, if it's a federal prisoner, to the government to get that. So there would be limited disclosure of information.

Now, the limited access for these data by law is for law enforcement identification purposes, judicial proceedings, and for criminal defense purposes so a defendant can have access to the samples and analyses performed in connection with his or her case. That one I think is a very ill-defined one, and I don't know how that's going to play out. When you say samples involved in the case, a database search could be 1.2 million individuals. Do you get access to all that? Do you get access to just the fact that you got a hit? I think those are still arguments being played out in the court today.

Now, access to the database is described, and also the cancellation if you don't meet the QC for quality assurance and the privacy requirements. In other words, if someone fails, like we've heard in the newspapers that some crime labs were not up to snuff, they would be taken out and a lot of their data may be expunged if it didn't meet the requirement.

What's imposed on the states is that to participate in CODIS or the national index system, you have to follow these requirements if you participate in CODIS or if you receive federal funding. So that's the lock that gets everybody into it. I'll leave there here because time-wise you can get these all yourselves. But state law, I wanted to bring up a couple of points. This is a little dated data. It may be a little different now, but about a year or two ago about 60 percent of the states did have provisions that penalized people for unauthorized disclosure of DNA information or giving up the samples. Most of it is at a misdemeanor level. Most states can have a felony level for tampering with the evidence, though, and I think that's more because those are traditional kinds of laws, not so much because of the database.

To touch on disease associations, I think I'm with a group of people who understand this, but there is a proposition that we have to be concerned about, that the markers that we use, although they don't encode themselves for proteins, may be associated with disease and provide some information about the person beyond just identity. There are some repeat sequences such as certain expansion repeats that are associated with diseases that are well known. But for the markers we have, they don't seem to have that kind of an association or that kind of functional effect on that. So the relative risk is rather low to provide information to date with the information we have on an association.

Not to confuse cause and effect with association. There's a big difference here between those. So I'll give one example that's known, and there's another one too, but this is just fine. If you look through one of the repeat sequence markers called THO1 that resides in an intron in the tyrosine hydroxylase gene, people have been interested in this gene because it's in the catecholamine pathway, so it might be associated with certain neuropsychiatric diseases, bipolar disease, schizophrenia. So there have been some studies done looking at populations of healthy and, let's say, people with schizophrenia, two studies actually, French and Tunisian, and they found that a particular allele which is relatively rare to have a higher risk in the individuals who have schizophrenia than in those who do not.

When you went back, there was no family history associated with it. Other studies done show no association with the 10 but maybe another allele showing up in that, and that's probably one of the problems I was talking with Francis during the break about the half million people, that I think you need to up the number, because a lot of these kinds of confusing studies, we have very heterogeneous populations, and you need to define them better, make them more homogeneous through a lot of admixture studies and things, so that you can get some of this haziness out of the way so you can find out what's real or not. But in the end, the relative risk would increase from one-half to 1 percent to 1 to 2 percent, hardly enough to be worried about. If I had a 1 to 2 percent risk, I certainly wouldn't be worried about taking any kind of drug therapy at this point in time.

So in conclusion, given how the technologies can be used, given the idea of some of the samples, the idea of expansion, there is one thing that a couple of us voted against, but we lost. Eric will tell you. They can use it for research purposes for forensic tools, developing other tests. I would argue it doesn't make a lot of sense, but that's in there. Privacy issues still abound, but there's a lot of laws in place in many states to give punishment if people use it beyond what it's supposed to be or tamper with it. The databases are not a problem. We all use the same genetic systems throughout the United States. We all use the same software and communication, and there's the same quality assurance standards are applied across the board.

Then there are some legal/social issues. The social ones for privacy as far as knowing something about the individual, probably very low for these markers. Other markers as we go down the line may present a problem. There are a lot of people who want to switch to SNPs because it's the designer marker of the day. There are technologies advancing to it. It's not trivial. To gain the amount of information that we get from the current battery of core loci, we would probably need around 70 or 80 SNPs, and that doesn't get into the issues of mixtures and other kinds of family relationship kinds of tests that would confuse that. That's not trivial to make a robust technology for 70 to 80 SNPs. While we have lots of chips and things, they're not robust enough today to be able to make it into the forensic arena, where we really demand a higher quality, reliable system.

So it's not going to happen quickly, but in some instances, like the World Trade Center where there are these victims, we've gotten down to the dregs of materials, highly degraded, SNPs could make sense. If you take 60 or 70 SNPs, you run out of real estate for unlinked loci, biologically speaking. So you have to keep that in mind, that eventually you're going to hit some marker somewhere that's close to some other gene, but maybe in that particular situation the humanitarian effort of identifying an individual might outweigh the risk, and that's something you have to think about.

So with that, I'm done. Thank you.

(Applause.)

DR. McCABE: Thank you, Bruce.

Our next speaker is Dr. Eric Juengst, whose topic is ethical, legal, and social implications of genetic technologies. Dr. Juengst is Associate Professor of Biomedical Ethics, Case Western Reserve University School of Medicine.

DR. JUENGST: Thank you, Ed.

It's an honor to be invited to address you at your inaugural meeting. I also had the honor to work with Bruce on the DNA advisory board for a couple of years, and I learned that he's considered a very lucky guy within the agency because he not only gets to look into the X Files but the Y Files as well.

(Laughter.)

DR. JUENGST: I want to give, like my predecessors, a survey of issues that I think will be on your plate, or could be, and with an eye to the future, what's coming down the road, and an eye on issues that are ripe for public policy development at the federal level.

This is an auspicious time to be launching this commission because, as Francis said, we have just celebrated the completion of the Human Genome Project, achieving what Walter Gilbert, Harvard biologist, said early on in the late '80s was the holy grail of human biology. Well, we've achieved the grail, and now we've got to live with it. The question is, once you've achieved the grail, what are you supposed to do with it? The legends don't tell us that. It's all about the quest.

But we do have to face living with the grail. Here is a paraphrase of Francis' famous chart. I've turned it upside-down to emphasize that grail-like aspect to it.

(Laughter.)

DR. JUENGST: The three sets of products, fruit, that the Genome Project will yield, going through three further areas of research are the technology development that will give us the microarrays and DNA chips that will improve our testing capacity to do genetic risk assessments of multi-site problems of complex traits of polygenic diseases; secondly, the research track through functional genomics, working out how the genes are regulated and expressed in cells that will underlie a new generation of gene therapies, gene therapies that are actually grounded in knowledge about how genomes work; and finally, the study of genetic variation, the population genomic studies that will bring us to a sense of our individual susceptibilities and how to tailor pharmaceutical interventions to individuals.

Well, I think each one of these tracks raises issues for us as a society, so I want to go through each one briefly.

This is the most familiar set of issues, the one that the research funded by the ELSI program at NIH has been preoccupied with for the most part over the last decade, the questions that spin out of new

generations of genetic risk assessments of various kinds. Here's another prediction about the fruit of the Genome Project from President Clinton in his campaign for reelection in '96: "I think it won't be too many years before parents will be able to go home from the hospitals with their newborn babies with a genetic map in their hands that will tell them, here's what your child's future will be like."

Well, this illustrates what to me is the driving issue behind almost all of the specific issues having to do with the integration of new genetic tests into society, which is our cultural tendency, not totally irrational, to over-interpret the meaning of genetic test results. Increasingly we're learning that genetic risk assessments that will be coming along will not have occult powers to tell the future of our experiences in life. But that's still the image, the occult magical ability to predict the future, that drives a lot of the fear and the issues in genetic testing.

What sorts of issues? Well, every time we launch a new genetic risk assessment test into the otherwise calm pond of our lives, we do get these concentric ripples of questions, questions for the families and individuals who might avail themselves of this information. Am I comfortable living with uncertainty? Do I want to know my downstream risks? What are my obligations to warn those cousins in California we no longer speak to about our familial risks? What are my obligations to protect the next generation from our familial risks? All those frank and tough moral questions that individuals will face.

It's hard to write public policy on those sorts of questions. We don't have a good uniform theory of moral dynamics of family life in our culture, so a lot of the discussion of those questions quickly flips over into the discussion of professional issues. The ethical issues that health care professionals face when they're trying to help these families and individuals work through those moral quandaries. Often it is the genetic counselors and the clinicians, as much as the pastors and the rabbis, who are helping them address these moral questions.

For the professionals, those moral questions translate almost verbatim into questions of professional ethics and policy. If they won't warn their cousins in California, do I as a professional have an obligation to breach confidentiality and a duty to warn in this context? What should be the standards of care in this area? When is a test ripe for prime-time use? And what should the limits of my service be? One of the hottest topics in that domain at the moment is a question of testing kids, pediatric testing at parental request for mutations that confer risk of late-onset disease late in life. I'll get back to that a little bit in a minute.

Finally, at the limits of those professional ethical questions are the public policy issues that we've already been talking about a bit, the questions about the regulation of commercial testing. It's the professionals' question about when a test is ripe for clinical use writ large at the policy level. And then the mechanisms we have to prevent genetic discrimination.

In terms of the criteria that get involved in evaluating tests, I'm picking up here in the fourth quadrant of Wylie's box, where she said that when you have a test with relatively little therapeutic prescription behind it and relatively poor predictive capacity, what do you do? Well, you do a careful evaluation of risks and benefits. What goes into that calculus? I call this the calculus of the eight P's, because there are these four alliterative categories that seem to me to make up that calculus.

The first is the predictive power of the test, and that is the heart of the issue about clinical validity that the Secretary's Advisory Committee or predecessors wrestled with a good bit. Working out what clinical validity and utility mean for genetic tests is still a task to dwell on. But secondly, there's the price of a genetic test, its psychosocial potency. What are its risks for stigmatization and discrimination? Not all genetic health problems are created equal. Some are tied to conditions that already carry a cultural burden of stigma, like cancer, whereas others would not carry that same level of stigma.

The third one is this interesting category of how to weigh in the patient's own autonomy and their privilege to decide what they want to buy or not buy from the health care system. The hottest

professional policy issue at the moment is the question of what sort of criteria ought to govern predictive testing for kids. But there's another example that I'll tell you about in a new category of genomics that I call ego genomics or cosmeticogenomics.

This is the enterprise of a company called Lab21 which now has counters at Bergdorf-Goodman's and Saks Fifth Avenue. If you go in, you can complete their skin profiler questionnaire and let the beauty consultant take a small sample of skin cells with a tape off your arm. They'll send that off to the lab and genotype it for four markers that they feel are relevant to good skin, collagen markers and other sorts of things, and then whip up a customized DNA face cream with appropriate levels of active ingredients to help boost any measured deficiencies and ship that off to you. Direct-to-consumer genetic testing, in Francis' mode.

DR. LANDER: What are the markers?

DR. JUENGST: I don't have those, but I can --

DR. LANDER: Do they say?

DR. JUENGST: Yes, they say.

DR. LANDER: Can you get a different cream depending on your genotype, or do they just sort of send the same cream?

DR. JUENGST: No, it's tailored to your genotype.

