Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Sixth Meeting
February 28-March 1, 2005
Bethesda, Maryland

Committee Members Present:

Reed V. Tuckson, M.D., Chair
Cynthia Berry, J.D.
Kevin Fitzgerald, S.J., Ph.D.
Barbara Willis Harrison, M.S.
C. Christopher Hook, M.D.
Debra G.B. Leonard, M.D., Ph.D.
Agnes Masny, R.N., M.P.H., M.S.N.
Edward McCabe, M.D., Ph.D.
Joseph Telfair, Dr.P.H., M.P.H., M.S.W.
Huntington Willard, Ph.D.
Emily Winn-Deen, Ph.D.
Kimberly Zellmer, J.D.

Ex Officios/Alternates Present:

Michael Carome, M.D., HHS/OHRP
Francis Collins, M.D., Ph.D., HHS/NIH
Martin Dannenfelser, HHS/ACF
Danielle Drell, Ph.D., DOE
Suzanne Feetham, Ph.D., R.N., HHS/HRSA
Ellen Fox, M.D., DVA
Melissa H. Fries, M.D., DOD
Robinsue Frohboese, J.D., Ph.D., HHS/OCR
Peter Gray, J.D., EEOC
Steven Gutman, M.D., M.B.A., HHS/FDA
Alan Guttmacher, M.D., HHS/NIH
Sherrie Hans, Ph.D., DVA
Muin Khoury, M.D., Ph.D., HHS/CDC
Tim Leshan, HHS/NIH
Willie E. May, Ph.D., DOC
James Rollins, M.D., HHS/CMS
Amy Turner, J.D., DOL
Howard Zucker, M.D., HHS/OPHS

Executive Secretary

Sarah Carr, OBA

Monday, February 28, 2005

Welcome and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, Chair, welcomed members and the public to the sixth meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). He noted that the public was made aware of the Committee's meeting through notices in the *Federal Register* and announcements on the SACGHS website and listserv.

Dr. Tuckson welcomed two new members to the Committee. Dr. Joseph Telfair is an associate professor from the Department of Maternal and Child Health at the, University of Alabama at Birmingham School of Public Health. Dr. Telfair also is serving as the SACGHS liaison to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC). Dr. Tuckson also welcomed Father Kevin Fitzgerald Chair in Catholic Health Care Ethics and a Research Associate Professor from the Department of Oncology at Georgetown University Medical Center.
In summarizing the tasks of the Committee, Dr. Tuckson said that in March 2004, SACGHS had identified 12 priority issues that warranted attention. He provided an overview of the milestones accomplished in each of these areas since the previous meeting. In particular, he noted that a letter was sent to the Secretary in December expressing concern about potential harms from direct-to-consumer (DTC) marketing, requesting clarification from the Food and Drug Administration (FDA) on its role in monitoring DTC marketing of genetic technologies, and requesting that the Department of Health and Human Services (HHS) collect data on the public health impact of DTC marketing in collaboration with the Federal Trade Commission (FTC).

Dr. Tuckson concluded his introductory remarks by providing an overview of the agenda for the 2-day meeting, which included sessions on genetic discrimination, coverage and reimbursement, and large population studies, updates on ACHDGDNC and the National Health Information Initiative, and time for public comments.

Update on SACGHS Efforts on Genetic Discrimination

Agnes Masny, R.N., M.P.H., M.S.N.
Chair, SACGHS Task Force on Genetic Discrimination
Cynthia Berry, J.D.
SACGHS Member

Dr. Tuckson introduced Ms. Agnes Masny and Ms. Cynthia Berry, who provided an update on the ongoing work of the SACGHS Task Force on Genetic Discrimination. Ms. Masny stated that the Committee had previously written two letters to former Secretary Thompson urging support for the enactment of Federal genetic nondiscrimination legislation. She referenced the session held at the October SACGHS meeting to gather the public's perspectives on the magnitude, scope, and impact of genetic discrimination and the fear of genetic discrimination in society. The Committee received testimony on the issue from members of the public, health care providers, and other stakeholders.

Ms. Masny provided an update on legislative activity since the last meeting, noting that the Genetic Information Non-Discrimination Act of 2005 (S. 306) was introduced earlier in the month. The bill prohibits group health plans and health insurers from denying coverage to a healthy individual or charging higher premiums based solely on a genetic predisposition to future disease and bars employers from using genetic information when making hiring, firing, job placement, or promotion decisions. The bill passed the Senate Health, Education, Labor, and Pensions Committee and was debated on the Senate Floor on February 16th, 2005. Ms. Masny said the Senate discussion included several references to the Committee's October session on genetic discrimination and its support for genetic non-discrimination legislation, as well as to former Secretary Thompson's responses to letters from the Committee.

In addition, she reported that the Executive Office of the President from the Office of Management and Budget distributed a Statement of Administration Policy (SAP) on February 16th, 2005 that favors enactment of legislation to prohibit the improper use of genetic information in health insurance and employment. According to this statement, the Administration supported Senate passage of S. 306 and planned to work with Congress to make genetic discrimination illegal and to provide individuals with fair and reasonable protections against the improper use of genetic information. Ms. Masny said that the day after the SAP was issued, the bill passed unanimously in the Senate. The House has yet to introduce any bills on genetic discrimination; however, the Task Force was hopeful that S. 306 would be introduced shortly.

Ms. Masny stated that at the SACGHS meeting in October 2004, the Committee recommended that the testimony and public comments it received be compiled and submitted to the Secretary. It was also suggested that they seek information from the Genetic Information Non-Discrimination and Employment (GINE) Coalition, America's Health Insurance Plans (AHIP), the Chamber of Commerce, and the Coalition for Genetic Fairness. The Department of Justice (DOJ) and the Equal Employment Opportunity Commission (EEOC) were asked to jointly analyze the extent to which current law protects the public against genetic discrimination in health insurance and employment. The Task Force developed a three-part plan to fulfill these goals in preparation for a report to the Secretary.

First, the public comments were compiled into one document and some of the most compelling testimony was used to write a script for a DVD on genetic discrimination. Second, outreach was conducted with the various stakeholders listed above. Third, a legal analysis on the extent of the safeguards of current legislation was in preparation with technical assistance from the Office of Civil Rights, the Centers for Medicare and Medicaid Services, DOJ, the Department of Labor, and EEOC.

Ms. Berry explained that the Task Force sought the varying perspectives and opinions of many stakeholders on genetic non-discrimination, including employers, health insurers, and consumers. She said that AHIP shared with them a letter they had sent on February 22nd to Chairman Boehner of the House Committee on Education and the Workforce and Chairman Barton of the House Committee on Energy and Commerce. The letter stated that AHIP opposes genetic discrimination and that consumers should be guaranteed adequate protections in this area. AHIP also expressed support for the protections established by the Health Insurance Portability and Accountability Act (HIPAA) and indicated its belief that S. 306 would not undermine quality improvement efforts or disease management programs. The organization stressed that it is committed to having a constructive role in this ongoing debate and urged Congress to address the issue at a deliberate and thoughtful pace.

The Task Force also heard the position of the U.S. Chamber of Commerce, which represents millions of businesses, State and local chambers of commerce, and business associations across the country. The Chamber believes that employers should have the ability to make decisions based on genetic information in cases where the workplace poses an imminent threat to the employee. For example, they believe an employer might need to reassign an employee who works with a particular hazardous material if the employee has a genetic predisposition that makes it likely that the material poses a threat. The Chamber believes there is no documentation of widespread genetic discrimination in the workplace and therefore the goal of any legislation should be focused on reducing employee *fear* of discrimination rather than discrimination itself. Ms. Berry stated that the Chamber of Commerce is concerned about the possibility of increased liability and frivolous lawsuits. The Chamber contends that current law provides sufficient protections for confidential medical information, including genetic information. In addition, the organization takes the position that damage provisions in the law should be limited to equitable relief, that one Federal standard should apply that preempts State law, and that the definition of "family" should be limited. Lastly, the Chamber believes that the study commission on this matter should be truly independent and not housed within EEOC.

Ms. Berry reported that the Task Force also spoke to the GINE Coalition, which is a group of employers, trade associations, and professional organizations formed to address concerns about genetic discrimination in the workplace and the confidentiality of genetic information. The GINE Coalition's Steering Committee includes representatives from the Chamber, the Society for Human Resource Management, the National Association of Manufacturers, the HR Policy Association, the Association for Human Resources, and various college and university professionals. Similar to the Chamber, the GINE Coalition contends that there is no appreciable evidence of genetic discrimination in the workplace. They focus on employment discrimination and are not involved in matters of health insurance discrimination. The organization has concerns about the unintended consequences of genetic non-discrimination legislation, unnecessary regulation, and the possibility of excessive litigation.

Ms. Berry stated that the Coalition for Genetic Fairness, on the other hand, strongly supports Federal genetic non-discrimination legislation. Its mission is to educate congressional policymakers and staff about the importance of implementing legal protections, including the passage of non-discrimination legislation at the Federal level. The Coalition feels that the current lack of Federal legislation creates an unfriendly climate for companies trying to develop innovative genetic technologies. The Coalition believes that patients and providers should be willing to participate in research supporting the development of new products and employers would benefit from predictability in this area. This organization is not convinced that current law provides sufficient clarity or protection, but believes that S. 306 would provide this clarity and protection for both employers and consumers.

