The Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Inaugural Meeting
June 11-12, 2003
Washington, DC

Welcome, Opening Remarks, and Induction of Members
Elias A. Zerhouni, M.D.
Director, National Institutes of Health

Dr. Zerhouni, on behalf of the Secretary of Health and Human Services (HHS), Tommy G. Thompson, opened the inaugural meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). He extended the Secretary's regrets for not being able to attend and expressed pleasure at being asked to open the meeting on his behalf.

Dr. Zerhouni said that it became clear to the Secretary that the scope and charter of SACGHS's predecessor committee, the Secretary's Advisory Committee on Genetic Testing (SACGT), needed to be broadened, especially in light of all the new developments in genetic research and technologies. He noted the Secretary's support for genetic research and the Human Genome Project (HGP) and its benefits for both research and healthcare.

Dr. Zerhouni said that all of the components of HHS support this Committee's efforts and are looking forward to its contributions. In addition, given the Secretary's commitment, as a policy maker and national leader, to ensuring that policies keep pace with scientific developments, it was not a surprise that he took a personal interest in the Committee's restructuring and rechartering. The National Institutes of Health (NIH) is honored to be the managing agency for SACGHS, providing staff and resources in support of its efforts.

Dr. Zerhouni remarked that the Committee will need to consider how the variety of applications arising from genetic research will redefine the practice of medicine. More importantly, it also will need to consider the downstream diagnostic technologies that are emerging from rapid DNA sequencing, DNA array technologies, and proteomics.

Advancement in research and integration will not be possible unless assurance can be provided to individuals that genetic information never will be used against them. Dr. Zerhouni noted that the President has called for Federal legislation to prevent the misuse of genetic information in health insurance and employment, and that the administration believes that the bipartisan Genetic Information Nondiscrimination Act of 2003 will represent a significant landmark if it is enacted into law. NIH, the National Human Genome Research Institute (NHGRI), and many others support this bill and have spent a great deal of time informing Congress about the issues surrounding genetic discrimination. Dr. Zerhouni stated that SACGHS's support for this legislation was also important.

Dr. Zerhouni explained that since its inception, the HGP project has been committed to spending three to five percent of its budget on studying the ethical, legal, and social issues raised by these new technologies through the ELSI Program (Ethical, Legal, and Social Implications Program). In addition to addressing ELSI issues, there is a need to focus further on the uses of genetic information in education, employment, and insurance, including health, disability, life, and long-term care, and to consider the use of genetics in bioterrorism and the impact of patent policy and licensing practices on access to genetic technologies. Many constituencies have expressed a need for guidance and clear policies, Dr. Zerhouni said, and now is the time to work aggressively to develop such guidance and policies. Dr. Zerhouni concluded that he is

confident the Committee's work will be supportive and informative. He then inducted the SACGHS members into service by having them recite the oath of office for governmental officials (the members are considered special government employees (SGEs) during their service on the committee).

Federal Advisory Committee Act Regulations
Valerie Hurt, J.D.
Office of the General Counsel, Public Health Division, HHS

Ms. Hurt provided an overview of the Federal Advisory Committee Act as it relates to SACGHS and its proceedings. The purpose of the Act is to ensure transparency in the proceedings of advisory committees, to provide the public with the opportunity to participate in and be informed about advisory committee activities, and to establish uniform standards and practices for obtaining advice from outside experts. She reviewed the rules regarding balanced membership, notification of meetings, and public availability of meeting minutes and committee reports, as well as the role of the committee's designated federal officer. She also explained that certain activities, such as work group or preparatory activities (e.g,, gathering information, conducting research, drafting position papers), are not subject to the open meeting requirements until these activities become part of the work of the full committee.

Ethics in Government Regulations
Holli Beckerman-Jaffe, J.D.
Office of the General Counsel, Ethics Division, HHS

Ms. Beckerman-Jaffe explained the various regulations to which advisory committee members are subject as SGEs and provided several examples of how these regulations apply in various situations. The Emoluments Clause prevents SGEs from accepting a gift, emolument, or official title from a foreign government entity (the only exception is for Congressionally-approved foreign gifts which are allowed under the Foreign Gift and Decorations Act). The financial conflict of interest statute prohibits SGEs from participating in a particular matter that will have a direct and predictable effect either on personal or imputed interests. To help SGEs understand the financial conflict of interest rules, committee members' interests are reviewed before every meeting. This review helps determine whether there are any specific matters that are anticipated to be discussed at a committee meeting that could foreseeably create a financial conflict of interest for the members. For matters of general applicability (e.g., a matter that could affect all members of a class in the same way), a waiver will be granted that allows the SGE to participate in the deliberations. Ms. Beckerman-Jaffe further explained to the committee members that participating in political activity (e.g., lobbying) is prohibited while they are serving in the role of SGE.

Existing Genetic Technologies and Their Integration into Healthcare and Public Health
Wylie Burke, M.D., Ph.D.
Chair, Department of Medical History and Ethics, University of Washington

Dr. Burke opened her presentation by noting that she would provide an overview of the current use of genetic technologies in healthcare and public health. She said that there are two basic ways to use genetic knowledge to benefit health. The first use is for diagnostic purposes—genetic testing can be used to identify those who have specific needs, make a genetic diagnosis, identify genetic susceptibility, and ultimately create the opportunity to tailor care based on the individual's genetic composition. The second use involves the tools of genetics and genomics to understand disease biology and increase our ability to treat a variety of health conditions. Although these two paths are not mutually exclusive, each has different implications.

One of the most dramatic examples of using information about genetic susceptibility to identify people with special needs—the most prevalent use of genetic information in the public health setting—is

newborn screening for phenylketonuria (PKU). This model involves identifying individuals very early in life who may have a particular condition and providing a specific treatment. It reflects the potential opportunities at one end of the spectrum where genetics is the predominant contributor to disease. Increasingly, genomics will provide the tools to identify genetic factors that contribute to common diseases (e.g., diabetes, heart disease, cancer) as one of multiple factors.

An example of the use of genetic testing in the course of clinical care is provided by the genetic condition called multiple endocrine neoplasia type 2, or MEN-II, a condition in which people inherit a very high predisposition to develop medullary thyroid cancer, a difficult-to-treat form of thyroid cancer. This condition is inherited in an autosomal dominant manner, and we know what gene is involved. Genetic testing has created new prevention opportunities for this and other diseases.

As the potential for predicting the risk of genetic disease is further developed, we may increasingly face therapeutic gaps—our ability to identify individuals at risk may outpace the development of treatment. For example, although we can identify whether or not a person has inherited the mutation that causes Huntington disease, we have no treatment available for the disease, which like MEN-II is an autosomal dominant condition. This makes the choice of testing for Huntington disease personal rather than medical. It means that the tradition in medical genetics of nondirective counseling applies very forcefully in this case, as the choice to be tested is ultimately that of the patient.

The concept of nondirective counseling also applies when genetic testing is used for reproductive decisionmaking. The same test for the Duchenne muscular dystrophy gene that would be used diagnostically also can be used to determine whether or not someone is a carrier of the mutation (to make decisions about reproduction or prenatal testing), but the implications are strikingly different. In the first case, the test is used in a straightforward manner to make a diagnosis; in the second, it involves highly personal matters. Another recent example is testing for the cystic fibrosis carrier state. An NIH consensus conference and, subsequently the American College of Obstetrics and Gynecology, recommended that this carrier test be offered to all pregnant women.

In discussing the contribution of genomics to current therapy, Dr. Burke discussed treatment developments in hemophilia as an example. Genomics played an important role in the development of a recombinant form of Factor VIII, the blood protein that is missing in this disorder, and it is being used in to develop new methods for producing Factor VIII without serum. The recombinant form of Factor VIII is now the standard of care in the United States, although its high cost is an issue.

The other important new wave in the use of genetic information in clinical settings is the use of genetic technologies to predict risk for common complex diseases. Increasingly we are able to find gene variants in many diseases that identify people at increased risk for the development of cancer, heart disease, and a variety of other common diseases. The question remains how we use that information effectively in clinical care. Dr. Burke reviewed the challenges involved by discussing the example of the common medical problem of venous thrombosis, or blood clots, the gene variants involved, and the variety of potential interventions including anticoagulation therapy for individuals at increased risk of venous thrombosis. Currently there are major risks involved in using anticoagulation therapy, and it is estimated that those on anticoagulation therapy have about a three percent risk per year of having a major bleeding event; 20 percent of these bleeding events may be fatal. Individuals who are heterozygous or homozygous for Factor V Lieden or prothrombin variants might be appropriate candidates for some level of anticoagulation therapy. A separate complication arises from variants of the CYP2C9 gene; individuals with particular variants have a metabolic impairment leading to severe toxicity when treated with the anticoagulant warfarin. She noted that it is important to ensure that we are really helping people if we use these therapies differently in someone at increased risk.

In order to assure benefit when using predictive genetic testing for common diseases, we must rigorously ask who we are trying to identify, what treatment we will then apply, and what level of risk associated with the treatment is reasonable. There is potential for unintended harms resulting from the use of genetic information. One could argue that providing unnecessary or unproven therapy is itself a significant risk that may result from identifying someone at risk for a disease with no clear treatment. For example, a variant of the APO lipoprotein E gene, APOE4, is associated with an increased risk of Alzheimer's disease. However, the magnitude of the increased risk is uncertain. Three expert panels have concluded that APOE4 testing for Alzheimer's disease is not a wise predictive test to use because of its indeterminate risk assessment and the lack of an available treatment.

There are a range of ethical concerns in predictive genetic testing that should influence how clinical practice guidelines for tests are developed and used. For purposes of discussion, the concerns can be categorized into four groups.

- For a highly predictive test with an effective treatment, access to the test should be assured.

- For a highly predictive test with no specific treatment available, adequate counseling should be provided and individual autonomy should be protected by ensuring that people make their own decisions based on full knowledge and their own preferences.