DR. LANDER: They say that, but I'm just curious if anybody has done a mass spec on the stuff.

DR. JUENGST: How would you know?

DR. LANDER: It would be worth buying a few of them just to find out.

DR. JUENGST: Here are the markers: collagen, elastin, hyaluronic acid, and ceramidides.

Well, gee, caveat emptor, let the buyer beware. Why not offer this as a commercial service to people who want to buy it? It might be junk science, but a lot of stuff at the cosmetics counter might fall into that category.

(Laughter.)

DR. LANDER: Actually, Eric, is it really an RT-PCR machine, in which case they're doing an RNA analysis?

DR. JUENGST: Yes.

DR. LANDER: On dead cells?

PARTICIPANT: On dead cells?

DR. LANDER: Cool!

(Laughter.)

DR. WINN-DEEN: It's in your briefing book, Eric.

DR. LANDER: Is it? RNA analysis on dead cells?

PARTICIPANT: Is Roche developing the test?

(Laughter.)

DR. JUENGST: Well, that raises the question of regulation in a way we haven't talked about much because we've been so focused on the regulation of clinical genetic testing in the context of clinical laboratories. I don't know what the protocol is like at their labs. They're quoted as saying they don't have the capacity at their lab to test for any interesting disease genes. But if they've got the capacity to test for these markers, I can't imagine it would be too hard to build other capacities, and what their security precautions are, et cetera, at Saks Fifth Avenue for the chain of custody of these samples, I don't know.

(Laughter.)

DR. JUENGST: And that brings us to the topic that several speakers have raised about the need to have a fuller social conversation about regulation in this area, and I just show this to show the kind of drum beat of recommendations from previous groups, your predecessors, in this direction, with the latest being your predecessor advisory Committee, which you'll hear more about later.

Well, quickly then, the second line, through functional genomics to gene therapy. Gene transfer research has had a rollercoaster history over the last decade of promise, failures, and successes, at least one notable success with its own back-bite, a cure of a disease in a cohort of patients, some of which then succumbed to the cure by developing a health problem that was the direct result of the gene insertion.

But for generic policy purposes, the lines have always been clear over the last decade what the limits of gene therapy were. These are the kinds of boundaries that your sibling Committee, the Recombinant DNA Advisory Committee, has always been happy to live with. That is, we don't entertain protocols that are designed to go beyond therapy to try to improve on human form and function in some way, and we don't entertain protocols that are intentionally designed to affect the germline, affect the next generation of a patient's family.

What's interesting I think looking down the road and what may be a topic for you folks, since it is beyond in some ways the RAC's purview, are the ways in which these boundaries are both getting pressed. On the one hand, people are finding -- well, there was an announcement in the literature a couple of years ago from a hospital, a report of the first case of human germline genetic modification resulting in normal, healthy children. Oh, we've done it. We've crossed that line. What's going on? That was kind of a surprise to the RAC, because it certainly had never come before them.

What they had done was to find a side door into germline genetic modification that didn't involve recombinant DNA and therefore was exempt from the guidelines, didn't have to come through the normal regulatory routes. What they were doing was essentially transplanting mitochondria in early embryos to prevent diseases of mitochondrial origin. So the intent was to prevent a disease in a prospective patient, the child that would grow from this early embryo. A side effect of it was that, of course, that child's children will inherit these new mitochondria as well, along with their DNA and the genes that they carry. The germline, in essence, in terms of a literal definition, has been tampered with, has been breached.

Now, whether that's a serious breach of concern to the world is a topic of conversation, but it does show you the way in which that boundary is starting to shake as we come up with new ways to influence the germline.

DR. LANDER: Eric, on that point, there's now a growing literature that mitochondrial haplotype is an associated factor with at least a small list, and I think it's going to be a growing list, of common diseases. So it's hardly a small point when you're talking about potential affects on neurological disorders,

diabetes, et cetera, et cetera.

DR. JUENGST: Okay. Very good.

DR. LANDER: I wouldn't put this in the box of the rare mitochondrial disease, necessarily.

DR. JUENGST: Yes. So it's worth paying attention to.

The other pressure comes under the rubric of prevention. A lot of our reviewed and approved somatic cell gene therapy protocols are essentially aimed at treating and preventing disease by strengthening the body. There's a class of protocols called the cancer vaccination protocols which are designed essentially to genetically tweak the patient's immune system to seek out and destroy cancer cells more effectively. Well, that's great for the patients who already have diagnosed cancer. You can see it being used prophylactically. I could use an upgraded immune system myself. To that extent, I will have been enhanced compared to the rest of the species.

So one of the questions that's come up in the policy domain is do we care about enhancements that are clearly designed to strengthen our resistance to disease, to pollution, to other kinds of environmental insults? Are those worrisome in the same ways that the other sorts of genetic engineering fantasies we've had in the past are worrisome, or not?

One of the things going on at your sister Committee in response to the side door issue is a discussion, or was a discussion several years ago about whether to expand the scope of the guidelines that govern their work, the guidelines governing gene transfer research, and you can see the extent to which the simple phrase "experiments involving deliberate transfer of recombinant DNA" have had to be expanded in order to capture the range of new possibilities for influencing genetic traits in human cells.

Eventually, my last slide was circa 2020. Now we're at circa 2030. There will be some other pressures on these lines as well. If we get a functioning, safe and effective somatic cell gene therapy, we will find ourselves in the situation of contemplating families which continue to pass on the pathological mutations are cured in every generation by another bout of expensive somatic cell gene therapy, and somebody is going to raise the question, "Good grief, wouldn't it be more efficient to go ahead and do this gene therapy in the germline once and for all for that family line?"

That's an argument that at least one public policy shop has taken seriously. The AAAS, the American Association for the Advancement of Science, had a working group on this topic a couple of years ago that's produced a report you might want to hear about at some point on human inheritable genetic modifications, suggesting some interim steps towards getting ready for the day when someone makes that efficiency argument persuasively. It's time to start thinking about germline gene therapy for therapeutic purposes.

At the same time, discussions are going on in other policy venues like the International Olympic Committee and the World Anti-Doping Association about the possible illegitimate and off-label uses of somatic cell gene therapies for performance enhancement in athletes. There's a class of gene therapy experiments for muscular dystrophy and other diseases that the athletic community sees as quite close to the kinds of blood doping they already do, and the World Anti-Doping Association has already begun to develop policies to address the day when athletes begin using these gene therapies off label, so to speak, to strengthen muscles, build oxygen-carrying capacity, block their pain, and speed their pace of healing from injury. Again, all uses that have perfectly good therapeutic and preventive applications in medicine -- we wouldn't want to stop the science that developed these interventions -- but which will have applications in other spheres that seem to cross that enhancement line.

Finally, a quick look at the issues raised by the third branch. The progeny of the Human Genome Project so far are all heavily invested in this third branch, being interested in doing comparative population

genomics, studies of human genetic variation. All of them share this basic strategy of collecting DNA samples from members of different human groups for comparative analysis. Right, that's what we want to do.

The first question that you stumble on, though, is, well, what are the groups? Which groups? Are we going to fall back onto 19th Century color lines and say, oh yes, they're red, yellow, black and white? The genetics community has taken us a good way down the road towards obfuscating those lines, pointing out that as biological concepts there's not too much reality to that, and that makes population genomics a particularly tricky tool to use without hurting yourself in the process. We're used to double-edged swords in medical genetics. Information is power. This is at least, to my mind, a quadruple-edged sword because of the implications of the results of these kinds of variation studies.

On the one hand, we are interested in the diversity in the genome, because that's what's going to give us a handle on specific population group susceptibilities and tailored health care interventions that might help address health disparities. On the other hand, of course, along with that, to the extent that it's successful, comes the ratcheting up of all our worries about genetic discrimination to the group level from the individual level if particular socially identified population groups become labelled as vulnerable to particular kinds of weaknesses and stigmatized in the process.

On the other hand, population geneticists like to remind us this graphic is way out of balance. The similarity blade should dwarf the diversity blade because we're much more alike than we are different in our genomes, and maybe this can be used to enhance inter-group solidarity. On the fourth hand, for some folks their biological differentness, their lineage is pretty important to their social identity, and it's not doing them a favor to homogenize them into the rest of society, partly for good historical and social reasons.

So I think one of the challenges that's going to face this field is to explain to the world the kinds of categories we in genomics want to put people and explain to the world in a way that doesn't exacerbate existing tensions between different human groups.

Ken Kidd has said -- and this is a typical kind of statement from one end of the spectrum within genetics -- "There's a virtual continuum of genetic variation around the world. There's no place you can draw a line and say there's a major difference on one side from what's on the other. One is talking about discrete, identifiable populations. There's no such thing as race in modern homo sapiens." Clearly true. On the other hand, just because you can't draw a line to distinguish day from night in the twilight doesn't mean you can't distinguish midday from midnight; and you could, by going to wildly separate parts of the globe, collect samples from people that would show genetic variation that seems to segregate into populations.

So what's the message we want to give the public about that? Ego genomics Part III, if you will. The world's first recreational genetic testing service is how they bill themselves, DNAPrint Genomics, a company in Florida that says it will measure your racial ancestry and racial proportions for you using DNA markers. Well, why would you want to do that? Perhaps for genealogy or to validate your eligibility for race-based college admissions or government entitlements. Here's some of their literature from their website. "Have you ever wondered if you're of purely Indo-European origin, or a blend of Indo-European or Native American or other ancestry? We can answer that. Capable of determining your precise ancestral proportions might reveal you're 80 percent African," et cetera, et cetera.

Who is interested in this test? Well, genealogists, the adopted. One customer used the test to hone his search for an organ donor. Another suspected he was of significant Native American heritage but had no way to prove it. The test gave him a sound basis by which to claim access to commercial opportunities reserved for Native Americans. "So whether you're just curious or your goal is to achieve social status of a particular group, we can help you do this."

Well, again, junk science? I personally don't know. There seems to be a lot of contention within the genetics community about whether this is realistic and meaningful or not. But it certainly feeds into our race consciousness in this culture, and you can see ways in which people's motivations for acquiring this test for themselves, for their children, for their potential spouses, would only go in the wrong direction. In fact, this is, again, luxury genomics that is a recreational service, but it has already been put to at least one serious use. They've used the DNAPrint testing procedures on a forensic sample to reorient a search for a suspect from one race to another.

So here we are. Here's my summary of the issues that I would like to put on your agenda. First is to continue our exploration of this calculus of the eight P's about how we validate genetic tests. Second is to continue the pursuit of good genetic protections, good protections against genetic discrimination. Third is to continue the discussion of the regulation of commercial genetic testing with an eye towards the direct-to-consumer uses.

If you're interested in going in the direction of gene transfer research and you can work that out with the RAC, then these questions about what to do about the side doors to germline intervention that are coming through the field of reproductive genetics and reproductive biology are interesting. Then how to regulate off-label uses of a medical procedure like gene therapy.