The Coalition has been undertaking a variety of legislative efforts, including supporting S. 306 as it moves over to the House. Coalition members are currently in discussion with members of Congress on both sides of the aisle. Ms. Berry noted that the goal of these efforts seems to be the introduction of the Senate bill in the House, rather than introduction of a different House version, which could delay passage of legislation. It appears that the Coalition hopes that a Republican will agree to serve as the lead sponsor of a House bill, along with Representative Slaughter, the Congresswoman who served as the lead sponsor of House genetic non-discrimination bills in previous Congresses. The Coalition will be working with the House Energy and Commerce Committee, the Education and Workforce Committee, and possibly the

Ways and Means Committee. Ms. Berry pointed out that one of the difficulties that delayed action on the legislation in the last session of Congress was its referral to three different committees, which made the process cumbersome.

Discussion

The full Committee discussed the extent to which various stakeholders are genuinely committed to passage of genetic non-discrimination legislation and whether there is a real chance that S. 306 will move forward. The group noted that there has been resistance to past legislative efforts and that, as reported by the Task Force, some organizations are very concerned about unintended consequences. Mr. Frank Swain, representing the Coalition for Genetic Fairness, assured the Committee that there is good reason to believe a bill will be introduced quickly in the House, followed by constructive hearings.

The Committee agreed that it was important to promptly brief and engage the new Secretary on this issue. Members discussed the optimal time to write a letter to him stating SACGHS' viewpoint and send the materials developed by the Task Force. Although the Committee ideally wanted to submit the letter, public comments, DVD, stakeholder analysis, and legal analysis at the same time, they acknowledged that more time was needed to complete some of the products. Dr. Edward McCabe felt strongly that the letter should be sent as soon as possible, along with any other materials that were ready.

After extensive discussion, the Committee agreed that a letter should be sent to the Secretary that recommended he: 1) convene a meeting with key stakeholders to hear their concerns, reiterate the Administration's position, and urge these groups to reach consensus; and 2) brief the House members on this issue to express the Administration's support for the pending legislation and to educate Congress. The Committee also approved the script for the DVD and agreed to quickly prepare and send the testimony from the public, the DVD, and the stakeholder analysis. . In addition, the Task Force was to expedite completion of the legal analysis so that it could reach the Secretary by June. It was hoped that the Secretary would use these materials to convey information to the Congressional committee chairs, sponsors of the House bill, and others who could influence the legislation.

National Health Information Initiative

Rex Cowdry, M.D., M.P.H.
Office of the National Health Information Technology Coordinator, DHHS

Dr. Rex Cowdry spoke on the President's National Health Information Initiative (NHII), which aims to use information technology to transform the way the Nation organizes, finances, and thinks about health care. The President decided to move forward with NHII based on 10 years of recommendations from various committees and publications. Dr. Cowdry began his presentation by describing problems with the current health care system in the areas of cost, efficiency, value, and quality. He noted that advancing technology, including genetic and genomic technologies, is a key driver of increases in U.S. health care costs.

Dr. Cowdry stated that the health care market is so fragmented that it does not provide sufficient information to allow providers or patients to make good decisions. Information is lacking in several areas, including the quality of care from various providers, outcomes, and the price of services. NHII is

an attempt to implement a system that will provide increasing information about outcomes and value, encourage choices, and incorporate incentives into the reimbursement system. Dr. Cowdry said that health information technology is key to a patient-centered, provider-friendly, and information-rich health care system. It will empower patients in a new way, allow providers to exercise judgment and compassion rather than spending time searching for data, and gather information that flows in both directions. The system will make information available from the real world of clinical practice and will provide surveillance capacities that do not currently exist.

Dr. Cowdry noted that it is challenging to bring about an interconnected system that promotes value and good care while also protecting privacy. To be effective, it must bring about virtual integration of the health care system. He described the framework for health information technology outlined by David Brailer, who was appointed in April 2004 as the National Coordinator of this effort.

The framework involves three different structures. The first is a nationwide network for health information sharing in which, the capacity to exchange secure information among authorized individuals is integrated into an existing physical network. Dr. Cowdry clarified that this does not mean that a centralized database will be used, but rather a federated system will be implemented in which various provider systems remain the secure repositories of information. Organizations within the same geographic regions will be able to exchange information with one another, ensuring that requestors have the appropriate authorizations to gather information and transfer it in an appropriate way.

The second structure is the so-called "regional health information organization" (RHIO). To date, RHIOs have been somewhat larger than local regions or States, despite the fact that State privacy and medical information laws vary and States implement health information technology in different ways; however, Dr. Cowdry said States are a natural geographic grouping for the structure.. NHII planners want to avoid a proliferation of different standards for information exchange to help ensure that systems have effective ways of communicating with one another.

The third structure is the adoption of electronic health records (EHRs) in local provider systems. Large hospitals and practices are likely to adopt EHRs to obtain efficiencies, as they are in a better position to see cost savings. Dr. Cowdry said that implementing EHRs currently is a losing economic proposition for most entities and that incentivizing use and/or performance and outcomes is the best way to move the adoption process forward. He stated that one of the challenges of the initiative would be to collaboratively build a set of incentives that will work for both the private sector and the Government in its role as a health care payer. Another key effort will be the development of a formal certification process for the system.

Dr. Cowdry described some of the key challenges to this new system, including the complexities of privacy and security, allowing partial opting out so that most, but not all information is in the system, and the question of ownership of information. He spoke about the risk that this work could result in silos; i.e., systems that don't communicate well with one another. Responsible payers must find a way of counteracting that risk by building an economic case for sharing information.

Other challenges mentioned by Dr. Cowdry included considering data from highly controlled clinical trials but not from real world settings; developing guidelines that are operational in an electronic health

system; and creating guidelines for providers that are individualized yet allow for exceptions. He said there is a danger of developing wasteful parallel systems for health information. There also are risks that the system will not be able to generate de-identified, large-scale data that provide comparative information about effectiveness and cost-effectiveness, that it will not be able track outcomes or identify adverse events, or that it will not routinely provide surveillance.

Discussion

Dr. Tuckson asked how the Committee could inform the process, particularly concerning the privacy and confidentiality of sensitive genetic information. Dr. Cowdry encouraged the Committee to discuss the issue of rights to information entered into the medical record. He suggested that the Committee support the technical processes that will allow de-identification of data so that family histories and genetic information can be gathered safely. Dr. Muin Khoury commented on the importance of integrating family history into medical records and the need for the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and other health care agencies to work together toward this goal. Dr. Khoury said the current organization of the health care system does not allow for family history data to be available in a useful way. He encouraged the Committee to work with Dr. Cowdry's office and other Federal agencies to change the health information infrastructure.

Dr. Cowdry noted that adoption of the system by providers will be critical. He stated that collection of the kind of detailed family history information that CDC or FDA would like to have must be balanced with time constraints placed on providers, who currently are paid only for short office visits that do not allow for extensive data collection. Dr. Telfair asked if there is any precedent for this kind of system that has successfully addressed the challenges Dr. Cowdry presented to the Committee. Dr. Cowdry described some regional organizations that are moderately well implemented or just underway. He recommended discussions with these groups to obtain information as the initiative moves forward.

Dr. Tuckson concluded the discussion by asking Dr. Cowdry to inform his office that SACGHS is very interested in collaborating on the issue of integrating family history into electronic health records and is willing to assist in this and other areas as needed. He said the Committee would send a follow-up letter asking for contact information for the health information technology committees with whom SACGHS should develop relationships so that additional specific information can be obtained. Dr. Tuckson asked Dr. Khoury and Dr. Alan Guttmacher to work together to draft the letter.

Report from the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC)

R. Rodney Howell, M.D.,
ACHDGDNC Chair

Dr. Tuckson stated that the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children is addressing many of the same issues as SACGHS regarding access, education, and appropriate standards for validation of genetic tests. In recognition of these common interests, there is an ongoing liaison between the two committees, represented by Dr. Telfair. Dr. Tuckson welcomed Dr. R. Rodney Howell, who provided an update on a uniform newborn screening panel and system.

Dr. Howell explained that newborn genetic testing has become extremely complex because of rapidly changing technology that allows many tests to be performed simultaneously using the same blood spot.

He described the Children's Health Care Act of 2000, which established the Advisory Committee and also directed HHS to provide screening, counseling, and health care services to benefit newborns and children at risk for heritable disorders. The legislation authorized the Secretary to award grants for demonstration programs to evaluate the effectiveness of these services and to monitor morbidity and mortality caused by these heritable disorders. Dr. Howell stated that the purpose of the Advisory Committee is spelled out in detail in the legislation: To provide the Secretary with advice and recommendations concerning grants and projects authorized under the law and to provide technical information to develop policies and priorities that will help States and local health agencies provide newborn and child screening, counseling, and health services. The Advisory Committee also provides guidance to the Secretary concerning the most appropriate application of universal newborn screening tests. Dr. Howell noted that the Advisory Committee's membership must be composed of: 1) individuals with medical, technical, and scientific expertise in heritable disorders or in providing screening, counseling, testing, or specialty services for newborns and children at risk for heritable disorders; 2) members of the public with special expertise about these conditions; and 3) representatives from Federal agencies, public health constituencies, and medical professional societies that can fulfill the duties of the committee.

In his discussion of the topic of screening for metabolic disease, Dr. Howell said that the original tenets guiding newborn screening were laid out in 1968 by the World Health Organization and these principles have remained in place. He explained that newborn screening for genetic disease is administered by the States and that last year, 4.1 million babies were screened in the United States. Newborn screening is the most common form of genetic testing, although it has not typically been thought of in that way. Dr. Howell stated that expanded newborn screening is moving across the country rapidly and that 36 States now have mass spectroscopy programs. Although States differ in the number of disorders they screen for, all States and jurisdictions screen for phenylketonuria, hypothyroidism, and galactosemia.
Dr. Howell noted that the Advisory Committee held three meetings that focused on newborn screening and related technology. This body reviewed a report by the American College of Medical Genetics (ACMG) that recommends mechanisms to help decide which screenings should be performed on a uniform basis. The Advisory Committee agreed with the premises of the report and planned to send a letter to that effect to the Secretary as soon as the full report is available. Based on the report's recommendations, the Advisory Committee formed subcommittees on education and training, follow up and treatment, and laboratory standards and procedures. Dr. Howell said these subcommittees were in the process of developing agendas and would be reporting back to the full Advisory Committee at the next meeting.