- For a test that is somewhat but not absolutely predictive of a disease with an available treatment, a careful consideration of risks and benefits similar to current medical practice is needed before deciding who should be tested and what treatment should be provided. This will be a very important area in clinical practice guideline development over the next 10 to 20 years.

- For a test with low predictive power for a disease with no available treatment, it is difficult to justify offering the test. If treatment becomes available the advisability of using the test would change.

On the horizon is pharmacogenetic testing, which involves identifying gene variants that predict whether people have a higher risk of adverse consequences to a therapy or using genetic tests to identify responders or nonresponders. Many pharmacogenetic tests are under development, and there is a great deal of potential for this kind of technology to be used in clinical practice. Like other diagnostic technologies, these tests have risks as well as benefits and they will need to be weighed carefully as the field moves forward.

Genome-based therapies are in development, but few have reached clinical care. The drug, Gleevec, is an example of a drug whose development was based on a molecular level understanding of the disease. Gleevec is a selective inhibitor of a particular tyrosine kinase that was developed to treat chronic myeloid leukemia and is now being used in the treatment of other cancers. Genetic research was crucial in identifying this specific kinase, providing one model of how genomic research will help develop new therapies.

Another interesting way in which an understanding of genomics can lead to a novel therapy can be seen by looking at a genetic therapy for a cytomegalovirus infection of the eye that is a complication of HIV. In this therapy, an RNA transcript inhibits the messenger RNA that is a crucial piece of the production of an essential protein for this virus.

Dr. Burke concluded by outlining three central questions that must be asked in the era of genomic healthcare:

- When does harm from genetic information outweigh its benefit? This is an important question to ask for all uses of genetic information—particularly for prediction.
- Who decides when new technologies have sufficient safety and efficacy for use, and on what basis?
- How do we ensure equitable access as these therapies are developed?

Emerging Genetic Technologies and Their Medical and Public Health Applications
Nicholas C. Dracopoli, Ph.D.
Vice President of Clinical Discovery Technology, Pharmaceutical Research Institute, Bristol-Myers Squibb

Dr. Dracopoli began by outlining the four main questions he would address in his presentation. 1) What genetic technologies for healthcare and public health are on the horizon? 2) What impact will these technologies have on the quality of healthcare, its accessibility and affordability? 3) What new issues will be raised by the further development and integration of these emerging genetic technologies? 4) What public policies need to be in place to allow for the evaluation, development, and integration of emerging genetic technologies?

According to Dr. Dracopoli, pharmacogenomic testing, which uses multiple technologies for different drugs and diseases, is already on the market, and its presence will increase rapidly over the next few years, with opportunities defined by medical need. Although there is no single "killer application" on the horizon, there are many targeted opportunities for a diverse list of new and existing drugs. One of the main issues in moving forward is how genetic advances that are being used in the drug discovery process will be translated to the clinical environment, as profiling technologies move rapidly from research to diagnostic laboratories and new market opportunities surface for drug development companies and third-party diagnostic companies.

Pharmacogenomics is the use of markers of biological variation at the protein, DNA, or RNA level to predict patient response to pharmaceuticals. It is used to identify who will and will not benefit, as well as who will and will not react adversely to a therapy before it is selected. This technology will help personalize medicine, reduce adverse reactions, and increase the number of patients who benefit from therapy. On a molecular level, pharmacogenomic tests are used to arrive at a more effective definition of disease by defining subclasses of diseases according to their response to pharmaceuticals.

In the field of oncology, pharmacogenomics is particularly important because there is enormous potential for increasing the efficacy of compounds. At the same time, the molecular pathology underlying a disease must be determined in order to achieve an increase in efficacy. For cancer, two underlying causes of variation in response to a drug must be investigated: genetic variation carried by all cells in an individual (referred to as germline variants) and new mutations in the tumor cells (somatic changes). Germline variants determine the individual's response to the drug; therefore drug transport and drug metabolism genes must be studied. Somatic changes in the tumor that affect important regulatory pathways or the drug target must also be explored to look for markers and patterns that then can predict individual response. Dr. Dracopoli noted that it is now clearly shown that the fate of a tumor essentially is hardwired relatively early in its evolution. At the time of biopsy, these tumor cells can be analyzed to obtain data that will help direct therapy more effectively.

These two avenues of investigation require different technological approaches. It is possible to test for some known genetic variants, and public databases are being developed to elucidate how these genetic

variances affect an individual's response to a drug. A promising area of research for profiling tumors, involves correlating individual gene expression profiles in tumors to drug outcome. The hope is to use these approaches with broad-based expression profiling methods as well as analysis of known mutations to place otherwise homogeneous cancer patients into multiple groupings and ask if those groupings show different responses to different therapeutics. This is an area that soon will have an impact in the clinic.

Pharmacogenomic profiling technologies include three categories of analysis: 1) protein (proteomics); 2) DNA, or SNP, genotyping (with about four million SNPs in the public domain, the challenge now is to type them); and 3) transcription, or RNA, profiling. From a pragmatic and cost-driven perspective, however, the RNA-based approach (transcriptional profiling) is the only one in which nearly all of the known messengers in any sample can be examined at a comparatively lower cost per gene.

In order to do profiling effectively and have interpretable results, the assumption is that the patterns seen within biological samples are not random and that there are a relatively limited number of patterns that can be found. In other words, there will be a limited number of events and pathways that can be changed, and any changes will occur in a consistent pattern that can be detected in biopsied cells. Thus, the profiling approach is essentially a massive pattern recognition process to seek sets of genes whose expression patterns are most correlated to the particular biological endpoints. With sufficient samples and enough repetition, some statistical predictability can arise from these types of analyses.

The difficulty in bringing this hypothesis to practice is going from using profiles to using assays; current tools are focused on drug discovery with the hope that there will be relatively few markers that can be used in clinical assays. We presently lack the ability to convert these profiles and the markers within them to assays that can be analyzed in a clinical laboratory environment. Major technical issues remain when applying these profiles to the large numbers of patients in the clinic.

Currently, investigations are focused on relatively large numbers of analytes or markers using small numbers of samples. In oncology, for example, the Herceptin model (to determine whether the drug should be added to standard chemotherapy treatment for breast cancer) involves measuring a single analyte for a single indication. Profiling methods would allow the use of as many as 50 to 70 markers to get full sensitivity, which would result in clinical information for multiple indications. The challenge is translating these quantitative measures across multi-analytes into practical application.

Technologies for public health that are on the horizon include high-capacity, low-cost profiling of DNA, RNA, protein, and metabolites and RNAi (RNA interference) for drug target validation. This is an evolving technology to study gene expression that will have enormous impact on target validation in drug development. New technology will be needed to deliver complex genetic and proteomic diagnostic tests in the clinical setting.

One of the impacts that emerging technologies are expected to have on the quality of healthcare and its accessibility and affordability is a better way to define disease causation that will lead eventually to better targeted therapeutic approaches. The molecular definition of disease will likely affect market segmentation broadly. However, because the market is already medically segmented, concerns about this outcome may be somewhat overstated. The molecular definition of disease also will lead to increased efficacy and safety that will in turn lead to lower attrition rates. Better diagnostics will result in more "orphan" diseases, as subsets of common diseases will be shown to be unresponsive to existing therapies, and this will result in new unmet medical needs. Also, pharmaceutical pricing also will begin to incorporate the costs of pharmacogenomic testing.

New issues raised by the further development and integration of these emerging genetic technologies include those involving the need for regulatory guidance for pharmacogenomic development, with new

policies needed to support co-development of diagnostics and therapeutics. There should be clear guidelines and regulatory requirements for the incorporation of pharmacogenomics into drug development.

The public policies that need to be in place to allow for the evaluation, development, and integration of emerging genetic technologies include those that provide for the protection of the privacy of genetic data, which should be treated similarly to other medical data; public funding for pharmacogenomic research, including databases and tissue banks; anonymized samples obtained with full informed consent; and support for public-private consortium efforts, such as the SNP Consortium and the Mouse Genome Sequencing Consortium. Support also is needed for public education about genomic sciences in order to assuage fears of modern genetic technologies generally.

The Financing of Genetic Technologies in the U.S. Healthcare System
John W. Rowe, M.D.
Chair and CEO, Aetna Healthcare

The impact of genetic tests will be influenced by the effectiveness of the partnerships among the producers, purchasers, and users of genetic tests. These groups will have to work effectively together to realize the promise of genetics to enhance the health status of individuals and populations. Dr. Rowe explained that the cost-effectiveness of genetic testing, from an insurer's point of view, is based on the degree of risk present in the population being tested and on the treatment and intervention available after testing. Directed testing for breast cancer and regular screening for colorectal cancer have been cited as examples of cost-saving applications of genetic testing.

Although some do not regard genetics tests as safe and fear that having a genetic test will subject them to discrimination in the workplace or with health insurance, fortunately, this is not the prevalent finding, noted Dr. Rowe. A nationwide Harris Interactive poll of 1,103 adults age 18 and older taken in May 2002 suggests that the fear of denial of health insurance and loss of privacy may be overstated. In this poll, more than four out of five people indicated they viewed genetic testing in a positive light. The more familiar people are with genetic testing, the more likely they are to say they would have it. In this poll, half of the respondents said that they would be interested in having a test for a very serious disease even if there were no known treatment or preventative measures.

Dr. Rowe then discussed state law regarding genetic testing, noting that all but two states, Idaho and North Dakota, have passed laws that affect individual and/or group insurance. In general, these laws specify that health plans may not: 1) establish rules for eligibility based on genetic test information; 2) require genetic tests; 3) use genetic information for risk selection or risk classification; or 4) disclose genetic information without express informed consent. However, most of the regulators that Aetna contacted were not aware of examples of the behaviors to which the laws were responding. Variation in state law creates a problem for health insurance companies, which serve 50 states and have to comply with that many different sets of laws.