Finally, this question about the social uses of population markers and the meaning, the interpretation of those markers for the general public I think is going to be an issue that will preoccupy us for a long time to come.

So here's a cartoon that I've been using for over a decade now, and it's finally apropos. "We've finished the genome map. Now we just can't figure out how to fold it." Well, folks, you are our map folders. That's your job in some ways, to figure out how to fold this genome map so we can use it to get to where we want to go. Thank you.

(Applause.)

DR. McCABE: Thank you, Eric.

Our last speaker in this group before the roundtable this afternoon is Dr. Lawrence Sung. His topic is genetic technologies and intellectual property issues. Dr. Sung is Assistant Professor of Law at the University of Maryland School of Law.

DR. SUNG: Good afternoon. I wanted to thank the Committee for having the opportunity here to come and address you today on the intersection between intellectual property rights and genetic technologies. I realize that you've had a very long day. You've heard a wealth of information in some ways. There's some information overload as a result of it, and I know we're drawing to a close, so I want to take somewhat of a more modest approach with regard to some of the intellectual property protection issues, really to set the stage for you, introduce the cast of characters, and tell you a little bit about the story. But understand that the story, certainly in large part, has not yet been written, and the parts that have been written are very likely to be rewritten as a result of what happens through their application to genetic technologies.

I've been asked to talk a little bit about intellectual property generally and then to focus on specific issues with regard to patent rights and to tell you a little bit more about what it means to obtain patent rights, particularly in biotechnology and some of the genetic arts; and then lastly, to conclude with some of the rising concerns that we see at this point in time and those that are on the horizon.

Now, I understand that there are a variety of individuals here with disparate expertise in intellectual property issues. For those that are more sophisticated, I do beg your indulgence somewhat, that there are certain portions that will be somewhat oversimplified to get through our presentation today. Understand

that intellectual property protection is a general matter, especially today is highly controversial. As a result of that, like any good attorney, I'm going to start with a disclaimer. I'm here neither to advocate a particular position for open access or exclusivity along those lines, but to give you as much of a balanced approach as possible, recognizing that with a balanced approach, like any good compromise, no one will really leave happy. I just recently finished grading law school exams, so I'm pretty steeled for that reaction generally.

(Laughter.)

DR. SUNG: What is intellectual property? It's designed to look at ingenuity and creativity and to place some type of value on that. The value that's placed through the legal component is really to look at a grant of exclusivity as a result of intellectual property. The subject matter that is embodied within that can be fairly loose, and there are a variety of different types of legal protections that are involved. We can look at patents, copyrights, trademarks, trade secrets, rights of publicity, and a whole host of smaller categories of intellectual property protection. Again, we'll probably focus most on patents today, but understand that there are a variety of mechanisms that exist for covering various types of subject matter.

Now, how is this different from real property census? Well, there's an exclusivity aspect to it in terms of the ability to use intellectual property. So if we look at a house or a car, for example, if I were to take a real property concern like my car, if I loan it to you, I can't use it myself, nor can anyone else use it because you are in the driver's seat. You're out there, you're using it to the exclusion of others. Intellectual property doesn't necessarily have that same constraint when it comes to the real property considerations because I can license my intellectual property repeatedly in a non-exclusive fashion to a variety of individuals, and indeed I may still be able to use it as a result of the negotiations that are involved with that. So that's how, on a fundamental level, it differs from the intellectual property standpoint.

Limitations to intellectual property are defined in the law. There are territorial restrictions to it, there are temporal restrictions to it. Each national jurisdiction has their own intellectual property law. So obtaining a U.S. patent, for example, does have no effect extra-territorially from the United States other than to seek corresponding protection in each of the individual nationalities. In addition, based on the way our laws have been framed, there is a temporal limitation. This is only for a temporary period of time. For patents it is a 20-year period from the day you file your patent application. In copyrights, that term seems to be extending every day. However, it is still somewhat limited, at least one day less than perpetuity.

The value of intellectual property, because it has a property characteristic, is fungible to an extent. You can buy and sell this. It can be somewhat of a commodity item. But I think as we go through our discussion today, you'll realize that there aren't that many comparables with regard to a lot of the technology that's involved. So valuation itself can be difficult, but it is fairly straightforward to assign a value for intellectual property generally.

Now, what do we do in terms of patent rights? Well, patent rights specifically, there are a variety of different rationales for why we have patent rights in the first place. Let me start off by saying it's based on the Constitution, so it's a legal doctrine. It is fairly entrenched. We look at, again, according inventors particularly rights to their ingenuity, their ability to bring this forward to us. But what are some of the underlying rationales for why that mechanism is in place?

We look at this and we say to ourselves, number one, by having you come and seek patent protection from the U.S. Patent Office, it requires you to disclose your information to the public. Otherwise, you could simply have maintained it as a trade secret. You might just not have told anybody about it and just practiced it along those lines. But here we have you coming to a centralized repository and making a dedication of information.

Now understand, in response to that the government, under certain circumstances, will give you that exclusivity for a limited period of time, which allows you to really adopt what's known in the economic area as a first mover advantage. You really are the first on the scene. It gives you a period of exclusivity to really develop it if you so want. You can also transfer it to others to have that exploitation occur.

But if we get to the original question about exclusivity, why do we like exclusivity? Well, there's certainly a theory behind this from an economic basis known as the public goods problem, just a highfalutin way of really talking about what I would characterize as the common household kitchen problem. If you've ever lived in a group house and you've ever walked downstairs in the middle of the night and looked at the kitchen sink, it's full of dirty dishes. What are you motivated to do at that particular point in time? Well, the economist would typically say that unless you had some sense of proprietariness to washing the dishes and having been able to reap the benefits of that by having clean dishes, you're less likely to wash dishes just for the entire house. Everyone gets to use it. You're much less motivated to go out and move things forward.

So that public goods issue is the reason that exclusivity is touted as being an important consideration. We've talked about information disclosure and an incentive to then innovate or to move forward because we've overcome the public goods issue. Well, what does innovation really mean through that incentive? Number one, you can reward inventors. You can say to them, "We're going to give you something as a result of your decision to disclose this to the public."

But more importantly, innovation is also achieved because we avoid what someone raised earlier as a potential cumulative problem, because if I know that someone else has worked on what I thought I want to work on, I'm more inclined to say, well, if they have exclusive rights to it and I'm not denied the ability to obtain exclusive rights, I'm going to do something different. I'm either going to design around it or I'm going to take a separate path that adds to the overall social wealth, because again, the disclosure adds to the information that is in the public domain, and I want to distinguish the public domain from necessarily what you can do at a particular time versus what the public is now aware of.

So disclosure is definitely an important characteristic to this. It contributes to the innovation that's involved. Arguably, there are some anachronistic characteristics. Certainly, 100 years ago, the U.S. Patent Office was a great centralized repository for scientific knowledge. If you wanted to find out what was cutting-edge technology at the time, you could easily go to the government institution, look through their files and say ah-ha, I understand what is really at the forefront of technology.

Nowadays, with the Internet, with a variety of other organizations and publications, it's somewhat anachronistic in that sense, but it still does have some continuing value along those lines. More importantly, the investment potential. As we get into our discussion about biotechnology, we recognize that there are differences among industries about how the industry sectors result from investment purposes and commercial considerations. In the biotechnology area, as you've certainly heard, the length of time between commercial development from an idea tends to be far greater on a time horizon than any other technology. So investment in this sector tends to be focused much more on intellectual property as opposed to a proven product or a commercially marketable product at that point in time. So again, there are some differences in sectors as we talk about patent rights generally.

The U.S. Patent and Trademark Office has its supporters, has its detractors, and the patent system in general in the United States, similarly you can find support either for or against it. An example of this is we'll go through some of the actual requirements for patentability to sort of lead you off with a sense of the frustration that can be involved. If you imagine yourself at the airport baggage claim counter, you're sitting there waiting for your bags to come off the conveyor belt and you're still wondering just all of these different questions that you have in your mind. Why isn't it that they go in in a particular order and come out in a particular order? Why is it that if I paid for this particular fare ticket, there isn't any priority basis? There really is no rhyme or reason similarly between your baggage claim experience and the U.S. Patent Office in this regard.

(Laughter.)

DR. SUNG: Things also get lost, one of the more important considerations.

Laughter.)

DR. SUNG: And this is, again, not an opportunity to bash the Patent Office. I think it has an almost insurmountable job as a result of it. But we've made a policy decision within United States taxpayer policy to not fund the U.S. Patent Office so that it does the most accurate, comprehensive job possible. We ask it to do a certain job within certain limitations, and that is following these particular guidelines with, again, limited resources. It sometimes shocks individuals to know that the average patent application is probably vested with about 30 hours of an examiner's time, regardless of technology. So you can well imagine that there are ones where you can barely scratch the surface of even understanding what's gone on within that period of time.

Again, they labor under quite difficult conditions there. So we see some results as a result of that, but there really is only so much that they can do in this regard.

Now, what are some of the requirements? One is that a patent right is only accorded to an inventor. It is not a matter of attribution, it's not a matter of credit. It's a matter of a legal definition as to who conceived and reduced a practice, a particular product or method? The conception is that eureka moment, that you can think of the reduction to practice as really being able to implement it in your mind and being able to describe it to someone in a manner that they too can ultimately go forth and use it, and that can occur one of two ways. Either you describe it in a publication, such as a patent application, or you can actually build a prototype or a model along those lines.

Inventorship is not coincident with ownership, at least at a practical level. Inventorship is the first supporting premise of ownership, but understand that in reality and in practice much of what is done in the patent area for inventorship purposes is automatically assigned to an employer, for example, through an employment contract or an employment policy. So there isn't this arms-length negotiation or transaction that occurs between an inventor and many owners as a result of that. Institutions may be owners in the United States, but they may not be inventors. It is unlike some other countries where actual institutions can be the inventor.

Conditions for patentability include that it has to be of the appropriate subject matter, that it has to be useful in some regard -- and we'll speak a little bit about that -- it has to be new or novel, and more beyond that it has to be non-obvious. The non-obviousness component is a little bit vague and ambiguous. But what it really goes to is that not only must you come to us with something that is different from anything we've ever seen before, but it needs to be so different that no one else would have thought to have done it, and that is an incremental step beyond simply bringing us something that's new.

More importantly, the disclosure requirements are important here, because again this is the quid pro quo. We are willing to give you a temporary right of exclusivity, but only if you teach us about your invention in a sufficient manner that others may be able to benefit from it. So again, we don't get into this cumulative problem where people have to read your patent and somehow figure it out and waste time doing so. We want everybody in the public to be vested so that they may stand on your shoulders and go beyond that point in time.

Now, in the biotechnology realm, why is this so difficult? Well, there are a number of different reasons for that. One is that we are dealing with natural subject matter, and there is an inherent consideration that people have in this. How can someone patent what is otherwise found in nature? Well, from a very strict legal perspective, that's really not what's happening, although no one ever likes to explain it that way because you don't get many takers. But essentially, what someone is saying is from a gene standpoint, I can patent an isolated, purified nucleic acid because it doesn't exist that way in nature. It

has a natural component to it, but what I'm actually claiming isn't what is in all of us the same way.