Discussion

Dr. Emily Winn-Dean asked if the Advisory Committee had examined the issue of genetic disease and discrimination. Dr. Howell said that, to date, there has not been a formal effort to address this issue.

Dr. Francis Collins asked about feedback from the States concerning use of tandem mass spectrometry (MS/MS). He was concerned that parents might experience anxiety if an abnormality is found in a

newborn but the screener is unsure of its clinical interpretation. He asked about preliminary data on the consequences of increasing the number of conditions that are screened, including many about which little is known or for which no intervention is available. Dr. Howell replied that the report he described included a recommendation to systematically examine this issue. However, he said experts agree that when an abnormality is detected in screening, health professionals should be informed. He also said a major research agenda is needed to follow screened individuals. He commented that tests such as MS/MS will pick up secondary conditions that no-one is looking for, which may or may not be associated with a primary condition.

Dr. Willie May asked if there are qualitative or quantitative studies on the accuracy or comparability of results across tests. Dr. Howell said yes, although they have not been extensive. He gave examples of quality assurance programs at CDC, the College of American Pathologists and ACMG that look at rare metabolic conditions. In addition, a Health Resources and Services Administration (HRSA)-funded regional cooperative group is piloting a training and education program for those who use MS/MS. Dr. Howell commented on the need to keep the false positive rate low without missing affected persons. He said that the quality assurance programs and the laboratory standards committee of the ACHDGDNC would be focusing on the issue of accuracy in testing.

Dr. McCabe commented on the need for large studies, such as those conducted by the Children's Oncology Group, since the natural history and influence of treatment on many of these disorders is not known. He read from a Newsweek article by Gina Kolata, making the point that many people take exception to newborn screening. The article stated, "The majority of newborn screening tests have failed, said Dr. Norman Fost, a professor of pediatrics and director of the program in medical ethics at the University of Wisconsin. Over the years, Dr. Fost said, thousands of normal kids have been killed or gotten brain damage by screening tests and treatments that turned out to be ineffective and very dangerous." Dr. McCabe emphasized that this quote, which is completely unfounded in the medical literature and in the experience of clinicians, does a disservice to a very effective public health strategy.

Public Comments

Judith Lewis, Ph.D., R.N.C.
Immediate Past President, International Society of Nurses in Genetics (ISONG)

Dr. Judith Lewis stated that the number of nurses practicing in the U.S. is not sufficient to meet current and projected workforce needs. There is an even more critical shortage of nurse educators. The crisis will become increasingly pronounced because many nurses are nearing retirement age. Dr. Lewis described the number of nurses in various specialty areas and the education and credentialing processes required for these positions. She noted that there are only five universities that provide Masters degrees for a specialty in genetics.. Dr. Lewis emphasized the importance of increasing the number and capacity of such programs to enhance the knowledge of nurses who incorporate genetics into their practice. Further, ensuring reimbursement of services for those who provide genetic services, including nurses and advance practice nurses, will help meet workforce needs.

Ms. Masny asked if the document, *American Nurses Association Scope and Standards of Practice*, developed by the American Nurses Association (ANA), could be made available to the Committee. Dr.

Lewis replied in the affirmative, and said there are three documents she considered important for the Committee to have available: the *Nursing Social Policy Statement*, which outlines nurses' social contract with patients and society; the *Scope and Standards of Practice* that apply to all nurses, and the *Scope and Standards of Practice of Genetic Clinical Nursing Practice*, currently in revision, which is jointly published by ISONG and ANA. She said the latter document, which will serve as a companion to the major standards of practice document, would be available later in the year.

Rick Carlson, J.D.
Clinical Professor of Policy Programs, University of Washington

Mr. Rick Carlson described his belief that within 5 to 10 years, the purchaser and payer roles in health care will be radically transformed, as their objectives now are to incrementally retreat from providing benefits and entitlements. He said that when these entities know more about the risks associated with the insured member population, they will no longer have an insurance product but an annuity product. Mr. Carlson said the model will change so that these payers will be looking at ways to manage known member costs over time.

Dr. McCabe asked Mr. Carlson how the concept of genetic nondiscrimination as a civil right fit in with his view. Mr. Carlson stated that, although he agrees philosophically that genetic non-discrimination should be a civil right, he felt that it may not become one until it is legislated.

Judith Cooksey, M.D., M.P.H.
Adjunct Associate Professor, Department of Epidemiology and Preventive Medicine, University of Maryland-Baltimore School of Medicine

Dr. Judith Cooksey is the principal investigator for a multi-disciplinary, multi-institutional effort to study the ways that genetic services are organized and delivered in the U.S. This effort takes place under a cooperative agreement called *Assessing Genetic Services and the Health Workforce*. Dr. Cooksey presented on an approach that applies some of this study's findings to an established conceptual framework that could evolve into a new way to assess the quality of medical care. Dr. Cooksey referred to a handout given to the Committee that described a seven-tiered model of the current genetic services infrastructure. These tiers included: genetic science, organizational resources, the health workforce, data systems and information transfer, financing and reimbursement systems, health services research, and policy development. Dr. Cooksey explained that the Institute of Medicine built on this conceptual framework and advanced it by identifying four process levels: the experience of patients and communities, microsystems of care, health care organizations, and the external health care environment. She stated that this model is in progress and that she will provide the Committee with an update in the future.

Dr. Tuckson asked how much data had been collected in the genetic services study. Dr. Cooksey replied that the researchers have amassed a vast amount of information and are in the process of writing a preliminary report. However, only a small amount of the data collected has been analyzed.

Pam Williams
Student, University of Oklahoma Health Science Center

Ms. Pam Williams is a student pursuing credentialing for advanced practice nursing in genetics. She told the Committee that many nurses and nursing students are concerned about the ways in which the diverse opportunities for genetic testing will impact patients. She stated that these nurses are hoping that funding will be available in the future to study the psychosocial and psychoneuroimmunological impacts of this information and encouraged the Committee to make this research interest known to their colleagues.

Discussion of Draft Coverage and Reimbursement Report

Facilitators:
Ms. Cynthia Berry, J.D., Chair, SACGHS Coverage and Reimbursement Task Force
Dr. Reed Tuckson, M.D., SACGHS Chair

Dr. Tuckson briefly reviewed the status of the report on coverage and reimbursement of genetic services. He said the Committee had appointed a Task Force to investigate coverage and reimbursement of genetic tests and services and that the resulting draft report being reviewed by the Committee represented expert perspectives from both the public and private sectors. The Committee had discussed some sections of the report at the October 2004 meeting. The remainder of the day was scheduled for a continuation of that review.

Ms. Berry updated the Committee on changes made to the report since the October meeting. She explained the Committee's primary charge for this discussion was to review each barrier and deliberate on each proposed recommendation. She hoped the members would be able to reach consensus on draft recommendations so that the Committee would be in a position to gather public comments after this meeting.

The first draft recommendation under consideration related to evidence-based coverage decisions. The Committee had previously discussed having a group or body develop a set of guiding principles concerning the types of genetic tests and services that should be covered. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) program had been mentioned as the type of group that could take on this responsibility. Dr. Debra Leonard and Dr. Khoury agreed that the Committee should bring EGAPP to the attention of the Secretary, but stated that EGAPP should be mentioned only as an example. The draft recommendation was reworded accordingly.

The second draft recommendation was developed in recognition of the fact that Medicare is often used as a model for private health plans in determining coverage of benefits. However, since genetic technologies may not be widely used by or appropriate for the elderly, the draft recommendation encouraged private health plans to make their own coverage determinations about genetic tests and services rather than using Medicare as a model. Dr. Winn-Deen noted that many issues in genetics would be falling into the private payer arena since many genetic tests identify risk factors early in life so that preventive measures can be taken. The Committee agreed to make several changes to the wording of the draft recommendation.

The third draft recommendation addressed the fact that Medicare has both national and local decision

making processes to determine coverage for genetic tests and services. It stated that this mixed approach is reasonable and encouraged the Centers for Medicare and Medicaid Services (CMS) to move forward with plans to develop a mechanism for evaluating new local coverage decisions to determine whether they should be adopted nationally. The Committee agreed to make several changes to the wording of the draft recommendation.

The fourth draft recommendation stated that preventive services, including predispositional genetic tests and services, should be covered under Medicare. The Committee agreed that the Secretary should urge Congress to authorize this coverage by adding a new preventive services benefit category. In addition, the Committee agreed that while legislation for a preventive service benefit category was being pursued, CMS could issue a national coverage decision stating that, in the presence of adequate scientific evidence, family history constitutes medical justification for a genetic test. . After some discussion, the Committee decided to confer with CMS about the appropriate wording of this draft recommendation.

The fifth draft recommendation urged the Secretary to provide States with information on genetic tests and services so that they have the best evidence available when making coverage decisions. The second part of the recommendation stated that HHS should continue to provide the States with grants to provide genetic testing services. Dr. Tuckson suggested adding language to the first part of the recommendation requesting that the Secretary provide the States with the guiding principles referred to in the first draft recommendation.