Aetna believes that a national standard would be a more effective arrangement. Two bills are currently in Congress that would move toward a national standard. H.R. 1910, which applies to individual and group health insurance policies, has the same prohibitions that state laws generally do, and allows for a private right of action. In the Senate, S. 1053 was approved by the Committee on Health, Education, Labor and Pensions in May 2003. Aetna strongly supports this bill, which applies to individual and group health insurance policies and prohibits: 1) rules for eligibility based on genetic information; 2) requiring genetic tests; and 3) the use of genetic information for risk selection or risk classification. It does, however, allow

for the use of information for treatment, payment, or healthcare operations such as disease prevention or disease management (as per the Health Insurance Portability and Accountability Act [HIPAA]). The Senate bill also expands the Employee Retirement Income Security Act[1] (ERISA) to include retroactive restoration of benefits. Dr. Rowe noted that health plans should follow the same prohibitions specified by state law.

With respect to the fear of genetic discrimination, Dr. Rowe noted that a study at Wake Forest University published in 2000 did not find one published case of genetic testing-based discrimination against individuals with group health insurance. This outcome is logical since insurance companies have no incentive to discriminate: on average, customers are self-insured, are age 32, and are enrolled with Aetna only two to four years before changing to another insurance company. In addition, short-term expenses are a main focus for insurance companies, and the major determinants of short-term expense are demographic characteristics rather than genetic information.

Another myth is that health insurance decisions are arbitrary. In reality, Aetna has a comprehensive process for coverage decisions, and its policies are based on current peer-reviewed literature and on the recommendations, standards, and guidelines of relevant professional colleges and societies. Aetna issues coverage policy bulletins and information on how its policies were created for each genetic test and provides this information to the public on its web site.

Also, to minimize confusion about state laws and genetic test coverage, Aetna offers a set of guidelines based on the test coverage recommendations developed by professional groups. The American Association of Health Plans has issued a set of guidelines that are very similar to those issued by Aetna.

Regarding coverage, Aetna's goal is to pay for tests that are shown to affect the course of clinical treatment, i.e., tests for diseases for which treatment exists and can be offered. If someone without symptoms seeks to be tested for Alzheimer disease (AD), for example, Aetna would not cover the test because there currently is no generally agreed-upon treatment prior to disease onset. The individual might present a number of nonhealth-related reasons (e.g., family planning, life planning, legal, and financial) for wanting to know his or her likelihood of getting AD, however in these cases, Aetna's position is that the individual should pay for the test.

Aetna's guiding principles for providing coverage for genetic tests are that health plans should make testing available to their self-insured plan sponsors and their fully insured customers if individuals are shown to be at risk and where results may affect the course of insured's treatment. In addition, the company covers genetic testing for a family member when the family member is not otherwise insured and results may affect the course of treatment of an at-risk insured individual. To facilitate the appropriate interpretation of genetic testing results, consultation with qualified counselors and physicians is covered. The company supports physician education in the appropriate interpretation and use of genetic tests, including guidance in the selection of medication (pharmacogenetics). Aetna works with physicians to promote confidentiality and to use genetic information for the maximum benefit of the member. Dr. Rowe noted that there should be no testing without counseling and stressed the importance of insurance companies covering counseling. He also pointed to the importance of the federal government providing support for physician education in the appropriate use of genetic testing and counseling.

Dr. Rowe remarked that third party payers should be allowed to have access to genetic test results because of the availability of insurer-sponsored disease management programs for people at risk for or with a disease. If an insurer has access to test results, individuals who would benefit from these programs could

[1] ERISA preempts state law and gives plan beneficiaries and participants the ability to sue for equitable relief in federal court. ERISA applies to self-insured employer-based group health plans.

be identified and enrolled. Also, if new information about a treatment becomes available during the pre-clinical stage of the disease, the insurer could alert the doctors in the network to inform patients with the disease about available treatments.

Future Directions in Genetic and Genomic Research

Francis S. Collins, M.D., Ph.D.
Director, National Human Genome Research Institute

Dr. Collins focused on the future direction of genetic and genomic research and provided some suggestions for areas that are ripe for further exploration by groups such as SACGHS. He noted that the HGP, which began in 1990, is not just about determining the sequences of the three billion chemical base pairs that make up human DNA; it is also about model organisms, map development, and the ethical, legal, and social issues involved, all of which should be valuable to this committee. NHGRI has developed a model for the future of the HGP based on a metaphorical model. The HGP provides the foundation that supports three "floors" of the metaphorical building: genomics to biology; genomics to health; and genomics to society. The vertical cross-cutting elements that touch on all three floors of this structure are: resources; technology development; legal, social, and ethical issues; education; training; and computational biology.

To discuss what will be going on in the three "floor" areas, Dr. Collins outlined the process by which a series of grand challenges were developed–challenges that, if accomplished, would make a profound impact on both research and the practice of medicine. The identification and conceptualization of these challenges took almost two years and involved input from more than 600 scientists, ethicists, and public policy experts.

Level 1: *Genomics to biology.* Understanding the 0.1 percent of the human genome that differs among individuals, along with knowing the complete structure of all the single nucleotide polymorphisms (SNPs) in the genome and how they correlate with their neighbors into haplotypes, will allow us to understand better diseases such as diabetes, hypertension, and mental illness, and differences in drug responsiveness. In addition, many additional genomes need to be sequenced, as the information gained by comparing genomes may be the best way to learn about human genome function. If the cost of sequencing a mammalian genome decreases to around $1,000 or less, there would be a profound effect on the practice of medicine. For example, if sequencing a person's genome became affordable, it would be tempting, with appropriate restrictions on access, to include it as part of each person's medical history.

Although comparative genomics provides a good window into function, other windows are also needed in order to increase understanding. For example, about five percent of the human genome shows evidence of being strongly conserved through evolution, yet we do not know the function of approximately two-thirds of the conserved sequences. This needs to be tackled in a robust manner with both experimental and computational approaches, with a focus on understanding how proteins interact with each other in order to construct themselves into pathways and networks that carry out function and how that goes wrong in the case of disease. We might eventually be able to develop a computational model of the cell in some considerable detail (moving from simple cells to complicated ones), allowing us to make predictions about biology without having to conduct bench experiments or at least by making hypotheses that could be confirmed at the bench. Built upon these many advances will be the clinical and nonmedical implications with which this committee is concerned.

Level 2: *Genomics to health*. This is the most relevant area regarding the future of genetics in terms of its medical applications. The genetic and environmental risk factors for all common diseases (studied in concert as opposed to separately) need to be identified. We must also develop "sentinel systems" for early detection of disease (before symptoms appear) and a molecular taxonomy of illness. There is a need to

develop and deploy high-throughput robotic screening of small molecules for academic researchers to identify compounds that act as agonists and antagonists for particular biological pathways of interest. These could become the first steps toward drug development in a greater partnership between academia and the private sector that many believe would be valuable. We also need to catalyze the development of large human cohorts in order to try to understand genotype-phenotype and environment correlations. These studies must be unbiased and have a large enrollment size, otherwise conclusions tend to be drawn that are not replicated because of modest contributions from any particular gene variant involved in a disease. In addition, it is important not to limit the study of genomics to any particular population, especially the majority population, if we wish to elucidate the role that genomics could play in reducing health disparities. Genomics also should be used to improve health in the developing world, by addressing diseases, such as malaria, that have been largely neglected.

What is needed to identify the causes of common disease? Most of us are carrying risks of future illness somewhere in our DNA, but for the most part we do not know precisely what they are for the most part. To identify the causes of common disease, a catalog of human variation is needed. We soon will have six million SNPs, which will be mapped in a way that organizes variation across the chromosomes (haplotypes). This will offer a shortcut to using the SNP catalog to identify the variants that are associated with common diseases. Improved technology is needed to apply this approach cost-effectively in order to make associations of a particular variant in a particular gene with disease risk or drug responsiveness.

Also needed are advanced methods for collecting environmental exposure data. To understand how genetic susceptibility interacts with the environment, those who understand genetics and those who focus on the environment must work together. In the United States, a large cohort study is needed that includes half a million individuals, including healthy people, who are carefully followed for several years. Careful records would be kept of the incidence of disease noted over time as well as records of diet and other environmental influences. Extensive DNA genotyping would be conducted as well. Such a study would finally provide the opportunity to determine in an unbiased way the effect of a particular variant on disease risk and how it interacts with environmental factors. Because disease-specific, case control studies often emphasize the more severe cases of disease and may tend to overestimate the genetic contribution, these large-scale cohort studies are needed to help answer many questions about common diseases. Other countries are planning or implementing such studies, including the United Kingdom, Iceland, and Japan. In addition, to move forward in addressing health disparities, there should be adequate sampling of minority populations.

If this is all is done correctly, i.e., we learn how to measure genotypes, how to collect environmental data, and how to carry out large-scale studies, within the next five to ten years, we will be able to identify the major genes contributing to common diseases and responses to major drug classes. Then, we will be positioned to offer a multiplex-like test to discover what an individual's susceptibility to future illness might be, focusing on diseases for which interventions are available. Although it will take time, eventually, we will be able to offer gene and drug therapies.

Level 3: *Genomics to society*. In this area, issues involved include discrimination and privacy, as well as intellectual property concerns. However, it is time to move beyond the debate over whether genes should be patented and pay more attention to other entities, such as haplotypes and expression data. Genetic privacy and protection of information must be enhanced to avoid genetic discrimination. In addition, we must encourage appropriate patenting and licensing practices to benefit the public; understand the relationship of genomics, race, and ethnicity, while bringing this to bear usefully on the often contentious dialog about race; assess the ramifications of advances in understanding genetic factors that influence behavior; and define the boundaries of the appropriate application of genomics in the nonmedical arena.

For example, eventually variations will be uncovered in the genome that are related to such things as intelligence and sexual orientation. It will be important to consider how this will be placed into our social discourse and understanding of ourselves and to ask whether there are boundaries that should not be crossed in the nonmedical arena and if so who establishes and enforces them.

Dr. Collins concluded by outlining a list of several issues on which he thought SACGHS might want to consider focusing its attention. The issues are as follows.