Another limitation to it is that patents, as well as other forms of intellectual property, are not really designed to protect information. So if I tell you about something through my patent, others should be able to use that information to the extent they are not somehow using the same product that you've claimed or the methodology that you've claimed. The difficulty in the biotechnology area is that distinction is blurred and in some senses can be co-extensive with one another.

For instance, if I have an isolated nucleic acid of a particular sequence, what's the difference really between the information and the actual structure that's involved? If I somehow use that information, am I also concurrently using the structure? And in some cases, the answer to that might be yes. So the dichotomy that sometimes exists between the two may not exist in this circumstance.

The next indication is what I call de facto industry standard. We are not dealing with a technology that allows you to adopt a different approach. Going from VHS to Betamax is an example of an industry standard design-around. The folks that were working in the VHS standard said, no, we're not getting the operating procedures that we'd like to using the Betamax format. Let's use another one. In fact, that became more successful to the demise of Betamax.

However, in this area, it's not as if we're going to wake up tomorrow and say forget DNA. I don't want anything to do with it. I'm going to try to develop things based on another design. There is much more of a cause and effect linear situation that we have here. So that is yet another distinction between this area of technology and others.

Now, doctrinal meta-stability, again another fancy term which essentially says that in this area I think that observation leads us to believe that there are certain rules and guidelines about science in general. The difference is that in certain other industries you may be able to climb the highest mountain, and then once you summit it look down and have a worldview. You may be able to say this is what we know now.

But I think in the biotechnology genetic area, a more apt sense of the landscape is that you go to the top of the mountain and you look, and all of a sudden there are 100 other mountains. There's a lot of uncharted territory that you may not even begun to have seen until you've gotten to that point and expended that amount of effort, and that may in turn change your own worldview about your mountain. Maybe it's no longer the highest one because you've seen yet another one that's higher. So there's a lot of change that can occur in this area. There's a lot of revisiting of old notions about science in this sense.

The last area is what I call an art maturity compression. What we have in this circumstance is that legal doctrine is being formed today based on case law that's being decided on technology in genomics and in biotechnology that is sometimes 20 years old. The period of time that it can sometimes take between filing a patent application to obtaining the patent can be 10 years. The period that it would take from that point forward to enter into litigation can be another 10 years. As a result of that, you look at what the courts are resolving at this point in time. It's not necessarily instructive because it's based on the facts and the law as they are applied to a scenario that had existed that's now obsolete.

So how much guidance do we really have from the judiciary in this regard? The difficulty, because of the way our patent system is set up, is the indication from the patent office is not the final say. If it were, I think it would be a lot easier to navigate around patent rights. But you really don't know the scope and extent of a patent right until the courts have had an opportunity to pass on it, and not just the trial court level but the appellate court, and perhaps all the way up to the Supreme Court, before really understanding what the overall scope of this will be.

But the reason that we allow this to occur is, again, it's not worth spending the money at an earlier time point because there are so many applications that are submitted, some for which will never reach any type of commercial maturity whatsoever. So rather than expend money up front for a more accurate,

comprehensive examination, we allow certain patents to issue knowing that they may be on the verge of invalidity, but at the same time we'd rather have interested private parties resolve the issue for the public because they are the most self-interested but also in the most financially capable position to do that. Again, that is inherently a difficult standard, because at what point in time are you comfortable knowing what the true scope of a patent right is? Until the very end, you really don't, and that's very difficult.

But predictability and probability in science changes quite dramatically. I mean, certainly we can look at the rapid advance of sciences, and if we're talking about a 10- to 20-year time frame, what is predictable at some later point certainly may not have been predictable much earlier.

The other issue that comes into play here is that there are routine methods of manufacture that can occur in biotechnology that still lend themselves to producing new and non-obvious products. So, for example, after we go through and discover technologies that would be useful in sequencing, in proteomics, in bioinformatics, we may be able to take those same standard protocols and methodologies and go into the vast array of information that still hasn't been touched and ultimately generate some type of data and develop that into a product or a method and obtain a patent to it.

That's very unsettling for most because they would say, well, what you've done is essentially applied routine methodologies to come up with something. Why should we accord an exclusive right as a result of that? There are specific circumstances where that does apply, but that is one of the areas that causes a great deal of consternation with regard to the scientific community.

How does this also work? Assuming that we are able to get patent protection, we dispense with the issue that is natural subject matter of some sort. We talk about its utility, having some practical application. These days, the patent office requires something that is of substantial, specific, and credible utility. As Dr. Collins had mentioned, we're beyond talking about gene fragments and gene patterns and ESTs and SNPs. There are a host of other newly-developed technologies that have emerged from that which require that same consideration.

But once you get the patent right, there is something else to be aware of. It is not as simple a proposition as you might think, because there is a dominant/subservient relationship between patents. I may be able to get patent protection, but yet that doesn't necessarily give me the right to use what I've patented, and that's quite surprising for most people because you feel like if you've purchased the property, if you've invested in it, you've gotten it, it's yours, and you get to do what you would like. However, the way the patent system works, it's entirely possible for your patent rights to be dependent on permission by another to use their technology, because there may be some interrelationship between the two.

As a result of that, you have a large thicket or web of patent rights, and sometimes it's very difficult to distinguish whether you have freedom to use this particular product, freedom to operate free and clear of that.

The timing, again, difficulty in this area. There is an obsolescence issue that needs to be considered, but also the long time to commercialization. The reason we see, for example, a heavier reliance on patents in the biotechnology genomics area is because there is such a long time period that's involved before proof of principle and actual commercial development. On the other side of that spectrum may be something like software development. It's increasingly conventional wisdom that software applications in the patent area, although feasible, may not be the best way to go, because certainly by the time you go through and wind yourself through the patent process, by then your software may be obsolete because things do move so much more rapidly in that area. However, as we have bioinformatics packages and applications, we may see a little bit of an overlap in those two areas.

Lastly, regulatory controls. We understand that certainly for commercialization and marketing of pharmaceutical products that result from earlier-stage inventions, those are subject to regulatory controls which again can delay the period of time that it would enable somebody to ultimately benefit from patent

protection. As a result of that, we allow certain extensions to patent term to recoup some of that administrative delay.

What are some of the concerns that have come up here? Well, certainly in any situation, we talk about the restriction. I can't seem to do something as a result of someone else having a patent right to this area, nor will I likely be able to design around it because things are rather more confined in the biotechnology sphere. Again, to look at an isolated incident like that and to say yes, this is a situation where a patent right has clearly blocked progress, we need to take it in the overall context that that may be true in that specific instance and there may not be any other way to design around or otherwise obtain permission to use this. But in the overall scheme of things, remember that the intent of the system overall is to spur innovation through design-around, if necessary.

Collaboration issues are rather difficult. There are hardly scientists nowadays who feel comfortable picking up the telephone as they might have done even five to ten years ago and calling a colleague at another institution and chatting things through, because effectively everybody has a material transfer agreement that they want you to take a look at and sign off on, or there may be considerations from various home institutions as to what level of disclosure you are providing to one or another of your colleagues. So there has been more of an impact in the practical sense on collegiality and collaboration with regard to research.

How much of that is arguable? There has not been a whole lot of empirical work done on what the true impact is of intellectual property protection on biotechnology advancement. I think that organizations like the NIH and various institutions are trying to take a leadership role in that regard to spur further study about that, because everything is rather anecdotal at this point in time. Again, you have so many different instances where somebody may say, well, if you look at BRCA1 and you look at what Myriad has done, that's an anathema and the patent system is horrible that it allows something like that. Once again, perhaps true, but in the overall scheme of things there may be a number of different other instances that we can point to that show the success of the patent system.

How does business work along these lines? What types of incentives are there for securing intellectual property protection for purposes of financial investment? What happens when there are prohibitions that are involved? How are they overcome? Are there cross-licensing schemes between patent holders in this regard to free up scientific advancement?

I'll conclude with just a couple of comments about some of the horizons. Certainly, whenever there is some controversy with regard to the patent system, there are violent efforts to try to change the patent laws themselves substantively. The problem is there are a lot of laws of unintended consequences that come into play with that. The existing U.S. patent system is based in large part on a law that was written in 1952. It is applicable broadly against all technologies. There have been some minute changes since that period of time, but certainly the law, being written at a time when there was hardly biotechnology and certainly no computer technology in that sense, is grappling with its ability to apply to certain new areas of technology.

Enforcement is another consideration. How are people more or less inclined to enforce their patent rights? Because understand that there are, because this is a private civil matter, lots of considerations about whether patent rights, once they are obtained, will actually be enforced. Because a patent is subject to being invalidated, you put your patent at risk by enforcing it against others. So there is a risk calculus that goes forward as to whether a patent holder will actually try to enforce their patent rights.

One of the examples that's typically referred to as to why patent rights aren't the end of the world with regard to genomics and biotechnology tends to be the Cohen/Boyer patent on early-stage methodology for genetic engineering. However, a lot of legal practitioners might have looked at that early-stage patent and said, well, it was invalid anyway. If you looked at it, there were certainly a lot of things in the public domain that would have suggested that that patent right would not have been upheld if it were enforced

aggressively. So perhaps when Stanford had licensed it at reasonable cost, and at times no cost, to certain entities, maybe that was the appropriate resolution of that. So understand that there is a lot of discretion and risk assessment that goes on in the enforcement area as well. Not simply because somebody has a patent will they enforce it in all circumstances.

The last point here is what I will refer to as the research use exemption. Increasingly, there has been a lot of discussion about whether or not base researchers, academics, as well as not-for-profits or non-profits should have the opportunity to have an exemption placed so that they will be exempt from patent infringement liability. The reason that this has taken on a little bit more of a conversational tone these days is because there are certainly a lot of researchers that were shocked in realizing that last year, when the U.S. Court of Appeals for the Federal Circuit issued a case called Mady vs. Duke University, that what they were doing was really an infringement.

Everyone had thought, no, they'll never come after us, we won't have this type of discussion, what I'm doing is not commercial in nature, and the Court put that to rest. It eliminated any exemption as a bona fide exemption against patent infringement. Now, certainly as a practical matter, it is unlikely in many circumstances that private companies will go against academic institutions in this regard, but the exemption itself is something that people would have liked to have an absolute immunity from. The Court of Appeals for the Federal Circuit, in their one-two punch, not just with the Mady decision last year but with a decision called Integra vs. Merck that issued just Friday, has come into it and said even early-stage research, research that may ultimately be used to underlie clinical research, is not going to be exempt from patent infringement.

So we are foreclosing those areas that we may look at under any type of recognized defense in terms of early-stage research, particularly with genomics and biotechnology. So that is definitely having an impact. The Mady vs. Duke University case is on appeal to the U.S. Supreme Court. The stage it's at is that the Supreme Court has asked for comments from the Solicitor General to weigh in on the scope of things, and the Solicitor General has submitted an amicus brief as a result of that. We will be pending resolution of that case going forward.