The sixth draft recommendation covered the need for health providers and payers to reach consensus on the use of CPT code modifiers. It called for a private sector group, such as the Genetic Test Coding Work Group, to be organized to analyze this issue. However, given that the American Medical Association has adopted these modifier codes, the Committee decided to delete this recommendation. There may be a need in the future to address any problems with their use.

The seventh draft recommendation pertained to the fact that the costs of performing genetic tests often exceed Medicare payment rates and asks the Secretary to direct CMS to address the variation in payment rates using its "inherent reasonableness" authority. The Committee agreed not to make any changes to the draft recommendation.

Discussion of the eighth draft recommendation focused on whether it was appropriate to direct a recommendation on reimbursement by private payers in a report to the Secretary. The Committee agreed that no specific recommendation should be made but that discussion of the issue itself will be retained in the body of the report.

The next draft recommendation pertained to reimbursement of genetic counseling services. At the October 2004 meeting, SACGHS requested information on the value and effectiveness of genetic counseling services provided by a range of health providers. A Genetic Counseling Services Work Group was formed and tasked with 1) providing a list of legitimate credentialing programs for genetic counseling services; 2) providing a list of the provider types that are qualified to offer and be reimbursed for these services; 3) conducting a literature review and analysis of evidence that demonstrates the value and effectiveness of genetic counseling services and the importance of reimbursing for these services; and 4) conducting a literature review and analysis of evidence that demonstrates whether licensure of

genetic counselors is needed, whether and which non-physician genetic counseling providers are qualified to provide these services without physician supervision, and whether harms are occurring because non-physician genetic counseling providers are not able to directly bill for their services. The Committee hoped the Work Group's findings would help them in crafting well-supported recommendations.

Report of the Genetic Counseling Services Work Group on Evidence Supporting the Value and Effectiveness of Genetic Counseling Services
W. Andrew Faucett, M.S., CGC
American Board of Genetic Counseling
Kelly E. Ormond, M.S., CGC
National Society of Genetic Counselors

Mr. Andrew Faucett of the American Board of Genetic Counseling (ABGC) stated that at one time everyone working in the field of genetics was credentialed through the American Board of Medical Genetics (ABMG), including physician geneticists, Ph.D. geneticists, and genetic counselors. When ABGC was formed in 1993, it took on the function of credentialing genetic counselors, while ABMG continued to credential physician geneticists and Ph.D. geneticists. Despite this separation, the exam for genetic counselors and medical geneticists has remained the same, and genetic counselors have fairly consistently scored as highly as physicians. In 2000, the credentialing standards for genetic counselors changed so that they were required to complete an accredited training program to be certified. In 2001, the Genetic Nursing Credentialing Commission (GNCC) began certifying Masters-trained nurses with a concentration in genetics, and in 2002, GNCC started a program for the certification of Bachelors-level nurses. Mr. Faucett stated that 59 percent of certified professionals are Masters-level trained genetics counselors, 35 percent are M.D. clinical geneticists, 5 percent are Ph.D. medical geneticists, and 1 percent are Bachelors-level nurses.

Mr. Faucett explained that the ABGC accreditation process is based on competencies in four areas: communication skills, critical thinking skills, counseling and psychosocial assessment skills, and professional ethics and values. Extensive instruction and evidence of a broad base of clinical training are also required.

Although the International Society of Nurses in Genetics (ISONG) was formed in 1988, the American Nurses Association (ANA) didn't recognize genetic nursing as a specialty until 1997. In 1998, ISONG established the document, *Scope and Standards of Genetic Nursing Practice,* and in 2001, ISONG founded GNCC as a separate entity that offers certification in genetics to advanced practice nurses. Mr. Faucett described the extensive requirements for GNCC certification. He remarked that some nursing special interest groups recognize nurses who are trained in genetics even if they are not certified, but emphasized that the only two groups currently offering Masters-level certification are ABGC and GNCC.

Ms. Kelly Ormond of the National Society of Genetic Counselors (NSGC) then addressed the Work Group's findings on licensure and value and effectiveness data. She said licensure of genetic counselors is a relevant topic because Masters-trained genetic counselors are among the few health professionals who are not currently licensed. She reported that there is very little documentation of harm resulting from non-licensure. The Work Group believes that the lack of documentation is due primarily to the absence

of a mechanism by which to report such cases to public health departments, resulting from the lack of licensure of genetic counselors. Ms. Ormond noted that Utah, California, and Illinois have enacted licensure and nine States are actively working on licensure efforts. In the opinion of the Work Group, two of the greatest barriers to licensure are cost concerns and a desire not to increase regulation of any profession or organization. Ms. Ormond described some of the benefits of licensure that have been seen anecdotally in Utah, such as an increase in the number of genetic counselors practicing in the state and increased recognition among payers of genetic counselors as independent or "incident to" providers.

Ms. Ormond described the collection of studies examined by the Work Group in an effort to assess the value and effectiveness of genetic counseling services. The studies were difficult to analyze because they included different types of heath care providers in varying settings. Many studies also included genetic testing, making it difficult to separate the outcomes of the counseling services from the test. In addition, outcomes were broadly defined and measured in different ways by different investigators. Among the different measures were knowledge, reproductive decision making, behavior change, satisfaction, interpersonal measures, psychological support, aid in decision making, or cost-effectiveness.

Ms. Ormond pointed out that years ago, genetic counseling services often were funded by block grants, which are now a much less reliable source of funding. As a result, many genetics nurses and genetic counselors are moving out of clinical settings and into research roles, which is affecting access.

Ms. Ormond addressed the current billing practices documented by NSGC and ISONG, which indicated that a minority of counseling providers is able to directly bill. NSGC's 2004 Professional Status Survey showed that its members saw approximately 1.2 million cases a year. Fifty-seven percent billed under the supervising physician's name, 9 percent billed under both their own and the physicians' names, and 14 percent did not bill for their services in any way. ISONG's 2005 survey indicated that 12 percent of genetic nurse specialists were nurse practitioners who could directly bill for their services. Approximately 70 percent of ISONG members deemed the adequacy of reimbursement to be poor.

In summary, Ms. Ormond said the Work Group reached three conclusions. First, the Work Group requested that SACGHS recognize non-physician providers credentialed by a national genetics organization as appropriate providers of genetic counseling services. Second, they recommended that the Committee advocate for the development of CPT codes specific to genetic counseling services for use by any qualified provider. Third, they proposed that SACGHS support the funding of further studies to assess the value and effectiveness of genetic counseling services provided by non-physicians, as that was a topic the Work Group found to be lacking data.

Discussion

Dr. Judith Cooksey and Dr. Judith Lewis joined Mr. Faucett and Ms. Ormond at the table for questions. Dr. Telfair asked if the Work Group included data on single-gene counselors. Ms. Ormond replied that they did not identify this group specifically but were aware that they are providing care. Dr. Cooksey added that the role of nurses in genetics has been significantly understudied and that there are few advanced programs for nurses in genetics. However, she believes the role of nurses will grow with respect to the provision of genetic counseling services.

Dr. Rollins asked if a meta-analysis was performed on the studies and whether the evidence was strong enough to support the idea that non-physician genetic counseling providers are more efficient than physicians in the area of genetic counseling. Ms. Ormond said there was not enough time for the Work Group to perform a meta-analysis. She then described in more detail the studies comparing genetic counselors with physicians. Dr. Cooksey expressed the idea that it is difficult to conduct these kinds of studies in a meaningful way because they compare different professionals practicing in different settings with different patient populations.

Dr. Tuckson asked if ABMG and ABGC consider GNCC an equivalent organization. Mr. Faucett said that all three organizations have received acceptance in the profession of genetic counseling. Dr. Tuckson also asked if it is legitimate for a person certified by ABMG, ABGC or GNCC to perform a full range of counseling services, to which Mr. Faucett replied in the affirmative. Dr. Tuckson asked whether there is any overlap in function among the genetic counseling provider, the physician and the testing laboratory in terms of providing genetic counseling services. Mr. Faucett said that academic centers and major medical centers use a team approach and there is usually no overlap in roles. Dr. Tuckson asked how the reimbursement process should work so that multiple persons are not performing and being paid for the same function. Dr. Cooksey stated that in conversations with over 200 providers, it was clear that duplication of effort is not the problem in genetic counseling. Because this function is time intensive, physicians are happy to delegate the job to non-physician genetic counseling providers. Dr. McCabe agreed, stating that although the costs of genetic services will be going up, it will be more cost-effective if the field enters into this relatively new area in a knowledgeable way. Dr. Guttmacher commented that the data rarely address health outcomes, and said a key question is which types of providers and settings achieve better or worse health outcomes.

Dr. Fitzgerald asked if there have been studies that looked at workforce capacity to see if there is a need to increase the number of non-physician genetic counseling providers. Ms. Ormond said that as a genetic counseling program director, she could attest to the fact that within the past 10 years, they have doubled the number of students accepted into the program annually and that the need for increased capacity is well documented. A large number of qualified applicants are being turned away, yet there is a significant national shortage of genetic counselors. Dr. Willard commented on the need for a solid evidence base demonstrating that genetic counseling is effective and that the approaches used lead to better health outcomes.

Continued Discussion of Draft Coverage and Reimbursement Report

The Committee returned to a discussion of barriers and recommendations in the report on coverage and reimbursement of genetic tests and services. The members agreed to insert relevant text from the Genetic Counseling Services Work Group report in the body of the Coverage and Reimbursement Report, as well as add the Work Group's full report as an appendix. A disclaimer will be added to the Work Group report stating that SACGHS does not necessarily endorse all of the conclusions.