? A federal legislative solution is needed to address genetic discrimination in health insurance and the workplace, as well as options for life, disability, and long-term care insurance. While it is commendable that a bill has made it through Senate committee, the House of Representatives should act quickly to achieve effective federal legislation to outlaw the use of predictive genetic information in health insurance and employment. There is also a need to explore the potential for discriminatory uses of genetics in adoption, education, and the military.

? Oversight of genetic tests is needed to ensure clinical validity. A special concern is the proliferation of direct consumer marketing of genetic tests, some of which are of questionable genetic validity. This needs to be addressed, for as such junk science grows, it only increases the likelihood that the public may begin to think genetics is junk science in general.

? Researchers are concerned that the current human subjects protection system is making it increasingly difficult to conduct studies. Although rigorous protections must be in place, many clinical investigators believe that the current framework is too complex and has made it difficult to conduct research. It is time to reconsider whether the balance in this area is appropriate and to make it easier to conduct the large-scale studies that are needed.

? Optimizing delivery of genetic services in the future includes workforce issues, particularly who will provide the expertise needed to interpret all of this information and the counseling the public should receive; issues involving who will have access to this information; cross-cultural issues related to how different people assess information; and reimbursement issues, all of which need to be addressed over the next few years, or this revolution in the availability of genetic information may encounter a major problem in healthcare economics.

Issues in the Use of Genetic Technologies in Bioterrorism
Claire M. Fraser, Ph.D.
President and Director, The Institute for Genomic Research (TIGR)

Dr. Fraser opened by noting that it would be equally appropriately to focus more generally on the use of genetic technologies in infectious disease when considering bioterrorism, because the technical and public health challenges are very much the same. The recent outbreak of severe acute respiratory syndrome (SARS) demonstrates the challenges society faces from natural disease outbreaks, which are much more likely to occur than deliberate acts of bioterrorism.

Nonetheless, using bioterrorism as a framework allows us to identify our current vulnerabilities, either from a naturally occurring or deliberately released biological agent. First, with few exceptions, we do not have adequate systems for rapidly and accurately detecting and recognizing a specific infectious agent. Second, we lack fundamental 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 fewer. As a corollary, we also lack fundamental knowledge of host response following exposure to infectious agents. Third, we do not have adequate forensic methods for the purposes of attribution,

whether the focus of the forensics investigation is human or microbial DNA. Fourth, our arsenal of available vaccines, antimicrobials, and antivirals is insufficient.

Given that as a background, it is not surprising that when the microbial genomics efforts began in the mid-1990s, some of the most important first organisms to be tackled were those that cause human disease. Currently, 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. The intent of the ongoing effort to sequence the genomes of human pathogens was to accelerate the development of new and better diagnostics, drugs, and vaccines for treating infectious disease, in particular, new antimicrobials.

In terms of bioterror agents, a number of years ago, a concerted effort among a number of federal agencies added these organisms to the list for genome sequence analysis. The smallpox genome sequence was completed in the early 1990s; since then, sequencing work has been conducted on all of the select agents under Category A and B (lists of infectious agents collected by the Centers for Disease Control and Prevention [CDC]).

The real power of having this information comes with the ability to do comparative genomics. In the microbial arena, some of the most interesting and informative comparisons have come from looking at differences between species. One of the big surprises in the microbial area to come from these analyses is the observation that the process of lateral gene transfer, or exchange of DNA in the environment, seems to have been playing a much bigger role than was previously thought in generating genetic diversity among microbial species and pathogens in particular.

This concept suggests that these genomes are not static; that is, there could be identifiable isolates with different properties that explain increased virulence or antibiotic resistance. As an example, Dr. Fraser described ongoing work at TIGR on a number of closely related organisms in the *Bacillus anthracis* (anthrax), *Bacillus cereus*, *Bacillus thuringiensis* group. *B. cereus*, an organism found in the soil, is an opportunistic pathogen in a small number of immunocompromised patients. *B. thuringiensis* (also known as the pesticide BT) is an insect pathogen. We now know from genomic information that *B. anthracis* and *B. cereus* have extremely similar genomes. The sizes of their genomes are almost identical at just over five million base pairs, and they both show a great deal of gene syntony (conservation of gene order in very large clusters). These findings confirm that these two organisms are very closely related and most likely shared a common ancestor at one time.

This type of work allows for comparison between, for example, virulence factors, transcriptional regulators, and binding sites for transcriptional regulators. Information gained about one organism could be crucial in determining key aspects of other closely related organisms. In addition, when Dr. Fraser and her colleagues compiled findings about related organisms, they were able to identify a much larger number of potential virulence factors than had previously been appreciated, giving investigators a way to begin to focus on a subset of genes and ask what role they have in virulence.

In the past few years, TIGR has also looked at differences between various isolates of *B. anthracis*, hoping to better understand the known phenotypic differences that have been previously described. There are some isolates of *B. anthracis* that are almost avirulent, and others, like the Ames strain that was sent through the U.S. mail, that are highly virulent. Understanding the differences could assist in the design of novel vaccines and drugs.

Dr. Fraser provided a brief history of the Ames isolate. It originally came from a dead cow in Texas in 1981, was sent to Fort Dietrich, and from there was distributed to laboratories around the world. Dr. Fraser's laboratory received an isolate from the United Kingdom for genome analysis. They compared it

to the isolate that came from the first patient to die of inhalation anthrax in Florida and found several polymorphic loci between the two strains. In October 2001, they were able to further distinguish a small number of Ames isolates that had previously been indistinguishable based on existing genotyping information. TIGR now is looking more broadly within *B. anthracis* to develop new tools to analyze closely related genomes and at the same time develop new methods for automated SNP discovery. Thus, *B. anthracis* serves as a useful model system for comparative genomics.

This and other work have shown that, in addition to the two major groups of *B. anthracis*, A and B, there is the previously identified Group C, originally isolated in Louisiana several years ago. It turns out that Group C Bacillus looks to be much more closely related to *B. cereus*, which may have been an ancestor of *B. anthracis.* These discoveries could provide insights into the origins of the more highly virulent isolates of *B. anthracis.*

The ultimate goal is to develop a comprehensive database of *B. anthracis* isolates. Databases like this should not be limited to *B. anthracis*. This kind of information could be critically important for all major human pathogens, for example, the family of corona viruses that cause SARS. Comparative information on variation could lead to determining where an outbreak first occurred, where it came from, and where it was last seen geographically. A better understanding of DNA variation among various bacterial isolates and strains will be important for a number of reasons, in terms of both epidemiological studies and microbial forensics.

In the case of bioterrorism, this kind of information would increase the ability to rapidly detect genetically modified strains and research vaccines and novel therapeutics. It is ironic, given this potential, as well as the need for novel antimicrobial agents for naturally occurring diseases, that a large number of pharmaceutical companies are shutting down their infectious disease research programs. Only one new class of antibiotics has been developed in the last 30 years. Moreover, many of the antibiotics in use today are becoming ineffective because microbes are developing resistance to them.

One area where the use of genomic data has had great success is vaccine research. Whether for infectious disease or bioterrorism, the goal is to develop new vaccines to protect all groups of civilians. In a very short period of time the complete sequence of a pathogen genome of interest can be generated. This information then can be mined using a number of available algorithms to look for potential new vaccine targets. However, as with therapeutics, Dr. Fraser pointed out that pharmaceutical companies have limited incentives to conduct vaccine research and development.

Finally, with the availability of the human genome sequence, we can think about tackling infectious disease from the point of view of the host. Some of the most exciting work that will come in this arena in the next few years will be exploring innate and adaptive immunity and host susceptibility to disease. The development of signature expression patterns that indicate host exposure to an agent would enable the identification of individuals exposed (perhaps to a biological warfare agent) before symptoms developed.

As progress is made in the area of microbial genomics, specifically biowarfare pathogens, there have been renewed discussions about whether some of this information should be kept out of the public domain. Dr. Fraser recommended more open databases because without sharing of this kind of information, successful preparedness measures cannot be developed.

Issues in the Use of Genetic Technologies in Forensics
Bruce Budowle, Ph.D.
Forensic Science Laboratory, Federal Bureau of Investigation

Dr. Budowle's presentation reviewed how DNA technologies are being used for forensic purposes; issues involving from whom samples are collected for criminal justice and identification purposes and whether samples should be made available for other uses; how federal and state forensic DNA policies and databases are coordinated; and a number of privacy issues and other legal and social concerns.

He defined forensic science as the application of science in the investigation of legal matters, with scientific knowledge and technology used to serve as witnesses in both criminal and civil matters. Although science may not offer definitive solutions for all scenarios, it does provide information about attribution, i.e., who committed the crime. It is objective in that a test can be made and evidence interpreted, but the test is only a tool used for the purpose of identification; it does not prove guilt or innocence.

Dr.Budowle outlined many of the applications of human identity testing that go beyond criminal cases: civil forensic cases; paternity testing; historical investigations; population studies; missing persons investigations; the identification of individuals following mass disasters; military DNA "dog tagging;" creating convicted felon DNA databases; and medical uses, such as solving patient sample mix-ups in hospitals.

Criminal forensic testing involves about 20,000 cases per year in the United States, 75 percent of which involve sexual assault, while paternity testing involves about 250,000 cases. These cases are now using DNA analysis instead of serology. The advantage of using DNA analysis is that a large variety of tissues can be used from a crime scene, such as blood, semen, tissue, bone, tooth, hair root, saliva, and urine. Methods of testing include RFLP/VNTR typing; PCR-HLA-DQA1 polymarker loci by reverse dot blot assay (SNP); PCR - D1S80 locus (VNTR) typing by electrophoresis and silver staining; PCR-STR loci typing by capillary electrophoresis and fluorescence; PCR-mitrochondrial DNA by capillary electrophoresis and fluorescence; PCR-Y STR loci by capillary electrophoresis and fluorescence; and PCR-SNPs.