DR. LANDER: How does the Solicitor General come down?

DR. SUNG: The Solicitor General really is taking a very broad-based approach. You would have imagined that the amicus would have been a little bit more focused in saying whether or not this is going to shape the foundation of science generally. I did not read that to be the case.

DR. LANDER: That is supportive or not supportive of the lower court decision?

DR. SUNG: It is supportive of the lower -- the reason it's hard for me to answer the question is because it's not as focused as that. There's certainly a recognition that the way the law has played out through the Supreme Court and the common law element along those lines does not really support a reversal on the law itself. So in some ways, this almost calls for a legislative remedy as opposed to a judicial one.

DR. LANDER: Are you done? Can I just follow up with that?

DR. SUNG: Sure.

DR. LANDER: You've given us a wonderful tour through the black letter law of all this, and that's all fine; and you've told us that in theory, anything we're unhappy about, any particular event might be outweighed by lots of other good things that make the whole thing fine. But in practice, we all live in practice, right?

DR. SUNG: Yes.

DR. LANDER: So you look at the biotechnology and you'd say have we created a morass where, in fact, work doesn't get done because companies are uncertain about the patent rights of people out there, and therefore they don't work on projects? My observation is that that really does occur, the typical thing. Do we see people increasingly expanding to things like pathway patent claims, all molecules X, undescribed as of today that might affect protein Y for disease Z? Will this block all second- and third-generation products against particular pathways?

Do we get into situations where Francis' $1,000 genome thing comes along and we can do your genome for $1,000, we can't actually peak at the BRCA1 but we can peak at this one but not that one, or whatever? Is it the case that because of the unusual nature of this industry that we have to actually look empirically as to whether we're really serving the public or not? Too often, the patent lawyers who talk about this in general tell us, well, it makes innovation, et cetera, but it is indeed an empirical question whether it does.

DR. SUNG: Yes, absolutely.

DR. LANDER: So what's your take? Are we on the right side right now, or do you think it's out of balance?

DR. SUNG: The funny thing is that everyone is on the right side on this issue. Yes, you can look at instances where there is a block in certain cases to progress. I think it's fair to say that. However, it's not just about saying whether there is forward progress or not in that area, but also whether or not certain instances of commercial exploitation would not have occurred but for patent rights that were in the mix. So not being able to just focus on one particular aspect is the difficulty here.

DR. LANDER: Sure. But again, you're saying it could be. So are there fruitful changes to the patent system, whether by law, by PTO change in regulations or whatever, that you would recommend to improve things given your read of what's going on?

DR. SUNG: I think there can be improved administration of what happens within the patent office itself. At this point in time the patent office is certainly loathe, because the courts essentially placed this on top of them, that you cannot make certain practices special. You cannot look at biotechnology inventions and say we are going to apply the law differently in that context. However, it does call for that, and really there are special circumstances where biotechnology inventions pull into place certain areas of the law that really require somewhat different considerations

So I think if there is an incremental improvement to be had here, that's probably it, to give the patent office the ability to really examine these inventions in a somewhat different light. Now, that may take an organic change within the law, so it's not something that has a great deal of momentum at this point in time. But again, I think that addresses your question.

DR. McCABE: Actually, this is a nice segue, because what I'd like to do is have all the speakers come to the table now.

Thank you very much, Dr. Sung.

(Applause.)

DR. McCABE: What I'd like to do is have all the speakers from the morning and the afternoon come to the table. We're going to run until about 5:30. The individuals who are making public comment are able to stay, and we only have three individuals making public comment.

The purpose of the discussion, I just want to make sure that the members of the Committee and the ex officios understand what the purpose of the discussion is now. It's to help begin us to focus on what our

priorities are. That's our job, to look at the seven issues that were presented to us and try to determine where our priorities are as we begin our deliberations tomorrow. So I think Eric's questioning of Dr. Sung about is there anything to fix here is quite appropriate, since certainly that was one of the issues.

DR. LEONARD: I'd like to start off with a comment on Eric's talk, which is that he followed the first ego genomics slide of DNA cream with a slide on CLIA testing, as if those two things were equivalent, and they are not. So I think that's very important for this Committee to realize, that there are regulations that control and advise CLIA-certified laboratories that are not in place for these other types. To put those two slides next to each other is a little disturbing in my mind, because that's my practice.

DR. McCABE: But I would also point out that that's why they're very careful in their Internet information to say that this is for recreational use. Similarly --

DR. LEONARD: No, I understand that. But it was just that --

DR. McCABE: But I also like to point out that that has become the code for non-CLIA, outside of the CLIA perspective.

DR. LEONARD: And I'm very concerned about that.

DR. McCABE: Because we saw that some of the information that was provided to us, that a company that is supposedly doing gender testing is really doing pH testing of urine and says this is for recreational use. So we need to recognize that that's why they're saying this really has no medical validity so they can avoid CLIA oversight.

DR. LEONARD: Right, and I'd just like to put those into two categories -- they're very different things -- and not put them together.

I have a question following up on Eric's question. Should medical information, medically useful information, be protected for exclusive use or non-use by patents, since once you have a patent you can do anything you want with it? When you raised concerns, your concerns were on research and business, but there are definite health care concerns raised by patents that were not at all addressed in your summary. I think this is a focus that is essential to this Committee.

DR. SUNG: No, and I think that there's a distinction I'd like to start off with. There may be information that is in the form of databases that raises a concern about how databases are used, for example. There's not presently protection for databases within the United States patent system or copyright system. There is, however, something that lawyers refer to as a sui generis database initiative that the Europeans have adopted, for example, that allows exclusivity to extend over database compilations of information as well.

Beyond that, the uses that you're talking about, to the extent that they bore safety and health-related issues may block access by the public, it is certainly at least contemplated within the mechanism for access to that through a variety of mechanisms. One of them is, for example, the federal government can step in and because of the health and safety-related issues mandate public access to this.

An example of this you can point to is with the Cipro anthrax situation, where the government certainly had made initial indications that it may proceed to appropriate the technology to Cipro and allow its manufacture by other competitors to the extent the patent holder buyer was not capable of meeting the demand for this and at the right price.

So there are mechanisms for that. The only recompense that a patent holder has is under something called a 1498 action. They may sue the U.S. Government for reasonable compensation as a result of that appropriation. That really smells a lot like a compulsory license. Essentially, you are forcing the patent

holder to accept the use of their technology without their permission but at a reasonable royalty, for example.

There are a variety of other mechanisms as well I'd be happy to share with you that can be used to allow public access to this. One other example is that again as an enforcement mechanism, a patent holder goes to court and asks for others to stop doing what they're doing without permission. So for example, if you had a pharmaceutical patent and decided for whatever reason you did not want to license this to anyone nor did you want to exploit it in any manner, the infringer can certainly have a voice at that hearing to say to the court this is inappropriate for an injunction. I should be allowed to continue to do this because it is of such great public health concerns, that the public be able to benefit from this, that you should not enjoin us, even though we're infringing, and again the mechanism for compensation is through damages in the form of a reasonable royalty, for example.

DR. LEONARD: True, but most of those infringing are in academic health centers and they don't have the money to be able to take a lawsuit to prove it in the courts.

DR. SUNG: No. Understood.

MS. BERRY: I have a question for Dr. Juengst.

I have a particular concern about preimplantation testing, and I wanted to ask you for some insights there because it's tricky. Really, regardless of what someone's views might be on elective termination or discarding embryos, I don't think it matters what their views are because I think in general, I have a sense but I would love your insights on, I think that the discomfort level increases as you get away from discovering a very, very serious disease problem, some defect where there's incompatibility with life and acting on that, and you move more towards personal preference, such as I want a child with certain eye color, or I want a boy, not a girl.

Do you have any insights to share about, really should people who are informed just be able to do whatever they want or should a line be drawn somewhere? If a line should be drawn, where do you draw it and who should draw it? The federal government, the physician or somebody else? It's a dicey one, but I would love to hear, based on your work, what your thoughts are.

DR. JUENGST: Sure. It's a good question. It's kind of the analog of that line between treatment and enhancement but in the selection world rather than in the treatment world.

I think you're right. The anxiety does increase as we move further away from trying to avoid serious disease and into selecting for traits that seem to have less relevance to the health of the prospective child and that's the line that I would focus on, is health and whether it's health-related or not.

Why do I focus there? Partly because that seems to me to be where the professions are focusing when they address these matters and the conversation that I'm most familiar with is a little further along in gestation but the question about the limits on prenatal diagnosis. What should we be willing to test for through amniocentesis or CVS at the patient's request?

One of the conversations that's moved the furthest has been the conversation about gender. Should we be willing to test prenatally for gender at the patient's request, and the argument of those who say no, that's a place we can draw a line as professionals has been we are health professionals. We're happy to help prospective parents make tough decisions that turn on the presence or absence of pathology in the fetus, but gender is not pathological one way or the other, therefore we can leave that off the menu. We don't have to offer that service. It's not part of our professional responsibility.

That answers another one of your questions. Who makes the decision? I think there is a role for the health professionals here to stand on their moral integrity and draw some lines based on the goals of their

business which is the promotion of health and the cure of disease, even against the charge of paternalism in that case, but they are a profession that has a specific goal. That seems to me to be one place to draw the line.

The danger with drawing those lines in public policy is illustrated by a Scandinavian case. I think it was Sweden where they did draw up a list in public policy of the conditions for which it would be appropriate to test for prenatally because they were worried about this expansion of tests and what happened was that became the approved list of conditions to test for prenatally and pretty soon was the expected list of conditions to test for prenatally and everybody got tested for all of them.

DR. HOOK: I want to follow up a little bit on Cynthia's comment about PGD and your concerns well expressed about the difficulty of keeping away from the so-called germline manipulation because I think on a very practical level, what we're seeing is that as PGD expands and it is expanding rapidly in terms of various mutations being tested for, disease conditions being tested for, as we develop means of therapy beyond viral vectors, non-viral transmission, the therapeutic efficacy is going to be to treat that embryo when there are fewer cells and you can ensure that there's adequate transmission of the so-called normal gene.

The end result of that will be, of course, that you're treating the individual but you can't avoid then treating the germline, and so I'm concerned that that distinction where people have held the ground for eugenic reasons is not going to hold at all.

DR. JUENGST: Well, and it just underlines the need to begin to put in place the sorts of things that the AAAS was recommending, which is basically to studies to get a better sense of what the actual risks are involved in germline transmission, something we don't know much about in the human case.

DR. HOOK: Then my next was a broader question to all of the panelists and maybe this is opening something, a can of worms, but it's an important question to me, and that is, we have a number of very important pragmatic issues that you've laid on the table for us, and one of our jobs is to prioritize those, and yet it seems through the ELSI project and HGP and a lot of these discussions at no point have we really come back and said or looked at the question what would be the good use of genetic information for the good of society? What's sort of the larger target we're trying to achieve with all of this?