The Committee turned to the recommendations on billing and reimbursement of genetic counseling services. Language was added recommending HHS evaluate the adequacy of genetic counseling billing codes. A sentence was modified to state that the Secretary should direct Government programs to reimburse prolonged service codes when documentation supports that they are "reasonable and

necessary." The Committee agreed that the recommendation regarding the need for an analysis of genetic counseling provider qualifications and billing and reimbursement mechanisms also should call for further research on the value and effectiveness of genetic counseling services. Due to time constraints, consensus was not reached on the final wording of all sections of the recommendation. The Committee planned to continue the discussion the next day.

Tuesday, March 1, 2005

Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Tuckson provided an overview of the morning's agenda, which included presentations outlining the possibilities and challenges of conducting large population studies that build on the knowledge gained from the Human Genome Project. Dr. Tuckson said such large population studies would focus on the genetic and environmental factors of common, complex diseases. Their proponents believe this work would contribute significantly to clinical and public health strategies. Because the studies would raise numerous scientific, logistical, ethical, legal, and social concerns, SACGHS had asked to learn more about them. Dr. Tuckson noted that the first three presentations would provide a broad understanding of large population studies. The next three presentations would explore logistical, ethical, legal, and social aspects.

Large Population Studies: Opportunities and Challenges

Conceptual Basis for Large Population Studies of Human Genetic Variation and Common Disease
David Goldstein, Ph.D.
Wolfson Professor of Genetics, University College of London

Dr. David Goldstein provided his view on why we should undertake large population studies and how it ought to be done. He described several motivations, stating that scientists not only want to be able to predict risk, but they also want to be able to intervene to prevent disease. In addition, they are interested in identifying genes and pathways that might help in the drug development process, as well as the genetic determinants of treatment response. The latter area, called pharmacogenetics, examines which drugs are safest and most effective for a given patient based on their genetic makeup.

Dr. Goldstein explained that common diseases are not caused by a one-to-one correspondence between a genetic difference and a disease. There are more than 10 million places in the human genome where individuals differ, and these variants change physiology in subtle ways. They influence the kinds of diseases people get through a complicated interaction with other genetic differences and the environment. The aim of a large population study would be to understand how such genetic differences influence health.

Turning to the technical aspects necessary to make progress in this area, Dr. Goldstein said the field is

very good at sequencing and genotyping, but has not made much progress relating genetic variation (referred to as single nucleotide polymorphisms or "SNPs") to human disease traits. Researchers have not been able to exhaustively compare the genetic variation of very large numbers of people who have the same health condition with those who do not have it. Dr. Goldstein described a method that is currently receiving attention, called "haplotype tagging." It uses knowledge of a small subset of SNPs to predict information about adjacent SNPs; selecting an appropriate subset of variable sites in one individual can provide information about genetic variation of others with the same trait. Using haplotype tagging, scientists are attempting to create a framework for relating the presence of particular SNPs with clinical traits, such as disease.

Dr. Goldstein described his work with a data set collected by the University College of London in collaboration with GlaxoSmithKline. The investigators looked at patterns of association among 55 genes that encode major drug metabolizing enzymes. They assayed variable sites in a number of individuals of European and Japanese ancestry to create the data set. The analysis demonstrated that haplotype tagging was effective in representing variations in different populations. In the 55 genes they analyzed, with an estimated 4,000 common polymorphisms, they showed that a subset of 200 polymorphisms represented the other 4,000. Dr. Goldstein felt that his study and others like it demonstrate that haplotype tagging is an efficient and economical method for representing common variation. He said that tagging will not be as useful for representing more rare variations and emphasized that substantial work remains.

He then made several points concerning the value of prospective health studies of people who are randomly sampled in the population. Over time, as some of those enrolled become affected by different common diseases, investigators could gain a wealth of knowledge based on the previous data collected. Although there would be advantages to these studies, investigators have not yet determined the amount and type of information that should be collected at the time of enrollment and the areas that should be studied first. He stated that those in genetics should interface carefully with those in health care to make sure they capitalize on the most important types of information. Dr. Goldstein closed by emphasizing the importance of obtaining detailed information about how patients respond to treatment. He believes there is an overemphasis on the study of predisposition directly, as opposed to treatment response.

Public Health Perspective on Large Population Studies of Human Genetic Variation, the Environment, and Common Disease
Gilbert S. Omenn, M.D., Ph.D.
Professor of Internal Medicine, Human Genetics, and Public Health, University of Michigan

Dr. Gilbert Omenn commented on the importance of the avalanche of genetic information becoming available, including the haplotype map ("HapMap") and the information existing on many candidate genes and alleles associated with particular risks. He opined that environmental and behavioral data sets must be improved and linked with genetic information. These data sets must have secure privacy and confidentiality protections in place. In this context, he said that the technologies to be developed will result in medical breakthroughs that will reduce health risks and allow for cost-effective treatment.

Dr. Omenn addressed the struggle concerning the terms "genetics" and "genomics." He views genetics as the broader historical scientific term, which encompasses genes and their roles in health and disease, physiology, and evolution. He defines genomics as a set of powerful new tools used in molecular

biology, biotechnology, and computational sciences to permit scientists to examine the entire complement of genes and gene products.

Speaking on CDC's role in large population studies, he described the National Health and Nutrition Examination Survey (NHANES), which is sponsored by the CDC National Center for Health Statistics and has collected 40 years of survey and laboratory data that have resulted in significant public health improvements. Ongoing data analysis is providing information on various environmental exposures. Dr. Omenn described NHANES as a rich data resource that is continuing today with the collection of DNA samples from approximately 7,000 people.

Dr. Omenn described the tools and approaches that are becoming available in public health, such as Geographic Information Systems (GIS), wireless devices to track exposure to pesticides, and spatial models for households at risk for lead poisoning. Biosensors and nanoscale devices permit feasible measurements of an individual's environmental exposures.

Dr. Omenn said the conceptual strategy for integrating exposure assessment technologies in human environmental health research must identify: priority diseases and plausible environmental factors; potential genetic determinants, pathways, and model systems for exploring genetic/environmental interactions; and target study populations for feasible measurement. The strategy should define the genetic determinants of susceptibility, conduct targeted exposure assessments, and identify and validate biomarkers. This information must then be brought together with descriptions of genetic and environmental interactions. The technologies and approaches used include literature searches and databases, computer-based pathway mapping, body burden assays, genomic screening, and biomarker studies. Dr. Omenn remarked on the importance of laboratory scientists linking sensors and molecular biomarkers in animals and humans with *in vitro* and *in vivo* studies to create a link between toxicology and epidemiology.

Explaining the work of the Environmental Protection Agency (EPA), Dr. Omenn said the agency has measurement and modeling programs that are directly relevant to the study of common disease in large populations, such as the Multimedia Integrated Modeling System (MIMS). It simulates ambient airborne substances in urban settings that can be applied to individual exposures. The agency also is working on prototypes and advanced human exposure modeling support tools for air pollution and homeland security.

From the public health perspective, Dr. Omenn said the fields of genetic research and environmental science share many common interests. Both are attempting to bring together the digital code of inherited information with environmental cues from nutrition, metabolism, lifestyle behaviors, pharmaceuticals, and chemical, physical, and infectious exposures.

Dr. Omenn believes genetics should be prominently included in protocols for health promotion and disease prevention, including host-pathogen interactions and drug and vaccine development, and that population-based studies are necessary to make sense of genetic variation. In his opinion, it would be tragic if extensive knowledge of genetic variation is not used to reduce health risks. Dr. Omenn then described two key findings from a Partnership for Prevention effort with the States on harnessing genetics to prevent disease and improve health. It concluded that: 1) The greatest opportunity of the

genomic era is to use personalized medicine to prevent or better manage chronic diseases; and 2) That genetics and genomics should be integrated into existing health, social, and environmental policies, rather than the establishment of stand alone genetics programs.

Overview of International and National Large Population Studies
Teri Manolio, M.D., Ph.D.
Director, Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute (NHLBI)

Dr. Teri Manolio provided a review of several national and international large-cohort studies and discussed their design. Biobank Japan, which began in 2003, is anticipated to include 300,000 people ages 20 and above. The focus is on 47 common, complex diseases and the goal is to examine their causes and the medication side effects related to genetic variation. Ultimately, it is hoped that new drugs and diagnostics will be developed, both to help the field and to provide a source of financial support for the study. Samples and data are being collected by a network of collaborating organizations and private universities, with 90,000 samples collected to date. Access to the data is limited to Japan and Japanese researchers.

CARTaGENE is a Canadian study that anticipates enrolling about 50,000 people, ages 25 to 74. It focuses on common diseases. GenomeEUtwin is taking place in seven European countries with 800,000 twin pairs. The investigators are focusing on seven key outcomes.

The Estonian project also is trying to find links among genes, environmental factors, and common diseases, with the goal of improving health care. The study began in 2002 and has recruited 10,000 subjects, with plans to enroll 100,000. There is a written informed consent document and subjects complete a 60- to 90-minute questionnaire that includes genealogical information on at least three to four generations. Data collected include height, weight, blood pressure, and heart rate, and a blood sample is taken. Personalized information can be provided to an individual's physician with his/her consent. Those who participate are called "gene donors" and they have access to a website at which they can ask questions about the project.

The Marshfield Personalized Medicine Project in Marshfield, Wisconsin began in 2002 and anticipates enrolling 40,000 subjects ages 18 and above. It is based out of the Marshfield Clinic, which is a large group of private clinics, and uses the Marshfield Epidemiologic Study Area in central Wisconsin, which has a longstanding electronic medical record program. The project requires completion of a written informed consent document and a 30-minute questionnaire as well as DNA and blood extraction. The study is intended to translate genetic data into knowledge that will enhance patient care. It has a large focus on adverse drug reactions.