The kinds of samples being tested range from bodies recovered after war or mass disaster to samples related to crimes, such as rape and homicide, with the data often being used to solve older cases or to exonerate individuals. In addition, sometimes a witness will want to avoid testifying or may not be considered credible; in these cases forensic evidence often can be useful. Nonhuman DNA applications include wildlife issues, such as smuggling, poaching, and population management.

Databases are used to solve cases by providing investigative leads, with DNA databases used to compare crime scene evidence to a database of DNA profiles obtained from convicted offenders. CODIS (the Combined DNA Index System), for example, is a hierarchical distributed database of convicted felons, with three levels: federal, state, and local. It enables crime laboratories at each level to exchange and compare DNA profiles electronically, linking crimes to each other and to convicted offenders.

Types of files that can be used in DNA databases include convicted offender files, forensic files, missing person files, relatives of missing persons files, human remains files, population statistics files, and suspect files. A number of DNA databases have been implemented or planned in numerous countries, and although there are different policies and practices among countries that employ forensic DNA databases, the genetic data are sufficiently compatible for exchange on an international level to assist in resolving crimes. In the United States, practices are the same from state to state. The success of these databases has led to an expansion of the crimes investigated and the inclusion of arrested persons and indicted persons

(in addition to those convicted of crimes) and terrorism-related offenders. Such expansion often raises important issues related to the rights of privacy and of the individual versus society, as well as questions involving who should be tested and why.

The data stored can include information related to persons convicted of specified crimes, crime scene specimens, unidentified human remains, relatives of missing persons (these data are there voluntarily only for purposes of possible identification and cannot be searched against any other data files; they can be removed upon request), and DNA samples. In forensics, it is important to err on the side of false exclusion rather than false inclusion; however, in a database it is more important to err on the side of false inclusion, because false exclusion may cause a match to be missed and the crime to remain unsolved. Thus, after DNA samples are collected and the DNA extracted, the sample is stored as a form of quality control, because it can be used to confirm an inclusion and resolve any mismatches. Samples also are kept because as technology changes (although it is unlikely that this technology will be changing for a long time for a number of reasons, including cost and stability), it would be necessary to reprocess those samples using the same set of genetic markers. However, using those samples for other purposes is a serious concern.

Important questions to ask regarding stored data and privacy include whether exonerated suspects can be searched against other cases at a later date and whether human remains can be searched against unsolved cases. Privacy protection for relatives of missing persons is also an important issue. Sometimes difficulties are created by a long lag time in analyzing cases and by issues that arise in preserving prosecutions. For example, old cases may fall under the statute of limitations, although some clever ways have been constructed to deal with unknown perpetrators by avoiding the statute of limitations, i.e., the John Doe warrant, which supplies no name but rather a genetic profile representing the individual. In addition, various jurisdictions are considering options such as extending or eliminating this statute. To address concerns that DNA data and samples might be used inappropriately, it is important that access be limited by law, regulation, and policies/procedures and that law enforcement identification markers are employed.

In the area of federal law, Dr. Budowle described the DNA Identification Act of 1994, which authorized a National DNA Identification Index; the requirements for participation; the type of information to be contained; who can create and access files; and quality control requirements. The Act provides that access to the national index can be cancelled if these quality control and privacy requirements are not met. Requirements are imposed if a state database participates in the CODIS system or if it receives federal funding. Sixty percent of the states have penalties for the unauthorized disclosure of DNA data and/or samples, mostly as misdemeanor offenses. Fifteen state laws have provisions that penalize tampering with or attempting to tamper with a DNA sample, mostly as felonies. State databases are easily coordinated, as they use the same software, communications, and quality assurance standards.

Regarding the use of forensics and disease associations, certain associations with STR (short tandem repeat) loci and disease have been reported, but the forensically employed STRs do not encode proteins and thus are not believed to be associated with characteristics that may affect the privacy of the individual. Relative risk is thought to be low in providing any information, although one STR – TH01 – might be associated with certain neuropsychiatric diseases. However, for TH01 as well as other genes, studies have shown that any relative risk increase is minimal and not sufficient to cause worry regarding the possibility of taking drug therapy.

To summarize and draw some conclusions, Dr. Budowle noted that one expansion of the use of samples is that they now can be used for research purposes to develop forensic tools. Privacy issues still abound, although many are covered by state laws. Generally, he noted, privacy issues are low for the markers currently used; however, in the future, other markers may present a problem. Although some in the field

would like to switch to SNPs, to get the same amount information that we get from the current battery of core loci, 70 to 80 SNPs would be needed. Other significant issues are involved in creating a robust technology for this number of SNPs. While SNPs are particularly important after mass attacks such as 9/11, their broad application will take time.

Ethical, Legal, and Social Implications of Genetic Technologies
Eric T. Juengst, Ph.D.
Associate Professor of Biomedical Ethics, Case Western Reserve University School of Medicine

Dr. Juengst presented a survey of issues that are within the purview of SACGHS, with an eye toward future developments, as well as issues that are ripe for public policy development at the Federal level. This is an auspicious time to launch this committee, Dr. Juengst said, because the HGP has been achieved and we now must decide what to do with it and how we will live with post-HGP genomics. From DNA chips to new genetic tests, from functional genomics to gene therapies, and from population genomics to pharmacogenomics, each area raises important issues for society.

Overinterpretation of the power of DNA testing is a cultural tendency; many think DNA tests can magically predict the future. This tends to drive much of the fear and many of the issues surrounding genetic testing. Each time a new genetic risk assessment test is launched, concentric ripples of questions form for the families and individuals who might avail themselves of the test. These questions include familial, professional and public issues. Much of the discussion involving familial issues (e.g., the right to know, obligations to kin) becomes part of the discussion of professional issues (e.g., standards of care, confidentiality, limits of service). For professionals, these moral questions translate into questions of professional ethics and policy. At the limits of the professional ethics questions are the public policy issues, such as the regulation of commercial testing and the mechanisms available to prevent discrimination based on genetic testing.

Considerations in the use of a new genetic test include an assessment of its predictive power, which is the heart of the clinical validity and utility issue that concerned SACGT, and psychosocial potency, or a test's risks for stigmatization and discrimination. Other issues include patient privileges, such as patient autonomy in making decisions about what to "buy" from the healthcare system. The sort of criteria that should cover predictive testing for children is one issue in this area that is receiving a great deal of attention at this time.

Face cream tailored to an individual's genotype through direct-to-consumer genetic testing (sometimes called "ego-genomics" or "cosmetic genetics") highlights the need for a fuller conversation about regulation of this area.

Gene transfer research has had a history of promises, failures, and successes over the past decade. One notable success involved curing a disease in a cohort of patients, some of whom later developed a health problem related to the gene insertion. However, for genetic policy purposes, the lines have been clear regarding gene therapy: protocols that go beyond therapy to attempt to enhance human form or function, or affect the germline, have not been allowed.

At the same time, these boundaries are being pressed. For example, an assisted reproductive technique was recently developed involving the transfer of ooplasm from a donor egg. Although the technique did not employ recombinant DNA technology and, therefore, was exempt from the current regulatory and oversight framework for gene therapy research, it did involve the transfer of mitochondrial DNA to a germ cell. While the intent of the technique was to overcome infertility in the parent (it could also be used to prevent diseases caused by mutations in mitochondrial DNA), because mitochondrial genes were transferred to a germ cell, it also had the effect of altering the germline of the offspring. As such, the

longstanding ethical boundary against human germline gene transfer, which is also embodied in the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, was crossed in this instance.

Pressures in these areas will only increase as we move toward developing safe and effective somatic cell gene therapies, for some will ask whether it would be more efficient to conduct germline therapy for a particular family line rather than treat every new generation of a family with more gene therapy. The American Association for the Advancement of Science formed a working group on this topic and produced a report on human inheritable genetic modifications. The working group suggested some interim steps toward preparing for the day when the efficiency argument is made persuasively. Modification of the germline for therapeutic purposes may well be in our future.

Discussions are ongoing at the International Olympic Committee and the World Anti-Doping Agency about the possible illegitimate and off-label uses of somatic cell gene therapy for performance enhancement for athletes. The Anti-Doping Agency has begun to create policies for the day when athletes start to use gene therapies to strengthen muscles, to block pain, or to accelerate the healing of injuries.

Comparative population genomics, or the study of human genetic variation, involves the comparative analysis of DNA samples from different population groups. The way in which these groups are designated is an issue. The genetic community has pointed out that there is little validity to the biological concept of race, making population genomics a tricky tool to use. Although we are interested in the diversity of the genome, it may increase discrimination and stigmatization, as genetic discrimination may occur if certain population groups are labeled in a way that suggests weaknesses or vulnerability. On the other hand, population geneticists are likely to remind us that we are much more alike than different, a fact that could be used to enhance intergroup solidarity. Also, some groups regard their lineages, identities, or differences as important to their social identity. The challenge is to explain the categorization of people in a way that does not increase existing tensions among groups. Furthermore, it is difficult to reconcile the 'continuum of genetic variation' with the apparent diversity of different groups.

For example, one company offers a service involving measuring racial ancestry and racial proportions using DNA markers. The service is used for genealogical purposes or to demonstrate eligibility for scholarships or government entitlements. This company is self-described as the world's first "recreational" genetic testing company. There is a great deal of contention within the genetic community regarding whether the test is valid, accurate or meaningful. It is an application that can feed into our culture's existing race consciousness. While the service may be used for the most part for recreational purposes, it has also been used on a forensic sample to shift a search for a suspect from one race to another.

As a summary of important issues to consider, Dr. Juengst suggested that the committee explore the matters discussed, including the predictive power and psychological ramifications of genetic tests and patient autonomy. There is also a need to continue the discussion surrounding discrimination as well as the need for regulation of commercial genetic testing with a specific focus on direct-to-consumer marketing. For gene transfer research, questions are arising about germline interventions that are coming through the field of reproductive medicine about how best to regulate off-label use of a medical process. Also, the social uses of population markers and the interpretation of those markers for the general public will be an issue that is likely to preoccupy us for many years. In effect, we have completed the genome map, but we have not figured out how to fold it and use it so it can take us where we want to go, a task that he said falls in part to the members of this committee.