We have these specific questions here and there, but what's the larger picture? What do we want to see accomplished? I'm curious as to your response about the feasibility of that project and is that something that you would recommend we try to take some time to grapple with?

DR. McCABE: Who would like to take that on from our speakers? Francis?

DR. COLLINS: I'm not sure I completely grasp the full thrust of your question. I think it's almost maybe not verbalized because it's so internalized and so assumed that the goals of studying the genome and applying genetic technology to medicine are to develop better ways to prevent, treat and cure disease, that that is the expectation of where we're headed.

DR. HOOK: That's one world view, but there are others who would say no, we should genetically improve the race or that we should have a completely laissez faire libertarian type of approach to the use of genetic materials so that people can benefit themselves and their children, not just the elimination of disease, and so yes, that is the assumption, but I'm not sure that there's been sufficient public discussion of some of these other goals which are very much out there for the use of this material.

DR. COLLINS: I guess historically I can say that with regard at least to the Genome Project, the enthusiasm for the enterprise, the fact that it did happen, that the Congress decided to fund it was all directly related to the expectation of medical benefit, and I think a lot of the people who worked on it were attracted to it, myself included, because of that assumption, and the other applications that you refer

to, such as "improving the race," assuming that we would know an improvement when we saw one, which is to my mind somewhat doubtful, really fall into the category of are these boundaries that we shouldn't cross?

I guess what I'm trying to say is I think we know the center of what this revolution is supposed to be about and it's a medical benefit area, and then there are these questions about, well, are there lines around the periphery where you start off in other directions that you really shouldn't be lurching across without a great deal of thought at the liberation, and our ELSI program has spent a lot of time thinking about those boundaries around the outside and not very much time worrying too much, I think, about the core because I think there's a lot less argument there about the benevolence of that enterprise to try to alleviate suffering and prevent disease.

We have a wealth of scholarship that focuses on some of the boundary questions, about enhancement, for instance, and including where the limits in terms of things like PGD, but that scholarship, that does not translate into policy deliberations. That's what this body is largely entrusted with.

In fact, just one more word of history and then I'll stop talking. One of the reasons that I think we have this Committee, if you sort of trace its origins back, is because in the first five years of the ELSI program, there was a working group which was internal to the Genome Center at that point which deliberated on many of the same issues that we're talking about today, but was located within the NIH, and was not perceived as having the kind of clout and credibility that it would take to actually get something to happen in terms of a policy deliberative body.

So one of the recommendations that was made back in, I think, 1995 by a group that looked at this was we need a higher level group that would be heard, that would have broad representation, would have the resources to study an issue in some detail and then make some recommendations of options that ought to be followed for cabinet member-level individuals to pay attention to and decide whether or not they agree they should be moved forward.

So in fact, this Committee, I think, is sort of third or fourth generation in that ELSI process, but it's probably the most mature and most potentially important generation yet because of the breadth of the charter and the challenge and the depth of expertise and the high level connection to the United States Government.

DR. McCABE: Any of the other speakers wish to comment on that?

(No response.)

MR. MARGUS: Yes, I've been wondering all day long if this Committee would have new ideas that could be generated that haven't already been generated by all the other previous generations. So that's one question. Maybe afterwards, any of you who have been on all these other predecessor Committees could come up with something of what you think, because the science has changed or because it was missed, maybe you think would be new today, I'd be really interested in hearing that.

What I wanted to talk about was Jack Rowe showed this slide that had the 40 percent, I think it was, or some number of people who were willing or eager to know information, even though it didn't have any value to them, or actionable things you could do.

So representing for a minute those 40 percent, I guess I want to ask Wylie for starters, you know, I see, especially with complex disease, people are going to start finding more and more of these genes that only account for a small fraction of the genetic variants but do ratchet up the risk a little bit.

So assuming that you have a good sensitive and reproducible test and assuming that a gateway for it were absolutely associated and everyone agreed on the statistics, assuming all that, that it's good science, are

you saying that if there's nothing you can do about it as far as -- no way you can change a diet or change your life or take a drug, that people really shouldn't be -- a test that's made available to people now?

DR. BURKE: Let me answer that, but let me first make a comment to your previous comment as a former member of SACGT. My sense in that process which was one of the Committees in this line of Committees was that there was a lot of good discussion and there was a lot more discussion yet to be had, and as Francis said, this Committee has a much larger charter and, I think, better able as a result of that charter to talk at the periphery outside of the health care application. So I wouldn't see it as things having been resolved, what else new is there to do, but rather a sort of ongoing and important widening conversation.

In terms of the specific point you made, why shouldn't people get an Apo E4 test if they want it, I actually think that's a legitimate question, and I think it's a very important conversation to have as part of the discussion that needs to go forward, but I would stick by the claim that I made earlier, that it's not a good medical test. So I'm really thinking about it in terms of the health care setting.

From my responsibility as a health care provider, which includes taking action to improve health outcome as my primary mission and in doing so making prudent use of resources, putting those two responsibilities together, I find it hard to justify using the resources of the commons. That is, the money that goes into health care coverage, to pursue that information because a particular patient wants it, particularly with the vast number of tests of this sort that are going to be available when the same resources could be used in other ways to improve health outcomes.

Now, having said that, I certainly don't mean to say that there isn't a legitimate conversation to be had about whether validated information should be made available in the same way, for example, that we make cosmetic procedures available. So I think that's a conversation that needs to go forward and as it goes forward, I think we do need to be attentive to the health care resources common and what's appropriate to use, take out of health care insurance dollars, and also simultaneously, I think particularly in view of the Internet sites that we saw, how tests that we think are legitimate to be had because they're valid but yet not really good medical tests might be offered in a responsible and legitimate and safe way.

MR. MARGUS: I'm really glad to hear you say that very last thing because what I would hope is that the direct delivery of genetic information isn't always going to be thought of in terms of kind of wild, junk science things. You have to separate the two things, and hopefully, it may not come soon enough, I don't know about Francis's schedule, but hopefully some day there will be so much genetic information that maybe the only way to deliver it is through completely different channels than we do now, but so I like seeing it separated.

So you're saying if people pay for it themselves, maybe it wouldn't be so bad. Your biggest objection today would probably be that the resources shouldn't be spent on tests that don't have any use.

DR. BURKE: Well, medical use, I want to separate that. I really think it is the responsibility of the health care system to use information to improve health outcome, and it seems to me that's what health care dollars are for.

Now, if we agree that there's going to be a long list of tests that are potentially available that give information that some individuals might want and we want to give it responsibly, what that means is we don't yet have the system to do that, and so I think that's why I feel like it's a whole big discussion. How do we decide what information is legitimate enough to offer? Are the existing commercial channels the right way to offer it? Do we need to think about some other system? I think there are a lot of questions there. I didn't mean to say that I was dismissing those possibilities.

DR. LEONARD: Also, can I just add one comment, that the 50 percent number, we have the Huntington disease experience, that on polling people, 50 percent of people would say they would want that test.

When it actually comes down to the genetic counseling and the actual utilization of the test, it is much lower than that. Once it's not just a question of theoretically would you use it, when it actually comes down to making that decision, it's much less than 50 percent.

MR. MARGUS: I'm not sure. Was the slide I was referring to the Huntington slide?

DR. LEONARD: No, but Huntington's is that similar --

MR. MARGUS: So it's got to make a difference. Maybe I'm wrong, but it seems like it's got to make a difference what the test is actually for, too. So it's an interesting thing about the twofold relative risk increase in Alzheimer's or if you're definitely going to get Huntington or something.

DR. BURKE: And I agree. I think people might be less afraid to get a test because it's just a twofold increase risk. They might be more receptive to that, but I would want the delivery system, whatever it is, to be one where people understand that they're getting risk information but that is not going to be followed by any medical recommendations.

MR. MARGUS: Well, the other thing is the population's going to disagree with you maybe on whether there is something you do about it or not. So while you might say there's nothing you can do about Alzheimer's risk today, last time I checked, there are lots of articles every week, someone saying something might work with Alzheimer's and there might be people who want to make that decision on their own.

Somebody mentioned -- I think it was Eric earlier today that used the word "patronizing" and just whenever it starts to wreak what some physician acting as God deciding when it's time to be finding out this information always scares you a little bit.

DR. BURKE: I agree. I think you're raising very important issues, and at the same time, I want to say that I think health professionals have a responsibility and that responsibility includes making a distinction between stuff that's been published but hasn't yet been validated and information or therapeutic options that have passed some threshold, and I think that's part of the discussion. Part of the discussion is what are the criteria by which we decide a genetic test is now really a legitimate health care service.

DR. JUENGST: Or a recreational service.

DR. McCABE: Reed, Kay, and then I'm going to ask some questions.

DR, TUCKSON: I'm going to be real interested in our discussion tomorrow about this prioritization.

I am struck by this conversation now with one starting point, and that is, that genetic information is inevitably, as some of you have pointed out, essentially the core of what medicine will be, and so the idea that this is somehow different or distinct from the practice of medicine, that you can separate perhaps these issues out, I mean, it's just all going to be mixed together all as one gamut at some point and really we're close to being there now.

So the question I hear asked, and I'm curious to see what your comments are, is it our job to do one of three things: to support and facilitate the enhancement of good things that can and could be achieved through the molecular biological revolution, things that will do the things that Francis so articulately described? Are we sort of here to think about what are all the ways in which we can make these good things happen faster, better, more evenly distributed through the society and so forth and so on, more intelligently used as, Wylie, you have articulately said? Is our job also to frustrate or limit bad applications? Are we to try to slow those things down, to put them in a different context, to provide information that says this is not a good thing, we would advise against this or there should be availability of information for more informed decisionmaking, better counseling? Or third, is our job to also think

about stopping things, stamping out things, ruling them out of bounds, making them impossible to be done?

We've had a couple of comments that made me wonder about that last thing because it just seems to me impossible to do. I mean, I don't know how you say to someone, you are not allowed to have a test that tells you the sex of your child. Now, it's not a good thing. It's not useful. It's a waste of money. You can't have it. Well, you can't stop that, and by the way, I guess at the same time, when you do the ultrasound, the physician is not allowed to tell you the little dangling thing there.

So you will not have this. I don't think you can do it, and I think one of these days, what we'll have to learn from experts is if you tried to have that kind of control, what would that mean to the society?

Wylie, I would say I really liked your points because they helped me to think about this question. I could tell you now from the point of view of what I do every day, the number of dumb stuff that people buy and the waste, the CT scans for the -- if you really loved her, you'd give her a whole body CT scan at the mall.

(Laughter.)

DR, TUCKSON: In Minneapolis at Christmastime. That is the dumbest thing in the world and it wastes gazillions of dollars and there's 41 million uninsured people who don't get access to aspirin, much less that, and it's immoral. However, there is no tool anywhere that allows you to stomp that out. So I don't know. Does anybody here think we should be stomping things out?