In Iceland, DeCODE Genetics is a biopharmaceutical company that applies discoveries in genetics to the development of drugs for common diseases. The Icelandic population has been geographically isolated on an island in the North Atlantic for hundreds of years, resulting in fewer variants to study. Because genealogy is an important part of the people's identity, there is an extensive genealogic database extending back to the settlement of the island in 900 A.D.. Many can trace their ancestry back six generations. Scientists can therefore look at two people with the same disease and see how they are

related to one another. The investigators anticipate enrolling the island's entire population of approximately 200,000 people of all ages to study 50 common diseases. Tremendous controversy was generated by this project, primarily because of their proposal for an opt-out consent for access to medical records and a "health sector database" that could be accessed by everyone. This idea was controversial and was eventually abandoned and replaced by written informed consent.

Dr. Manolio described the pros and cons of major cohort studies. They are very expensive, take a long time to conduct, require access to large numbers of people, are broad-based, and are sometimes criticized as "fishing expeditions." However, they provide risk information that cannot be obtained any other way, are understandable to the public and media, and can identify modifiable risk factors for potential preventive interventions. Ideal design characteristics of these studies are: large numbers of subjects; representative samples that can be generalized and are diverse in geography, socioeconomic status, and race/ethnicity (when studying the U.S. population); extensive characterization of exposures, risk factors, and diseases at enrollment; repeated interim measures to assess change in measures taken at enrollment and to add new exposure measures; and a comprehensive, standardized assessment of outcomes. Without these characteristics, biases can be introduced that affect study results and lead to erroneous conclusions.

Dr. Manolio remarked that case-control studies in particular have had problems when appropriate design strategies are not followed. Three assumptions must be made to ensure a bias-free case-control study: 1) the cases must represent all persons who develop the disease or condition; 2) the controls must be representative of the general "healthy" population who do not develop the disease; and 3) the collection of risk factor and exposure information must be the same for cases and controls. The advantages of case-control studies are that: they may be the only way to study rare diseases; existing records often can be used; multiple etiologic factors can be studied simultaneously; they can be less time-consuming and expensive; and if the assumptions are met, the inferences are reliable. The disadvantages are that: data obtained through recall or from records may not be valid; selection of an appropriate comparison group may be difficult; biases may create spurious evidence of associations between risk factors and disease; rare exposures usually cannot be studied; and the temporal relationship between exposure and disease can be difficult to determine.

Dr. Manolio suggested that "nesting" a case-control study within a prospective study might provide the best of both worlds. Collecting and storing biologic samples and images allows the investigator to wait for cases to accrue and then exposures can be measured in a limited sample of non-cases. She said this design can be applied and expanded to other types of study concepts.

Ethical, Legal, and Social Issues of Large Population Studies
Mylene Deschenes, LL.M.
Executive Director, Public Population Project in Genomics

Ms. Mylene Deschenes stated that researchers first looked primarily at single gene disorders and are now increasingly studying common, complex diseases with a focus on national and international collaborations. The field has moved from research on small, traditional biobanks (such as samples in a freezer) to studies that rely on large human genetic research databases (HGRDs). She defined HGRDs as collections of information organized in a systematic way for research purposes and from which genetic material and related data can be derived. Large-scale databases generally include at least 10,000

individuals.

She addressed the current struggle to develop a legal and ethical framework for HGRDs. There is proliferation and specialization of national and international legislation and declarations, some of which have been adopted by various organizations such as the World Health Organization (WHO) and the Human Genome Organization (HUGO). Some countries have implemented legislation that specifically relates to HGRDs, while others apply their pre-existing legislation to all research. This variety of systems is confusing and demonstrates the need for harmonization of principles and terminology across jurisdictions. Several countries, such as Israel, Australia, France, Germany and Canada, are actively addressing these discrepancies in rules and terminology.

Ms. Deschenes stated that the lack of internationally agreed-upon rules is detrimental to research collaboration, database compatibility, and data sharing. Organizations such as WHO are now acknowledging this problem. At the national level, she said there is a need to recognize that HGRDs are not time-limited research projects but rather resources that will be used in the future for multiple applications. Traditional consent and privacy legislation was not written with HGRDs in mind.

Ms. Deschenes said the field needs a coherent and comprehensive regulatory framework that will protect participants and structure the conduct of this large-scale research. A consensus is emerging on the areas that need attention. Traditional consent mechanisms should be changed to take into account the obligations to protect participants' identities over many years. In addition, ethical oversight and monitoring mechanisms should be put in place at the inception of a new database. The professional and public dialogue must be strengthened so that the public can become active participants in the research.

Ms. Deschenes turned to a discussion of the key elements that should be considered when establishing an HGRD. The first element is ensuring the legitimacy of the database by making sure it is well protected with appropriate checks and balances. The use of tremendous financial and other resources must be justified, and the benefits to be provided must be communicated to stakeholders and the media. In countries such as Estonia and Iceland, legislation was passed to establish and legitimize their HGRDs, and the scientists themselves have started other initiatives. They have adapted the science to the community's needs based on open discussion. However, transnational enterprises, such as the HapMap, GenomEUtwin, and the Public Population Project in Genomics (P3G), are more complex; success in these projects depends on trust and communication among the participants based on a common understanding of the scientific, ethical, legal and social issues.

The second key element in establishing an HGRD involves building trust on various levels. Establishing trust with the public depends primarily on communication with the community from the start. Ideally, all groups should be represented in the sampled population. However, the reality is that financial constraints do affect the selection process. Ms. Deschenes remarked that those who collect data should be properly trained and sensitive to the ethical, legal and social issues involved. She said trust also is built through use of an appropriate consent process. Investigators must address the public's concerns in this area. The research team must make decisions about providing individual feedback and about whether to share results with the public. The commercial aspects of the project must be taken into consideration, as matters of free, public access versus intellectual property rights may arise. Industry involvement can provide the financial resources needed for these kinds of studies, but how to involve industry is an

important question that is yet to be answered.

The third element cited was the need to ensure adequate checks and balances in the governing of HGRDs. A project's framework and protocol assessment need a "stamp of approval" from authorities and should have input from the public. Ongoing review procedures should be a component of the project. Ms. Deschenes closed by stating that it is challenging but important for investigators to conduct ongoing monitoring of their research projects and the public resources used, and they must make necessary adjustments to the protocol over time.

Dichotomy between Social Identity and Ancestry in Large Population Studies
Charles Rotimi, Ph.D.
Acting Director, National Human Genome Center, Howard University

Dr. Charles Rotimi spoke on the representation of different groups in large population studies in terms of social identity and ancestry. He explained that investigators seek different "levels of resolution," depending on the purpose of the study. In the case of large-cohort studies, the levels of resolution relate to the characteristics of the population being studied. He said that in the human population, groups of people are socially identified (and self-identify) in an ever-evolving way that reflects political, economic and other non-genetic factors. He believes this idea should be taken into account during study design.

Dr. Rotimi pointed out that understanding the etiology of disease differs from eliminating disparities in health care, although they overlap substantially. He said the prevalence of disease in a certain population might be related to one of these factors or both. It is the responsibility of the scientist to define specifically how one or both are being investigated. In some cases, it is clear that disparities in health care are the primary cause of disease; however the ways in which health disparities play out in different ethnic groups may need to be considered when developing strategies for conducting large-cohort studies.

He reiterated that the design strategy must clarify which variables are being examined, and stated that ancestry is an important variable to consider. He made the point that the ancestral history of African Americans is very broad, representing a diverse genetic history from many countries, yet scientists often group all African Americans together as if their characteristics are uniform and homogeneous. In such cases, group identity is being confused with group ancestry. The same thinking holds true for the "Hispanic population," a label the U.S. Census applies to those with such varying ancestries as Mexico, South America, Cuba, and Puerto Rico. Dr. Rotimi said that individuals typically called "Asian" include those who have ancestors in at least seven countries. He stated that much information is lost when people are grouped together and studied as if they have the same biological ancestry. Dr. Rotimi closed by emphasizing that, when designing large-cohort studies, scientists must acknowledge that there will be some level of compromise in defining the population studied, because ancestry is matter of gradation and not absolute.

The UK Biobank
John Newton, Ph.D.
Chief Executive Officer, UK Biobank

Dr. John Newton spoke on the UK Biobank, an infrastructure designed to support long-term prospective studies of genes and the environment and their relationship to health and illness. This work is possible because of the transformation of biomedical science following the Human Genome Project. Dr. Newton stressed the importance of following up on the results of the Human Genome Project to produce broader science that improves public health. He said prospective studies must begin soon, as it can take 10 or 20 years to obtain meaningful results. However, this urgency should be balanced with careful attention to the quality, value, comprehensiveness and scope of future results. Dr. Newton noted that the study questions have yet to be formulated. He stated that large population studies are feasible and that the public responds well to them.

Dr. Newton then provided more detail on Biobank, which will enroll 500,000 participants ages 40 to 69. The data collected at baseline will include environmental exposures, physiological variables, a neuropsychiatric evaluation, biochemical markers, and biological samples (DNA, blood, and urine). The subjects will be tracked through the U.K.'s National Health Service, the Biobank Corporation's registration data, and records on universal health care coverage. Dr. Newton said these routine sources will help with additional validation exercises for future questionnaires. The project has estimated the number of participants who are likely to develop conditions such as diabetes, coronary heart disease, Parkinson's disease, and rheumatoid arthritis 5 years from baseline. Investigators plan to study the subjects indefinitely over a period of decades.