Genetic Technologies and Intellectual Property Issues
Lawrence Sung, Ph.D., J.D.
Assistant Professor of Law, University of Maryland School of Law

Dr. Sung discussed intellectual property generally and then focused on some specific issues involving the role and impact of patent rights and what it means to obtain patent rights. He also outlined some current concerns and some that are on the horizon.

Intellectual property can include patents, trademarks, copyrights, trade secrets and other less common protections. It is designed to place value on ingenuity and creativity through a grant of exclusivity. The fundamental difference between intellectual and real property is that real property involves physical exclusivity, while intellectual property does not necessarily have this constraint and can be used repeatedly and at the same time by many individuals. Limitations to intellectual property as defined in the law include those that are territorial and temporal. Since each national jurisdiction has its own intellectual property law, a United States patent would have no effect outside this country unless one seeks corresponding protection within other nations. The granting of a patent also involves a temporal limitation: a patent is issued for 20 years from the day the patent application is filed. A patent has the characteristic of tangible property to an extent since it can be bought and sold.

Many rationales exist for assigning patent rights. By seeking patent protection from the United States Patent and Trademark Office (PTO), an inventor is required to disclose certain information to the public in exchange for receiving exclusivity for a defined period of time. Thus, a patent provides the inventor a right of temporary exclusivity, while allowing others to benefit from the disclosure of information regarding the invention to the public through the patent process. The exclusivity of a patent is important because it is a response to what is known as the "public goods issue," meaning that an inventor needs some sense of ownership in order to be motivated to investigate areas other than those of which the public is already aware. Exclusivity also encourages research in new, uncharted areas, which adds to the store of public knowledge and improves social welfare.

Although in the past PTO was a good source for determining what was at the forefront of technology, today, with the Internet and other sources of information available, PTO is somewhat anachronistic. Furthermore, only limited resources are available for the task, which means that PTO is not funded to perform the most accurate, comprehensive job possible but rather is tasked with a very specific job of narrow scope. In fact, the average patent application is vested with about 30 hours of examiner time regardless of technology.

Inventorship is the first supporting premise of ownership, but inventorship is not coincident with ownership. In practice, although much of what is done in the patent area is assigned to an employer as an owner, institutions cannot be considered inventors in the United States, and a patent right can be accorded only to an inventor. To be patented, an invention must be of an appropriate subject matter, useful, new or novel, and nonobvious—that is, it must be significantly different from what already is in existence.

Biotechnology differs from other areas when it comes to patents in that it does not deal with natural subject matter. When a patent is sought in this area, what is being patented is not an entity as it is found in nature. For example, an isolated purified nucleic acid can be patented because it is not found that way in nature (although it has a natural component). There also exists a structure/information dichotomy, as patents are not designed to protect the information that is disclosed in the process of getting the patent. This information can be used as long as the product itself is not used. The difficulty arises because the information and the product often are coextensive. In addition, biotechnology relies on a *de facto* industry standard; it is not an area that allows one to take a radically different approach. "Doctrinal metastability" is another issue, meaning that although observation leads us to believe there are certain rules and

guidelines that can be followed in some areas of science, in the realm of biotechnology, reaching a mountain peak does not necessarily solve a problem; it is more likely to change one's worldview by bringing into view many other mountains that need to be climbed.

It can often take ten years from the time a patent is filed to the time it is awarded, and the litigation that follows can take another ten years. This phenomenon is known as art maturity compression. The scope or extent of a patent right is unknown until the courts have had a chance to review it, with court resolutions often based on the facts and the law as applied to a scenario that has become obsolete. Also, certain patents are issued knowing that they may be on verge of invalidity, but the system relies on interested private parties solving the problem rather than the public. In addition, routine methods of manufacture in biotechnology still lend themselves to the production of new and nonobvious products. This is an area of consternation within the scientific community, because if a routine method can be applied to create a product, why should a patent be deserved?

Assuming patent protection is obtained, it is often difficult to distinguish whether a patent holder has the freedom to use a particular product. That is, having a patent does not necessarily give the patent holder the right to use it, as it is possible for a patent right to depend on permission to use another technology (dominance/subservience relationship). The length of time to commercialization also can be a problem, as the commercialization and marketing of pharmaceutical products that result from earlier stage inventions are subject to regulatory controls that can delay the period during which someone can benefit from patent protection. Extensions sometimes are allowed for recouping some of this administrative delay.

Some are concerned that in the area of biotechnology, the process of seeking patent rights has hindered progress and scientific collaboration. It could be argued, however, that although the granting of a patent right may have blocked progress in cases in which there is no other way to design around a patent or to get permission to use it; in the overall scheme, the intent of the patent process is to spur innovation through encouraging the development of a design-around if necessary. Regarding collaboration, it is much more difficult today to discuss a project with a colleague than it was just five or ten years ago. This is due in part due to material transfer agreements that need to be signed or level of disclosure issues that need to be resolved at various institutions. The full impact of these issues on progress in the biotechnology field is anecdotal at this point, with more empirical research needed.

Looking to the future, Dr. Sung noted that the existing patent system is based on law written in 1952, applied broadly to all technologies, and that currently we are grappling with our ability to apply this law to new areas of technology. An important issue involves how people are more or less inclined to enforce their patent rights, as enforcement entails some risk, with some patents becoming invalidated during the process. A good deal of discretion and risk assessment goes on in this area, said Dr. Sung. Discussion is increasing regarding whether or not researchers, academics, and nonprofits should be exempt from patent infringement liability. Many researchers were shocked when they learned last year of the decision of *Madey v Duke University* that ruled that the research being conducted at Duke really did constitute an infringement. As a practical matter, it is unlikely that private companies will go after academia in this regard, but some would like to have absolute immunity. Another case, *Integra* v. *Merck*, demonstrates that even early stage research will not be exempt from patent infringement, something that could clearly have an impact.

Roundtable Discussion

Following all the presentations, a roundtable discussion took place with the presenters.[2] A wide range of topics were discussed, and are briefly summarized below.

[2] Dr. Rowe was not able to participate.

? In theory, problems with the patent system might be outweighed by the good that the system achieves. However, in practice, there are concerns that important work does not get done because of uncertainty about patent rights. The patent system serves the interests of business and inventors and promotes innovation; however, serving the public health may be left out of the equation. Are changes needed to improve the system? Should medical information be protected for exclusive use or nonuse through patents (what about patents' effect on healthcare as opposed to research or business)? The courts say one cannot make certain technologies special in the area of patents, but perhaps the nature of biotechnology may require special consideration and an organic change in the law.

? Do regulations in place for clinical laboratories (Clinical Laboratory Improvement Amendments [CLIA]) apply to laboratories selling "ego-genomics" tests?

? Concerns regarding preimplantation genetic testing would increase if it were applied toward nonmedical traits such as eye color. Should these technologies be available for anyone or should lines be drawn and, if so, where and by whom? Can we really prohibit a test such as gender testing? Would public policy in this area create any unintended consequences?

? More attention should be paid to the development of gene therapies given the difficulty we may have in avoiding germ line modification.

? What would be a good use of genetic information for society? What do we want to see accomplished and what is worth doing? There is a general assumption that the core benefits of this technology should be the prevention, treatments and cures of the disease. Are there other legitimate uses for genetic technologies? What are legitimate uses of public resources? Should people be able to obtain personal genetic information even if only for information purposes? Has there been too much focus on preventing harms and not enough on promoting goods?

? Environmental factors over time will have a strong impact on disease prevalence. Can we really understand genetics without a clearer understanding of the role of the environment in gene expression?

Public Comments

Robin Bennett, M.S., CGC
National Society of Genetic Counselors (NSGC)

NSGC represents over 2,000 genetic counselors with specialized education, training and experience in medical genetics and counseling in an array of medical specialties. NSGC asked SACGHS to address the following areas of concern: prevention of harm from genetic testing, support for clinical genetics research, and access to genetic services.

Genetic testing is part of a process that must involve pre- and post-test counseling to enable consumers to make well-informed decisions and should be voluntary. Consumers and their families have the right to expect that the correct genetic tests have been ordered, that specimens have been sent to a CLIA-certified laboratory, that costs of genetic testing are known, and that the test results have been interpreted correctly. Ms. Bennett encouraged SACGHS to advocate for genetic counseling as an important component of genetic testing.

Also, there should be oversight of genetic tests as they move from research to clinical practice, and oversight of companies providing genetic tests with little or no clinical validity or utility is essential. It is important for quality assurance measures for laboratory analysis to be enforced and to ensure high-quality pre- and post-analytical phases of testing.

Furthermore, Ms. Bennett indicated that SACGHS should support education of health professionals, insurance companies, judicial systems, lawmakers and consumers about appropriate uses of genetic testing. Strong genetic discrimination laws for insurance and employment must be enacted and enforced. Fear of genetic discrimination causes underutilization of genetic services and inhibits individuals who would benefit from genetic testing from using this technology. Licensure of genetic counselors would help ensure that consumers receive quality genetic services from individuals with appropriate training.

There also needs to be increased support for clinical genetics research. The only way to truly answer questions about genotype/phenotype correlations as well as appropriate patient management is through large-scale cooperative research studies. NSGC strongly supports large-scale cooperative research studies and believes that such studies will provide valuable information to our patients and their families. These studies must continue to include the ethical, legal, social and financial aspects of genetic testing.

Access to genetic services should be assured regardless of socioeconomic status, race, culture, education, geographic location, ability to pay, or method of payment. To meet the exponential demand of the public for genetic service providers, there needs to be an increased training of a culturally competent family-centered genetic workforce of genetic counselors and medical geneticists. Currently, there are 26 programs accredited by the American Board of Genetic Counseling. Each program receives 75 to 100 qualified applicants. There are about five qualified applicants for every available training slot. Genetic counseling should be recognized by the Health Research and Services Administration (HRSA) as a specific allied health profession with access to federal support for training programs. Ms. Bennett agreed to provide SACGHS with a proposal for what it would cost to support an adequate number of genetic counseling training programs and for improving the diversity of the workforce.