DR. McCABE: Any comments among the speakers? Reed was very shy on SACGT and I'm glad that he's overcome this in the interval.

(Laughter.)

DR. COLLINS: After that passionate speech, it's somewhat difficult to respond as I'm about to, that yes, I think there are some things, some boundaries, that we ought to be willing to say we should not cross that, and I think the public expects that, both in the scientific and the medical communities and in a body such as this, but we ought to choose them extremely carefully.

I will give you the example of reproductive cloning. We should not be pursuing reproductive cloning of human beings. That's my view. I think that's the view of the majority. I think in many ways, it's sort of a disgrace that we haven't figured out a way in this country how to implement that consensus at the legislative level, which is another story but we haven't, but okay, that's a pretty drastic example where the evidence, whether you come from a safety perspective or a more broader philosophical perspective, is overwhelming. But we better reserve our drawing sharp lines and boundaries for that kind of very egregious circumstance and not start applying them willy-nilly in other places.

Let me just say, I'm really glad that you had in your first list of things this Committee might do the effort to try to enable, to try to benefit, to try to speed up the advantages and what we all hope will come out of this because I think we have -- I'll even say this is maybe a bit of a problem for our own ELSI program. We focused more on the bad things that could happen than perhaps we should have on how to enable the good things to happen.

DR. McCABE: Nick, did you have a comment?

DR. DRACOPOLI: I would just add, I think there is one force that will in some sense get rid of the bad stuff and we hope that eventually would be the market. As long as this stuff is safe, I'm not sure the cosmetic issues you can get at Saks are really the issue that you need to be focusing on because they'll be on to metabonomic screening of urine next and then on to something else. I mean, how stable and

longlasting that is, as long as what they're providing is essentially not hurting people, I would argue that the marketplace will eventually get rid of that. That's trivial. It's fluff. It gives us all a bad name, but it will go away eventually.

Really, I think the value of what you can do here is enabling the good and the important stuff that gets to the issues that Francis was talking about. We all believe as scientists that this can have an enormous impact on medicine and the way medicine is applied in the future and if you can enable the good stuff, this is really where you need to be focusing and not worrying about, I think, the things that don't harm people. I believe we would all agree on the bad use of genetic information.

DR. McCABE: Any other comments in response to Reed?

(No response.)

DR. FELIX-AARON: I'd like to connect points made in Wylie's presentation and Francis's presentation, and I'd like to focus my question on the middle of the spectrum, on diabetes, heart disease, these common conditions, and how genes and the environment interact, and so I've observed over time that conditions like diabetes, obesity and this seems to be rising in the majority population, but in low-income and minority populations, these conditions are very prevalent, and I'd also like to sort of place on top of that our interest in finding and intervening on the genetic level without a clear sense of how the environment reacts with the expression of these genes because I would like to hear your comments on that.

For example, in the communities where there seems to be some sort of genetic predisposition and that explains why some conditions are more prevalent today than they were, say, 30 or 40 years ago, the question I have is how much has the genetic background in these populations changed versus the environment? I mean, do we get a sense of the contributions to those patterns of disease versus how much is environmental and how much is genetic? Because I think we really need to understand, because I think that for the future, it may be that diseases that are prevalent now will be prevalent 20 and 50 years down the line as our environment continues to change.

So I think we have the opportunity now to understand the interface and the interaction between the environment and the genetics and not only on an individual level, sort of people's diet, but sort of their neighborhoods, how they live, their working environments, and how does that relate to sort of the diseases that we will see 50 years down the line.

DR. BURKE: Well, I agree with your comments, and I actually think that there are two ways in which genomic research, the kind of genomic research that I think we're all agreeing we'd like to see promoted might contribute. If you see a rising prevalence of a disease over 10, 20, 30 years, asthma for example, rising prevalence of asthma, I think we can be fairly certain that what's changing that's resulting in that changing prevalence is something in the environment. There's no reason to think genotypes are changing over that kind of time frame, and yet at the same time, we know that genetics makes a major contribution.

I think genomic studies will, Number 1, get us closer to understanding the disease biology and thus identify, for example, drug targets and potentially innovative therapies, but speaking more specifically to the environmental issues and why I think it's so important in these large data banks that both genes and environments are studied, I think understanding the underlying genetic susceptibilities may allow us to much more precisely understand which are the key environmental factors, may help us to identify them better, may help us to understand what environmental interventions may make the most difference, possibly different ones with different kids or understand at what age the critical interventions can occur.

So I think there are going to be many common diseases where our opportunities to intervene are going to remain environmental or drug-related, drug therapy-related, but where genomics will enable us to do a better job.

DR. McCABE: I think many people have commented that one of the fallouts of the Human Genome Project will be a heightened sensitivity about the environment because what we'll begin to realize is that reactions, disease that we thought was idiosyncratic, is really stratifying across certain genomic relationships and it will give us an appreciation that got lost in all of the noise before. So I think it's an intriguing situation, that this genetic determinism that we've been living with could end up actually giving us insight into environment that we would not have had without it.

What I want to ask the speakers is just if you have any ideas about how we ought to go about our task of prioritizing the issues that we need to raise. Are there issues that we -- this was dealt with a little bit before, but I'll come back to it -- should avoid, issues that we should definitely take up? Should we deal with the issues as they are today or should we be trying to anticipate issues that are on the horizon, emerging issues?

So really, how should we begin to shape our discussions in the Committee? Eric?

DR. JUENGST: In terms of your prioritization problem, one strategy would be to look for overlap between the presentations that you've heard today and see where people are bringing up the same or similar kinds of themes. Not that we're representative or authoritative, but at least it's some form of robustness. And then, I would also urge you to be anticipatory and be willing to look down the road, in addition to trying to address the immediate urgent problems.

DR. McCABE: Other comments? Francis?

DR. COLLINS: Well, I was probably already more directive than you expected in the brief presentation I made earlier this afternoon. I won't reiterate what those four suggested priorities might be, but I do think it's probably very important for this Committee to jump in on one or two topics early where you can make real headway. I noticed that in fact the charter for this Committee was signed in September of 2002, and it obviously takes awhile to get things up and going and at the present time it's a two-year charter, and then they'll consider again what happens next. So it would be really good if this Committee had some deliverables to put forward by the sort of fall of 2004, which isn't very far off.

So I think it would be good in your panoply of considerations to try to pick some topic or two for which there could be real forward motion in terms of a product, an output in that kind of time table, recognizing that's pretty challenging with this just being the first meeting here today.

I also think, and this is just obvious stuff, that it would be most appropriate to pick topics that are well within the charter of what the Committee is asked to do. Obviously it's a pretty broad charter, so maybe that won't be too hard, and also topics that are not currently being undertaken by another highly ranked group and there are a number of them that need to be sort of looked at to see what their intentions are at the moment.

Also, of course, you ought to pick things where the expertise that you need is well represented amongst the membership.

DR. McCABE: Other comments from others? Because this is what we will spend the bulk of tomorrow dealing with. Any guidance? Yes?

MS. WILLIS: I just had a question for Dr. Fraser. I was just fascinated by your talk and some of the issues that are there and following Dr. Collins and what he was saying about not trying to do repetitive efforts that other organizations are doing, and I was wondering, is there any organization or Committee or anyone who's devoted to maybe pointing pharmaceutical companies back toward making antibiotics or paying attention to issues of microbial genetics and uses and bioterrorism?

DR. FRASER: I'm certainly not aware of any Committees that are tapping that issue, but it's one of the

things, in thinking about what I presented, that I find most disturbing. It's disturbing no matter what, but I think it's even more disturbing in the context of all the possibilities and all of the potential breakthroughs from having this new starting point as a result of the significant federal investment in microbial genomics. I think that that's a very, very serious issue and it gets back to the issue of the need for the appropriate public/private partnerships.

This is certainly something that has been discussed now within the context of the biodefense arena, and I confess I don't necessarily understand all of what the bioshield initiative is, but that's certainly an example of trying to provide new vaccines, new drugs, new reagents, to increase our overall level of preparedness. I think that we should take a lesson from that and acknowledge that going forward, while those are the most definitely serious concerns, I really think what's going to be more important and deserves as much, if not more, attention is dealing with the issue of emerging infectious diseases and how we prepare ourselves for tackling those in the future.

DR, TUCKSON: Just the extraordinary experience with SARS, where the world was able to move so rapidly and so quickly to decode that genome, does that indicate to us that the infrastructure is in place and that this is an area that is pretty good, it's pretty okay, and it ain't broke, don't fix it? Do we need to sort of push for more in that direction?

DR. FRASER: I would agree that the infrastructure is very much in place and that there's a tremendous amount that could be done with the current infrastructure, and I think the message that I've been taking out to various groups is that if there's really a concern that we're not prepared at the appropriate level, and I think that is indeed the case, that someone needs to put their money where their mouth is and invest in the research, making use of available infrastructure, so that when the next SARS comes along, we're not reacting.

The one positive point is that we seem to be able to react more quickly now, but constantly being in a reactive mode I don't think is the most sensible way to go.

DR. McCABE: Thank you very much. Thank you to all of our speakers. Your input has been extremely valuable to us as we proceed with our deliberations. I know some of you are involved with the Committee. I hope others of you will continue to follow the efforts of this Committee and provide input to us, if you feel that it would be useful to us. So thank you very much for helping us with this inaugural Committee meeting. Thank you.

Now, we will move into public comment. I think it's important to recognize that we always invite public comment. This is an extremely important part of the process for us, and we look forward to contributions from the public.

We've had some written comment. These are in Tab 2 of your notebooks and in the table folders. Just to give you who those are from, Kathleen Zeitz, J.D., from the Nebraska Breast Cancer Action Network, Diane Dormond from the National Organization for Rare Disorders, the Oncology Nursing Society, the National Society of Genetic Counselors, which has signed up to make oral remarks, I think, tomorrow, and Mark Bale from the U.K. Human Genetics Commission Secretariat.

We had three individuals but one of them has graciously volunteered to move until tomorrow morning, so we have two. First will be Dr. Thomas Hooyman from the Catholic Health Initiatives, and I would ask all of you to try and stick to three or four minutes, so that we have some time for questions to you.

DR. HOOYMAN: Thank you. I will certainly attempt that, and I very much appreciate the time with the Committee to provide some public comments from the perspective of Catholic Health Initiatives. We're a national Catholic health care system based in Denver, Colorado, with, as you can see, our particular size out of the Catholic tradition. I work as a theologian ethicist within that organization and welcome the opportunity today to be here.

I wanted to give just a very brief comment regarding how we would approach not just the area of genetics and advances within that field but generally the broader question of the relationship out of a faith-based organization, such as Catholic Health Initiatives, in regard to science as a whole.

I think it's interesting, some of the questions that were raised just before. I won't go through these, but the last dot in particular sort of raises the question that from a particular perspective out of a Judeo-Christian background, that by our very nature, we're limited, and it's interesting as we listen to comments and discussion through the course of this meeting, that there's a certain sense that there's an unlimited possibility where human genetics, the Genome Project, and various advances within genetics may lead us, and so I think there's somewhat of a philosophical tension there.