Dr. Newton explained the scientific objectives of the project, which address public health factors, clinical medicine, and biomarker-disease associations. The first objective is to determine the separate and combined effects of genes and the environment on the common causes of illness through nested case-control studies, prevalence studies, and exposure-based cohort studies. The second objective is to genotype one half million people within 5 years for a limited number of SNPs. Finally, the study aims to identify biomarkers as early risk factors. Dr. Newton said the overall goal of this and other large population studies is to understand disease models in a way that has never before been possible.

Prospective studies, said Dr. Newton, will allow for genetic information to be available for all people in the study, regardless of the severity of disease. In addition, samples taken at baseline will provide proteomic information. The data also will provide a resource for investigating genetic risk factors for various diseases and other determinants of health and disease. Case-control studies that provide information only on the disease being studied, on the other hand, cannot predict these unforeseen outcomes. Additional benefits of prospective studies he cited are the promotion of high standards for ethics and governance in the field, broadened access to expensive research resources, opportunities to collaborate internationally, and their efficient and economic approach.

Most of the approximately $110 million of funds for the Biobank (about one percent of the amount spent on biomedical research in the U.K.) is from the Medical Research Council and the Wellcome Trust, a large biomedical research charity. Other funders include the Department of Health and Scottish Executive. Dr. Newton stated that the value of the resources available in Biobank will increase

continually as time passes.

Biobank is an independent company that receives advice from a separate Science Committee and a separate Ethics and Governance Council. Implementation will be conducted by six regional collaborating centers that represent scientific groups around the country, including 22 universities. Dr. Newton explained that the system was developed with an emphasis on process and project planning in its early stages. The project uses modern, efficient methodologies in patient recruitment, data collection, information technology (IT), genotyping, and genomics. There is strong central coordination and distributed scientific collaboration.

Dr. Newton addressed recruitment processes, stating that direct mail will be used to attract participants. The project will start slowly in the first year to ensure that sound procedures are in place before it is implemented on a large scale. Subjects will enter Biobank through the dedicated clinic that will conduct data collection. Samples and data will be transported to a central resource and archived. The blood will be stored in a way that makes it possible to do genetic, proteomic and metabolic studies. Dr. Newton said data management systems are in development by commercial suppliers who are being advised by experienced researchers.

Dr. Newton stated that Biobank participants will be volunteers who can withdraw at any time. They will be asked to provide broad consent to future use and assured of data security and confidentiality. Biobank will retain control of the samples, but there will be full access to the data for appropriate purposes. Biobank will have internal and external reviews of the science and ethics of potential uses.
Dr. Newton emphasized the importance of collaboration and said others should be encouraged to conduct similar studies. The systems used, however, must have the ability to interact with one another. He made the point that large-scale studies are more easily conducted in countries with universal health care coverage, such as Canada and the Scandinavian countries.

Dr. Newton displayed the timeline and provided an update on Biobank activities. The main study will be started in January 2006. They are currently piloting the clinical and molecular processes, establishing the IT infrastructure and clinical applications, developing a recruitment strategy, writing the protocol and questionnaire, refining the ethics and governance framework, and implementing laboratory processes. Dr. Newton closed by citing the unique features of Biobank, which include its size, unprecedented biological resources, the ability to recall subsets of individuals for intensive phenotyping, extensive use of written records, and an ethical approach that encourages public participation.

Federal Perspectives on the Need for a Large Population Study

Ruth Brenner, M.D., M.P.H.
National Institute of Child Health and Human Development (NICHD)

Dr. Ruth Brenner spoke on a large-scale Federal study known as the National Children's Study, which was authorized by the Children's Health Act of 2000. The Act authorizes NICHD to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development. This national prospective cohort study, to be conducted by a consortium of multiple agencies, will begin prior to participants' birth and continue

through age 21. The study is hypothesis-driven with primary outcomes related to child health and development.

The focus is on children because they have an increased vulnerability to environmental exposures, critical windows of vulnerability during development, immature mechanisms for detoxification and protection, and differences in metabolism and behavior that may yield higher exposure than adults in the same environments. The study is being conducted now because of the increasing concern about numerous exposures, diseases, and conditions of children, coupled with the fact that technological capabilities now make it possible. The longitudinal study design will allow inferences about causality, the study of multiple outcomes, multiple exposures, and mediating pathways between exposure and disease. Recall bias in relation to exposure will be minimized.

Dr. Brenner reviewed recent milestones and the study's current status. The decision to use a national probability sampling method was made in 2004. In the first stage, 101 study locations were drawn from a list of all counties in the U.S. In the second stage, the investigators will be selecting segments or groups of households within the study locations. They anticipate having a highly clustered sample to facilitate the study of community characteristics and to increase logistical efficiency. Dr. Brenner remarked that from the initial list of study locations, eight were selected to serve as potential vanguard locations.

The study will enroll women and their partners prior to or early in pregnancy, with follow up of children until 21 years of age. Enrollment will take place over a 4-year period and data will be collected through face-to-face visits and remote data collections. Data will be collected via questionnaires and interviews, environmental samples and observations in the home and community, clinical and behavioral assessments, and biologic samples (blood, urine, cord blood, placenta, and breast milk). Dr. Brenner stated that the initial centers will probably be selected in late 2005 and the initial protocol will be completed and piloted in 2006. It is hoped that the first participants will be enrolled in early 2007.

The investigators plan to continue to hold meetings, peer reviews, workshops, and consultations. In September 2004, they held a workshop on the collection and use of genetic information that brought together experts in the Federal Government (NIH, EPA, CDC, and FDA) to explore opportunities and challenges and to provide recommendations to NCS. The workshop focused on the appropriate collection and storage of biologic samples. Dr. Brenner closed by stating that the workshop report and recommendations will be available on the NCS website.

Stephan D. Fihn, M.D., M.P.H.
Department of Veterans Affairs

Dr. Stephan Fihn spoke about the early stages of the proposed VA Genomic Medicine Program, an idea that has been evolving in the VA for 2 to 3 years. The goals would be to research the role of genetic factors in the cause and prevention of disease; develop clinical programs targeting therapeutic drug response and preventing adverse reactions; and develop information systems to confidentially manage genetic data for patient care and research. Dr. Fihn pointed out that the VA is interested in this project because their system is the largest integrated health care system in the U.S. and possibly in the world. In addition, the VA has a very stable patient population. The approximately 5 million users have electronic health records that contain copious amounts of data. There also is a large intramural research program at

the VA that currently has many investigators working in genomics on a small scale and a number of existing resources that could be used, including several sanctioned DNA repositories.

Since it is a Federal health care system, the VA would insist on absolute control and ownership over all materials and information gathered. They have a stringent set of policies for human subjects protections, intellectual property, conflict of interest, privacy, and scientific merit evaluation process in place. They are in the process of designing additional protections that would involve an independent oversight board composed of both Federal and private representatives.

Dr. Fihn closed by describing the challenges they face, such as the protection of confidentiality, the development of collaborations with other researchers, funding, intellectual property issues, and decisions on the types of specimens to acquire.

Alan Guttmacher, M.D.
National Human Genome Research Institute

Dr. Alan Guttmacher spoke on the working concept known as the American Gene-Environment Study (AGES). He explained that it is not actually a study, but a large resource that would be available to the research community. He said there are various approaches to discovering and quantifying genetic and environmental contributions to disease risk, and among them are case-control studies and prospective, population-based cohort studies. Dr. Guttmacher said that although case-control studies have benefits, they also have several shortcomings, including a frequent bias toward the more severe end of the disease spectrum, a recall bias for environmental exposures and family history, and an inability to identify predictive biomarkers that signal the future onset of disease.

Although other countries are planning large population studies of genes, environment, and health, Dr. Guttmacher stated that these will not adequately substitute for a major project based in the U.S. The primary reasons are that other countries do not reflect the population groups or the environmental factors found in the U.S. and that access to data from other countries' studies by U.S. researchers will be limited.

Dr. Guttmacher said that an AGES Working Group was convened during the previous 6 to 9 months to consider a U.S. prospective cohort study. He listed the group's major recommendations, as follows: 1) the cohort should be chosen to match the most recent U.S. Census on the characteristics of age, sex, race/ethnicity, geographic region, education, and urban/rural residence; 2) the household should be the primary sampling unit and roughly 30 percent of cases should consist of biologically-related individuals. The cohort also should be of significant size to achieve adequate power for most common diseases and quantitative traits, although he said it is not easy to determine the ideal number of participants. The Working Group recommended a clinical exam with a 4-hour baseline assessment. During the exam, a core group of measures should be collected on all participants, with other measures collected that are age-specific.

Biological specimens should have core laboratory measurements taken and undergo genotyping/DNA sequencing. Dr. Guttmacher explained that follow-up telephone or e-mail contact should occur every 6 months, with re-examination every 4 years. Public consultation should be extensive, through such means as town meetings and focus groups. The investigators should seek open-ended informed consent and have

an encrypted database to protect privacy and confidentiality. He said that, although it would be challenging, a central institutional review board (IRB) would be highly advantageous. The data should be immediately accessible to all investigators who have IRB approval.

Muin J. Khoury, M.D., Ph.D.
CDC Office of Genomics and Disease Prevention

Dr. Muin Khoury spoke on building the knowledge base on genes and population health and provided his perspective on the need for global collaboration. He emphasized three key messages: 1) the need for global collaboration in biobanks and population-based cohort studies, because pooled analyses will increase the chance of finding true associations relevant to public health; 2) the need for systematic integration of all human genome epidemiology studies, regardless of the type of study design; and 3) the need for evidence-based processes that use human genome epidemiologic data to assess the value of genomic information in health care and disease prevention. He stated that epidemiological data can be used to characterize the prevalence of gene variants in a population and help determine how these factors affect the relative and absolute risks for disease.