Lastly, to assure uniform access to genetic services, there must be improved insurance reimbursement for genetic services. Many insurance companies do not cover the cost of genetic services or they limit coverage of these services to only pregnancies. Few plans cover genetic counseling in the setting of prevention.

David Sundwall, M.D.
American Clinical Laboratory Association (ACLA)

ACLA is a not-for-profit organization representing the nation's leading independent clinical laboratories. ACLA member companies provide services in every state and provide the majority of lab testing done by commercial laboratories nationwide. Genetic testing is likely to be an increasingly important component of preventive medicine and will likely enhance the ability of clinicians to make accurate diagnoses and tailor treatments to make them more effective. Furthermore, the development of new genetic tests likely will be the focus of a significant amount of biomedical research.

There must be appropriate and feasible regulation of diagnostic testing. ACLA understands that the government has to provide some oversight of genetic testing. Such tests have enormous potential to prevent and treat disease and the Federal government has a role in ensuring that such tests are valid and appropriately used. However, ACLA believes that there is a significant risk to over-regulation and that regulatory mechanisms imposed by HHS should be carefully considered and take into account the well-acknowledged and medically accepted role of clinical laboratories in fostering genetic testing advances. ACLA does not believe such regulation should be generally applicable to clinical laboratory science and

services. Regulations need to be thought of in two perspectives: the quality of the laboratory and the interpretation of the laboratory results.

Dr. Sundwall noted that he is the incoming chair of the Clinical Laboratory Improvement Act Advisory Committee (CLIAC). In September, CLIAC will revisit the issue of the regulation or oversight of genetic testing and will address the issue of direct access testing. CLIAC is very concerned about unethical and inappropriate promotion of testing as well as non-medical uses of testing.

Joann Boughman
Executive Vice President, American Society of Human Genetics (ASHG)

ASHG is the primary professional organization for human geneticists, with nearly 8,000 members, including researchers, academicians, clinicians, laboratorians, genetic counselors and nurses.

ASHG believes that a focus on translational research in genetics is needed and that results of research must continue to be broadly shared. However, industry-based researchers as well as academicians who develop marketable intellectual property must be able to obtain and protect intellectual property. Securing the balance between the protection of intellectual property and public and patient access to genetic services is of great concern. ASHG encourages SACGHS to further engage in substantive discussions around some of these issues in patenting and licensing.

Dr. Boughman listed several other issues for SACGHS to consider:

- Interpretation of the HIPAA privacy rule, by Institutional Review Boards (IRBs) and others, especially as it relates to genetics research
- Access and cost of testing as well as cost recovery
- Systematic and systemic quality control mechanisms
- Complexities of multiplex testing and genome scanning
- Adequate interpretation of test results
- Protection of research subjects
- Genetic nondiscrimination
- Preparing future genetics professionals to meet the challenges of research, teaching and providing care
- Public education and outreach
- The transition from the clinical trial and FDA approval processes to postmarket follow-up

Status of Congressional Efforts to Pass Legislation Against Genetic Discrimination
Kim Monk
Senior Health Policy Advisor, Senate Committee on Health, Education, Labor, and Pensions

Ms. Monk described the history of genetic nondiscrimination legislation as it has come through the Senate and the Health, Education, Labor, and Pensions (HELP) Committee and the major issues surrounding the development of the Genetic Information Nondiscrimination Act of 2003. She noted that although few abuses in genetic discrimination have been observed so far, to realize the promise of the HGP and to ensure coverage of genetic testing by insurance companies, a clear Federal standard for protecting genetic information is needed. Ms. Monk said that, even though some argue that there is no need for legislation if problems are minimal, now is the ideal time to take action. Such a bill also is needed to address the fact that many are afraid to undergo genetic testing. Title I of the act prohibits discrimination in health insurance based on genetic information and protects the privacy of genetic

information. Title II includes employment provisions, treating the use of genetic information in the same manner as other forms of employment discrimination.

Because earlier bills in this area were drafted before draft privacy regulations existed, the committee looked carefully at the privacy regulations and how they address the use and disclosure of all medical information, including genetic information. The committee held hearings to determine whether the privacy regulations adequately address genetic information and redrafted the privacy provisions in the bill to reflect the final comprehensive privacy regulations issued by this administration. After studying the regulations and consulting with experts, the HELP Committee concluded that the Privacy Rule does cover genetic information, except that they allow for the use and disclosure of information, including genetic information, for purposes of treatment, payment and healthcare operations. Healthcare operations include underwriting and reinsurance, which are inherently discriminatory and thus run counter to the goals of the Genetic Information Nondiscrimination Act of 2003. The HELP Committee therefore agreed that when it comes to the use and disclosure of genetic information, the Privacy Rule should govern. Furthermore, insurance companies should not be allowed to use, disclose, or collect genetic information for purposes of underwriting. The bill includes language indicating that it does not interfere with privacy rights and remedies as conferred by state law. There are some exceptions under the Privacy Rule for groups fewer than 50 that self-administer their company's health plan.

The bill also bans insurers from collecting genetic information prior to enrolling an individual in a plan. This means an insurance company cannot create a database and solicit and collect information just for the sake of having it in the event that an individual applies for coverage. The bill prohibits the collection of genetic information about an individual before enrollment. After enrollment, the Privacy Rule governs with respect to how the insurance company can obtain information and when authorization is required to obtain it for treatment, payment and healthcare operations, including wellness and disease management programs. The bill also bans insurance companies from requiring or requesting that an individual take a genetic test (which is not currently law). The bill is limited to health insurance and does not cover life or other kinds of insurance.

Regarding the issue of disclosure, Ms. Monk noted that there are many opportunities for inadvertently acquiring genetic information, particularly if it is defined broadly to include family history. The bill used terms such as "collect" and "purchase" and steered away from the nebulous term "acquire." It also added a provision that creates a safe harbor for the inadvertent collection or acquisition of genetic information, such as may be learned from reading an obituary.

In addition to governing the flow of information, the bill prohibits discrimination by banning group health plans and health insurance issuers from adjusting the premium or contribution amounts or establishing enrollment restrictions on a group as a whole on the basis of genetic information. It also prohibits health insurance issuers in the individual market from using genetic information about enrollees or their family members to adjust premiums or contribution amounts or as a condition of eligibility. This is going beyond current law, which at this time addresses premium rates and enrollment restrictions for individual members of a group, not the group as a whole. The provisions of the bill relating to nondiscrimination in health insurance were built on the framework of current law and are based on Title I of HIPAA (which addresses traditional insurance issues, including portability and nondiscrimination).

The enforcement structure and penalties for violations are the same as those created by the Social Security Act for the HHS privacy standards and are to be enforced by the HHS Office of Civil Rights. Although the remedy structure that exists now under Title I of HIPAA was closely followed, some important changes were made in terms of enforceability and consumer friendliness when developing the nondiscrimination in health insurance provisions.

First, language was added stating that if someone in a group plan believes he or she was denied coverage based on genetic information, that individual can opt out of the administrative process, get an injunction, and take the issue directly to court for a ruling. Second, if the court mandates that the individual must continue to seek an administrative remedy, the bill states that if the health plan is ultimately found to be at fault, it must restore coverage retroactively to the time of denial. There are no exceptions to the nondiscrimination ban in health insurance.

Currently under HIPAA, states are responsible for the enforcement of the individual health insurance market, and if the states fail to enforce, HHS would be the secondary enforcement authority. The Department of Labor (DOL) enforces against the group market, but DOL does not have the authority to levy a penalty. It relies instead on the Internal Revenue Service (IRS) to impose a penalty that consists of an excise tax. Under the new bill, the DOL Secretary can levy a civil monetary penalty that applies only to genetic information violations. Penalties apply for both denying coverage and raising premiums, which are treated as the same violation. This will give DOL the ability to determine not only whether a plan is HIPAA compliant, but also compliant with the protections for genetic information, and to impose penalties if violations are found. The bill also allows the court the discretion to award the HIPAA civil monetary penalty to the individual.

Under Title II of the bill, the rights and remedies that would flow for a genetic employment discrimination case would be the same as those provided for other forms of employment discrimination including race under Title VII of the Civil Rights Act of 1964 or disability under the Americans with Disabilities Act (ADA). One issue considered was whether a disparate impact claim for genetics should be provided, which is something that ADA provides. Disparate impact refers to a situation in which, even if an employer does not intentionally or blatantly act in a discriminatory manner, if the effect of its employment practice is to discriminate against a protected group or class of people, then that constitutes discrimination. However, showing that the practice is part of the normal practice of business can constitute a defense against a disparate impact claim. In the end, the HELP Committee decided not to include a disparate impact provision. Instead, the bill would establish a commission to assess the need for this type of protection in the law.

There is a strong desire on both sides of Congress to move this bill forward quickly, and it is hoped that given the range of Senators supporting this bill, from Senators Kennedy and Daschle to Senators Gregg, Frist, and Snowe, it has a good chance of passing.

Legacy of SACGT
Edward R.B. McCabe, M.D., Ph.D.
Chair, SACGT and SACGHS

Dr. McCabe provided a brief history of SACGT, which functioned as a committee from 1999 to 2002. Its mandate was to identify policy issues raised by the use and development of genetic testing and to make policy and procedural recommendations to the Secretary of HHS on how such issues should be addressed. These issues included the safe and effective incorporation of genetic technologies into healthcare, the effectiveness of existing and future measures for oversight of genetic tests, and research needs related to the committee's purview.

The policy recommendations of SACGT included a report on oversight of genetic tests and methodology for classifying genetic tests into different scrutiny levels. SACGT wrote letters to HHS Secretary Shalala, and later Secretary Thompson, supporting Federal legislation to prohibit genetic discrimination in health insurance and employment. Recommendations also were made about the need to assess the impact of gene patenting and licensing on access to genetic tests, as well as informed consent in genetic research. The recommendation regarding informed consent requested clarification of the Federal regulations with

respect to when informed consent of family members of primary research subjects is needed in order for the family information to be considered in research.