The other thing I want to say is that there is nothing out of the Catholic tradition that is inherently opposed to the work of the Human Genome Project or advances in genetics at large, and I think sometimes there can be sort of a biased perspective right away that a faith-based organization, such as CHI, would be opposed to that, and we are not in principle.

Just very briefly, a few ethical concerns that we would have in general in regards to the area of genetics. What I'm concerned about is the potential advances that may exist within this area of genetics may become mired in the apparent irreconcilable dispute that has already existed within our society around the beginning-of-life issues, and from our perspective, it would be a shame that if we would have potential advances within this area sidetracked by those ongoing beginning-of-life disputes. It's just a recognizing of them in the first place.

Secondly, as you've already heard, in our consumeristic society, whether it's the coming up with new discoveries for your makeup or the skin disorders or what have you, or just the enhancements of that, if the services are provided, if they're available, as what was mentioned before, consumers will go after it, and as a provider of health care, being in a variety across this country, that imposes a significant burden upon us as a provider not only in the area of capital, of making investments within the capital infrastructure for laboratory services and equipment itself, but also with regards to personnel. So there's a tension there that we have to deal with, I think, and that the work of the Committee should address.

Final just general concern, as has already been mentioned, with the 40-plus million people who do not have access to health care already, how we will look at this question in the area of justice and expanding access to just the basic care, such as what was mentioned before, just aspirin.

As a provider, Dr. Juengst had already spoken of testing and therapy and also pharmacogenomics. Just looking at now what's possible, as you're all very familiar with, just the area of genetic testing, we have patients in our clinics that are approaching a variety of family practice physicians, internists, oncologists, what have you, that are already proceeding with these particular tests and the fundamental policy questions that I've outlined here are really unresolved.

So I would look towards and encourage the looking for priority work around for the Committee for your work in the coming year to possibly address some answers to some of these key policy questions. Appropriate genetic testing for disease processes where there's no proven treatment, the sharing of that information with family members or others, and then if there is such a responsibility, how could that be regulated, as you've already been discussing.

As an employer, we employ approximately 67,000 individuals within our organization, and so there are several concerns that we would have as an employer. In order to remain competitive, our benefits plan will need to continue to evolve into to include genetic services. Otherwise, we'll have key employees who would be going to competitive organizations. So that's going to impose additional financial pressures to us.

Secondly, as has already been mentioned, we see this also as an employer and we're one of those

organizations that ERISA preempts us, we're self-insured, so the local state regulations don't apply to us, as you were discussing before, but just how we on go maintaining the privacy and confidentiality of our own employee databases and with regards to their private health information, in regards to HIPAA, and also a final point, as internally within our organization, we would not discriminate against our own employees based upon their genetic makeup.

Some suggestions for your work agenda as you are currently doing via the webcast and just as mandated by Congress is to engage the public, not only just to engage them but to provide an increased awareness and understanding of the public and the potentiality of what will result from the work of this group and with the project human genetics going forward.

It's interesting. We have a grave concern around education of health care professionals. I don't think I heard anything through the course of today of the dearth or the lack of qualified, certified genetic counselors. We did an asset map within our organization just to see what services, who do we have available, and we have two certified genetic counselors out of an organization of possibly $6 billion in revenue.

So I think nationally, there's only 2,000 certified genetic counselors, and I think you'll hear probably public comments from that organization tomorrow, but we really need a comprehensive approach for dealing with education, not just genetic counselors but health professionals in general.

Perhaps, and it's probably the most difficult challenge that you may have, is to develop some kind of ethical framework going forward of how all the variety of genetic advances may be evaluated, and in a pluralistic society, I mean that's the heart of our society in the democratic environment, that's where the debate occurs, but I think, just as Dr. Collins mentioned before, there was a line that he was drawing in reproductive cloning. Well, what is that framework and where else can those lines be drawn? I think some of your discussion's already occurred around that area.

Finally, I was struck a few days ago, perhaps some of you had seen it, there was a photograph on the front page of the New York Times of a woman in South Africa collecting water with a bucket going down to basically a muddy pool in a roadside collecting the water for the day for her family, and I think there's a need that we have to maintain a global perspective over balancing our needs as a society just around genetic testing perhaps or other genetic advances in regards to global needs, for instance South Africa, just in the basic idea of public health and access to water.

In conclusion, we would like to maintain a very optimistic view of where the work of the Committee will proceed and with medical genomics in general. We're also somewhat cautious about the potential hazards, and as I'm sure you've sort of picked up within the comments thus far, we'd like to remain in a collaborative fashion with the work of the Committee as you go forward, and we very much applaud the work of the Secretary at this point and the Committee of the whole.

Thank you.

DR. McCABE: Thank you very much.

Any questions for Dr. Hooyman? Yes?

DR. SHEKAR: Not a question, but a comment.

DR. McCABE: Please identify yourself.

DR. SHEKAR: Sorry. Sam Shekar, representing HRSA, the Health Resources and Services Administration in HHS.

Just a comment, that in terms of the issue of health professions education, we did a study through Judith Cooksey, who was here earlier today, earlier with regards to genetic counselors in the United States and the issue about training is a very serious one. In fact, we only have 1,800 or so genetics counselors in the entire country. So in terms of the translation of research into practice, the issue of workforce training is an important one and one that we would suggest or recommend is also a priority area that needs to be looked into.

DR. McCABE: Thank you.

Other comments? Yes, please.

MR. DANNENFELSER: You raised the issue of cloning. Dr. Collins did as well. He mentioned reproductive cloning, where there seems to be a general consensus that that should not be allowed. The controversy seems to be more in the area of experimental cloning or what is often called therapeutic cloning, and it seems that the term "therapeutic" is supposed to refer to providing therapy for benefit to the person receiving the treatment, and that in fact is not the case with what some call therapeutic cloning. It is really cloning for the purposes of experimentation, and I just wonder if that's an issue of concern to you.

DR. McCABE: Just for the record, that was Mr. Dannenfelser from the Administration for Children and Families.

DR. HOOYMAN: The concern that we would have would be out of that slide on the ethical framework, the very first dot, the protection and the inherent dignity of the human being. There'd be nothing opposed to cloning of therapeutic cloning, for instance, if I needed new kidneys or a heart and you could take cells and somehow come up with a new heart for me or kidney. My human dignity and my totality is being protected.

I think obviously that other point of saying getting into the beginning-of-life issues or depending upon what's being presented out of the Catholic tradition, there are going to be some very serious concerns around the protection of life. So I don't think it's irreconcilable. I think it depends upon what the technology's presenting and there again to be again to, through a democratic process, be able to work out what's accepted public policy.

DR. McCABE: Thank you very much.

DR. HOOYMAN: Thank you.

DR. McCABE: Our next speaker is Dr. Kathy Hudson from the Genetics and Public Policy Center, Johns Hopkins University.

DR. HUDSON: You all deserve an award in endurance and stamina.

My name's Kathy Hudson. I'm the Director of the Genetics and Public Policy Center at Johns Hopkins University, and I wanted to speak today to just let you know that we exist and that we'd like to be a resource for you. We were created by the Pew Charitable Trust about a year ago in order to create resources for decisionmakers in considering issues that are emerging from advances in human genetics, and so I'd like to just familiarize you with some of the resources that we have available and would welcome input from you as you begin your deliberations in how we might be helpful.

We currently have a major initiative underway in reproductive genetics. As you know, there are now over 900 genetic tests that are available, either clinically or in development, and we can do genetic testing at virtually any point in the reproductive cycle. We can test parents. We can select gametes. We can test embryos. We can test fetuses, and we can test newborns.

The goals of the initiative are here. The one that I would like to highlight with you is some of the work that we have done to assess the public's knowledge and attitudes and values not only about reproductive genetics but about human genetics in general. A folder was passed around, I think, that includes this report, which is part of the center's effort to understand what the public is thinking, what the public values, what the public priorities are. This was an initial pulse-taking of where Americans are, and we are now following up on that with detailed qualitative research.

In April of this year, we did 21 focus groups in five cities around the country, and after recovering from our exhaustion, we're now evaluating the large amount of data coming out of those focus groups. This summer, we're going to be doing 200 interviews with individuals with specialized expertise or experience or perspective with relationship to reproductive genetics, and then this fall, we're going to try to validate some of the hypotheses that come out of that, test the hypotheses that come out of that qualitative work with a larger more robust survey.

The other thing that I'd like to make you aware of is the extensive information resources that are available on our website, which is www.dnapolicy.org. We have an extensive bibliography on science, ethics, policy, and law related to reproductive genetics and genetics more broadly, much of that having been annotated in-house by our staff.

Our major goal at the center is to develop a set of policy options. So we're not going to be developing a single recommendation of this is where the country should go in dealing with the development and use of reproductive genetics; rather, we're going to try to develop a broad base of analysis and then take that analysis and put it together with what we learned from the public about their values, what they hope for, what they're concerned about, and develop a diverse set of policy options that you as a Committee and others in government and in the private sector can consider as you make decisions to move forward.

Again, I invite your input, particularly as we're developing this survey for this fall, that if there are questions that you have about what the public's thinking about certain issues that come under your deliberations, we'd be happy to think about how we might be able to work together to answer some of those questions.

Thank you.

DR. McCABE: Thank you very much.

Questions or comments for Dr. Hudson?

DR. REEDE: It's more of a general comment, and it relates to many of the presentations that we've heard today, and it's reflected in everything from building the huge data bank and the need to make sure that it's inclusive in terms of race, ethnicity, diversity. It relates to comments about the workforce and the low numbers in the workforce, but we haven't really spoken about who is represented within that workforce and is there diversity represented within that workforce. It relates to Jack Rowe's comments about certain racial or ethnic groups' concerns about genetic testing and being involved in genetic-type issues and the comment that part of what needs to be done is educating our physicians to better deal across communities which is true in general, but also, how do you have better representation there.

I would carry it here in terms of as we seek a better understanding of the public's perception about genetics, making sure that we're inclusive and that our understanding is representative of our entire society and we're getting the perceptions from the various racial/ethnic groups and that this work is not done as an afterthought. So after we've put our data bank in place or after we have put our workforce agenda in place or after we have done our surveys, we then come back and say what about the diversity issue.

DR. McCABE: Thank you.

Other questions or comments for Kathy?

(No response.)

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

I just want to remind everyone that we start at 8:30 tomorrow morning, not 9:00 as this morning. So we will start a half hour earlier tomorrow morning. We will begin with public comment.

Also, to remind the members of the Committee, the ex officios, that there is the dinner tonight at Toscana West, 14th and I Streets. It's at 7:00. We will meet in the lobby and walk over. So we will meet at 6:45 in the lobby of the hotel to walk over to dinner. If you haven't done so at this point in time, please give the folks at the registration desk a check for the dinner tonight.

(Whereupon, at 5:53 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday, June 12, 2003.)