SACGT's report on oversight was a comprehensive assessment of the adequacy of oversight of genetic tests, which involved a broad multifaceted public consultation process and a consideration of all options. The report, titled "Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT," recommended increased federal involvement in the oversight of new genetic tests through flexible regulation by the Food and Drug Administration (FDA), augmentation of CLIA, and development of a collaborative postmarket data collection effort by CDC.

Dr. McCabe noted that FDA is presently considering developing a proposed rule classifying analyte-specific reagents used in high-risk, in-house tests, including genetic tests as Class II special controls or Class III premarket approval devices, depending on their intended use and risk profile. CDC and the Centers for Medicare & Medicaid Services (CMS) are in the process of preparing a Notice of Proposed Rulemaking to develop a genetic testing specialty under CLIA. Dr. McCabe suggested that FDA could be invited to provide an update on where the agency stands on oversight of genetic tests.

Regarding the methodology for classifying genetic tests, SACGT considered several options but concluded that classifying genetic tests based on criteria applied in a simple linear fashion for oversight purposes was infeasible. In part, this is because the same test used in different contexts may perform quite differently. It is not the test that necessarily needs stringent oversight, but rather how the test is used. SACGT's decision to defer further work on methodology also was based on significant progress made by FDA to develop an innovative regulatory process for genetic tests, including a template for facilitating and ensuring appropriate review of relevant data.

Additional reports in development when SACGT's charter expired were genetic education of health professionals; public understanding of genetic testing; informed consent in clinical and public health practice; reimbursement of genetic education and counseling services; and the development, translation, oversight, availability and accessibility of genetic tests for rare diseases. Each of these reports was in various stages of completion, although none had been formally approved by the full committee. These materials are available to SACGHS should they wish to consult them.

Priority Issues Identified by the Ex Officio Agencies and Departments
Sarah Carr
Executive Secretary, SACGHS

Ms. Carr reported the results of a survey conducted of the *ex officio* members of the 16 federal agencies represented on SACGHS, asking for their perspectives on the issues they think are important for the Committee to consider.

The seven areas of inquiry, or functional categories set forth in the SACGHS charter were used to organize the request, although respondents were under no obligation to adhere to that framework. The seven areas are:

- Assessing the integration of genetic technologies into healthcare and public health;
- Studying the clinical, ethical, legal and societal implications of new medical applications and emerging technological approaches to clinical testing;
- Identifying opportunities and gaps in research and data collection efforts;
- Exploring the use of genetics in bioterrorism;
- Examining the impact of patent policy and licensing practices on access to genetic technologies;

? Analyzing uses of genetic information in education, employment, insurance and the law; and
? Serving as a public forum for the discussion of emerging ethical, legal and social issues raised by genetic technologies.

In reviewing and identifying priorities in these seven areas, the agency representatives also were asked to consider the following:

? Will the committee's advice on any given issue significantly benefit society? Conversely, will failure to address the issue prolong any negative impacts it may be having?
? Is federal guidance or regulation on the issue warranted?
? Is there a governmental interest in receiving advice on the issue?
? Is there media attention or public concern about the issue?
? Is there a need for public discussion and understanding of the issue?
? Do sufficient data exist on the issue so that the committee can develop informed policy advice?
? Is there another body addressing the issue or another body better equipped to address the issue?
? Does the committee possess the expertise necessary to undertake a study of the issue?

The agencies identified a large number of high priority issues. The issues identified the most frequently were: the use of genetic information in insurance, employment, education and law; the ethical, legal and social (ELSI) implications associated with the use of genetic technologies to screen for traits; standards for clinical readiness; the ELSI implications of new health applications; gene banking; the use of genetics in bioterrorism; the impact of patenting and licensing on access; genetic literacy of the public; the need for additional oversight; and the impact of the Privacy Rule.

SACGHS Discussion and Priority Setting

The Committee discussed the scope of its mandate and decided it was best to focus on areas where the agencies thought a need or gap existed in current federal efforts. Among the issues that the Committee discussed were:

? Direct-to-consumer advertising of genetic tests;
? CLIA guidance in the area of oversight of genetic tests, including any involvement of CMS;
? FDA's current efforts in the area of pharmacogenetics;
? The extent to which actual genetic discrimination in insurance or employment has been documented;
? The extent to which the ELSI program at NHGRI and the President's Bioethics Council are discussing preimplantation genetic diagnosis;
? Guidance for practitioners translating genetic technologies into practice;
? The types of genetics education being provided to health professionals, including what accrediting or certifying bodies or boards are doing in this area;
? Public education activities;
? Diversity in the genetics workforce;
? The level of expertise and activities in federal agencies related to genetics;
? Prospects for and issues surrounding large population studies to evaluate genotype-phenotype correlations and the genetic basis of common diseases; and
? Regulatory and nonregulatory solutions for some of these questions.

For the near term, the Committee unanimously agreed that before its October 22-23, 2003 meeting it would write a letter to HHS Secretary Thompson advocating enactment of Federal legal protections

against genetic discrimination in health insurance and employment, supporting Senate genetic nondiscrimination bill S.1053 and encouraging efforts to press for passage in the full Senate and House of Representatives and enactment into law.

It also decided to actively pursue additional information regarding the supply, diversity, certification and education and training of the healthcare workforce in genetics. HRSA is in the midst of a genetic workforce study that is looking at both specialists and primary care. HRSA offered to provide the Committee with updates as they are available and take the lead in gathering data from other agencies as well. In addition, the National Coalition for Health Professional Education in Genetics and ASHG have already collected data related to this topic. In assessing the data and forecasting future needs, it is important also to include public health professionals, as they often are excluded from such analyses.

SACGHS agreed to the following action plan prior to its next meeting:

- ? HRSA to compile information on Federal agency efforts to address issue;
- ? ASHG to compile information on efforts of various professional societies and organizations to address issue; and
- ? NSGC to develop plan for gathering data on what is needed to increase the number, diversity and quality of training of genetic counselors.

Further actions, if any, to address these issues would be determined following the presentations.

An update was requested on oversight of genetic technologies, laboratories and marketing, following on the initial activities and recommendations of SACGT. The Committee will ask FDA, CLIAC, CDC, CMS, and the Federal Trade Commission (FTC) for briefings at the October meeting on the agencies' role in oversight of these areas and the status of current efforts to strengthen their role in oversight of these areas.

Another item selected for further discussion and analysis is the assertion that large population studies and resources are needed to advance understanding of genotype-phenotype correlations and the genetic basis of common diseases. Dr. Guttmacher of NHGRI explained that in recent weeks CDC, HRSA and NIH have been discussing the need for and a scientific approach to a large population-based study that would examine genotype/phenotype correlations across a normal population. Such an evidence base could provide information crucial to translating genomic information into clinical application. Similar efforts underway include BioBank in the UK and Decode in Iceland. In the United States, the Marshfield Clinic and others have started discussions about initiating similar studies in US populations, enrolling as many as one-half million to one million people. There has been discussion of the possibility of asking the Institute of Medicine (IOM) to conduct an expedited review of such a study to provide scientific and other perspectives. The complexity of the design of such a large study, as well as the attendant ethical and legal concerns, deserve careful consideration, said Dr. Guttmacher. Issues to be addressed are whether a series of studies would be more desirable than one large study, whether subpopulations will be identified and the extent to which associated medical and environmental data would be collected. He also noted that such a study would be costly, requiring funding by multiple agencies, even beyond HHS, and requiring support from the private sector. A representative of the Agency for Healthcare Research and Quality (AHRQ) suggested that NIH consult with that agency, as it routinely assesses practices and trends in clinical care.

Committee discussion focused on whether SACGHS should be reviewing the scientific aspects of a proposed study or staying more focused on the interrelationship between the development of new knowledge and its practical translation into the healthcare delivery system.

Questions for an IOM study might relate to whether the science and the state of phenotypic or clinical evaluation are ready for large population studies to look at the effects of genes and environment on disease pathogenesis and, if so, what are the optimal ways of mounting such studies, and, if not, what gaps in knowledge need to be addressed. Dr. Guttmacher noted that the federal agencies will be meeting with the IOM about a study and certainly would appreciate SACGHS' input, but once the study is commissioned, the IOM acts as an independent entity.

The Committee agreed that staff would work with the agencies interested in pursuing such a large-scale study to gather information about its status and issues of concern as it moves forward. At its October meeting, the Committee asked for a briefing by NIH and relevant agencies on their exploration into the creation of a resource to use in large population studies. The Committee may elect to provide advice to the Secretary on the need for such a study and the legal and ethical considerations involved in such a study.

The Committee also identified three topics that it may want to study in more detail at a later date. These were genetic discrimination; healthcare-related issues (i.e., integration, insurance coverage and reimbursement, affordability and disparities in access); and, the effects of patents and licensing practices on access to clinical genetic technologies. With regard to genetic discrimination, a suggestion was made that SACGHS explore with the Equal Employment Opportunity Commission and consumer and professional groups the source and impact of fear about misuse of genetic information and the extent to which there may be barriers to the reporting of genetic discrimination. Two specific suggestions were related to healthcare issues. First, the Committee would request an HHS presentation on Departmental efforts to address health disparities to learn more about how genetics is included and considered. Committee members further indicated that they were interested in the multiple dimensions of health disparities, including geographic, economic, cultural and linguistic factors as well as race and ethnicity. Second, the Committee would ask AHRQ to organize a session on the diffusion of innovation and its implications for access to technologies.

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We certify that, to the best of our knowledge, the foregoing meeting minutes of the Secretary's Advisory Committee on Genetics, Health, and Society are accurate and correct.

/s/	/s/
Edward R.B. McCabe, M.D., Ph.D.	Sarah Carr
SACGHS Chair	SACGHS Executive Secretary