Dr. Khoury discussed the myth that association studies are inferior. He explained that some association studies have not been designed well, with problems such as the cases and controls coming from different populations that are not comparable. These poor quality studies have led some in the field of genetics to dismiss all association studies, which is unfortunate. He also addressed the misnomer that cohort studies are inherently superior to case-control studies. He stated that a well-designed population-based case-control study is far superior to a poorly-designed cohort study and that case-control studies can be very valuable, especially for rare outcomes.

Dr. Khoury said CDC has been working with global partners since 2001 to understand human genome academiology by gathering and analyzing literature on the subject. He reported that more than 15,000 association studies, mostly case-control, have been published in the past 3 years. An increasing number of studies focus on gene-gene and gene-environment interaction, and some provide prevalence data on different genetic variants in populations. CDC is analyzing a 5 percent random sample of this database of literature to examine the quality of the association studies.

Dr. Khoury described CDC's collaboration with NIH to estimate the prevalence of the top 50 genes of public health significance using a sample of approximately 8,000 individuals who participated in NHANES. He gave another example of a population-based, case-control study that uses surveillance systems to examine the association between genes and environment and birth defects.

Concerning the need to integrate epidemiologic evidence on genes and population health, Dr. Khoury said there are now unmanageable amounts of data, but the sample sizes are small in individual studies and there are small, expected effect sizes for gene-disease associations. Most genes are not expected to contribute by themselves to the etiology of the diseases studied. Large sample sizes and replication across studies are needed to discover the relative risks or odds ratios.

Dr. Khoury stated that the knowledge base on genes and population health can be built through the following approaches: a single large population cohort study; systematic synthesis of data from existing

and planned cohort studies; systematic synthesis of data from all epidemiologic studies (cohorts, case-control, other); accelerated systematic synthesis of group and individual data using collaborative networks; and consortia of all types of studies (cohorts, case control, other).

He then described the Human Genome Epidemiology Network (HuGENet), developed by CDC and many partners in 1998. HuGENet is a global collaboration of individuals and organizations formed to assess the population impact of genomics and determine how this emerging field can be used to improve health and prevent disease. The network currently includes about 700 people from 40 countries and it is open to anyone who wants to join. They provide technical assistance and training through workshops and have been developing a knowledge base so that information can be disseminated for both policy and practice purposes. Dr. Khoury said they have been sponsoring systematic reviews of gene disease associations in collaboration with six journals and have a database of 200 meta-analyses of other gene disease associations. HuGENet is developing an information-sharing system among 14 other networks around the world, some of which study cancer or heart disease. HuGENet also is collaborating with various biobanks.

Dr. Khoury described a CDC meeting held in Atlanta in collaboration with P3G and NIH to discuss the harmonization of epidemiologic data. It resulted in a statement, currently in development, about the publication of studies that will be derived from biobanks. The statement is related to a worldwide movement for standards for epidemiologic studies outside genetics. This collaboration is trying to influence the conduct of biobank projects and studies through the development of similar criteria.

Roundtable Discussion with Session Participants

Dr. McCabe began by asking Dr. Brenner and Dr. Guttmacher how they would address the barriers created by the numerous IRBs that would necessarily be involved in a multi-center, large population study. Based on his experience, he cited the IRBs in community hospitals as particularly problematic. Dr. Guttmacher acknowledged the challenges in this area, but suggested that a somewhat centralized IRB mechanism that would allow for the roles of individual institutions and local communities was a possible approach. He stated that the issue raised by Dr. McCabe also has become a concern for biomedical researchers, as multi-center studies have become more common. He stated that the non-genetics communities have looked at the question of centralizing large studies and have begun to develop some models that would provide guidance. Dr. McCabe stated he wanted to highlight this barrier in the report if it moves forward.

Dr. Fitzgerald asked whether the speakers believe that the public, whom several described as in favor of large population studies, actually understand the implications of the risks and benefits, such as the harmonization of various databases. He noted the variability of numerous subpopulations and subgroups, who may see these projects differently, and asked to what extent does their input they influence these projects. Dr. Newton said there are different levels at which public perspectives are considered, from the study participant level to the public at large. He also noted that direct access is available to the various institutions that represent the public and speak on their behalf. Dr. Rotimi added that those in the community who safeguard the public's interest should be involved in the design phase. Dr. Deschenes commented that to be respectful of communities, investigators should talk with the community first, before trying to exchange with other biobanks.

Dr. Winn-Deen commented that Dr. Brenner was the only speaker who mentioned that an act of Congress was needed to fund his study. She asked about the mechanism by which this took place and whether he thought it would be required for other large studies. Dr. Brenner replied that the Children's Health Act authorized the study but did not fund it. Dr. Guttmacher said that innovative techniques would be required to obtain funding for a large-scale study, such as a public/private partnership. Dr. Manolio stated that the Women's Health Initiative also was funded that way.

Dr. Tuckson asked Dr. Brenner whether funds have been appropriated for the National Children's Study and she replied that they have not. Existing agency budgets have provided for initiation of the study, but additional funding will be required by 2006.

Ms. Barbara Harrison asked Dr. Rotimi his opinion on whether "race" is still valid to use when sampling populations and, if so, how to use it. Dr. Rotimi said the way to use the concept depends on the research questions. The study design must include under its umbrella the variables the investigators want to measure. Ms. Harrison asked Dr. Guttmacher how to address the fact that, unlike the populations in some of the studies described, many in the U.S. do not use medical institutions for their health care and, therefore, cannot be recruited by that means. Dr. Guttmacher stated that he sees the household as the recruitment unit, which avoids the bias of using medical centers that many people do not access. He commented on the issue of race by saying that even though the social definitions of race are limited, they are so widely accepted that they are useful in reflecting the spectrum of American society. Dr. Goldstein added that if investigators want information about all racial and ethnic groups, they must think carefully about the ways to represent each group in the sampling design.

Dr. Tuckson asked whether NIH, CDC, and the other Government agencies present were working together on the issue of large population studies, including a plan to coordinate resources and approach the Secretary. Dr. Guttmacher and Dr. Khoury replied that extensive conversations have taken place among the agencies and their efforts would interrelate and be complementary. Dr. Tuckson then asked if any document had been prepared for the Secretary's review that would illustrate how the pieces would come together, and the response was no. Dr. May asked if all the agencies are funded through the same appropriations committee. Dr. Guttmacher responded that they are, with the exception of the VA.

Dr. Telfair asked about the extent to which the presenters are engaged in evaluation activities, specifically formative evaluation. He wondered whether the investigators would be analyzing the process along the way. Dr. Newton said that evaluation is taking place at every level in their company and that long-term evaluation is considered important. Dr. Guttmacher stated that they have planned an extensive evaluation that that will coordinate longitudinal science with clear benchmarks along the way.

Dr. Leonard asked whether there would be access to specimens and whether the investigators plan to sequence and map the haplotypes of all the genomes of the all participants and make that data available. She also asked if specimens would be collected over time. Dr. Guttmacher replied that, as the science advances and depending on the costs, they hope to do sequencing and store genotypic data that could be shared with those who have IRB approval. He said that it would be more difficult to share specimens because of financial considerations and fixed volume, but that there may be ways to do it. Dr. Newton said they are trying to predict the volume of specimens will be needed to meet the needs of researchers. Their samples will be sent to a small number of accredited laboratories that will use only very small

amounts. The investigators plan to obtain more samples from participants over time, although they may not be the same samples for everyone.

Committee Discussion

Dr. Willard asked if the Committee needed additional information before developing recommendations for the Secretary on the issue of a large population study. He noted that the idea of a national or global IRB had been raised and asked if there were any related comments. In response, Dr. Michael Carome provided the perspective of the Office for Human Research Protections on the use of central IRBs for multi-center trials. He said the Office's regulations have a provision that allows for cooperative or joint review arrangements for multi-center trials. In recent years, these joint arrangements have become increasingly useful, as the number of such trials has increased and many IRBs are overburdened. He said there is no benefit in having duplicate reviews of the same study at numerous IRBs. He noted key factors that centralized IRBs should take into consideration, such as gaining an understanding of the local context at the site of the research and finding appropriate individuals to review who do not have conflicts of interest. Dr. Carome said the kind of model discussed during the morning sessions could be implemented with no regulatory or policy changes within OHRP. He described the major barrier to this model as those institutions and major medical centers that are not willing to accept an IRB review from another entity. Their reasons for resistance are a mix of cultural, sociological and legal factors. Dr. McCabe agreed that the culture of these institutions is a significant problem and that to conduct the kind of genomic studies needed, the local IRBs need education to understand that national experts can perform better reviews. He pointed out that such an educational effort could be recommended to the Secretary.

Dr. McCabe commented that the presentations were exciting, and that although it is critical to build on the knowledge gained through the Human Genome Project, he did not feel that he had enough information to recommend a large population study to the Secretary. Dr. Fitzgerald also expressed concerns and asked the Committee what kind of information they would need to go forward.

On the subject of public consultation, Dr. Fitzgerald asked whether data exists on the best approaches to engage the public and whether investigators had looked extensively at that data. He felt that this type of information could provide guidance on how to include the public in the design process. Other complex questions also must be addressed during the design stages, such as who will have access to new treatments as they are developed. Dr. McCabe mentioned the focus groups model used by the Genetics and Public Policy Center for engaging the public. They have a scientific approach that they believe provides the right balance of information. Dr. Fitzgerald noted that there are other groups using a similar model, such as the focus groups and town hall meetings used by Canadians to examine some of their health care issues. He recommended gathering information from these groups to inform the process under discussion.

Mr. Berry suggested making a recommendation to the Secretary that all HHS public awareness campaigns address the issue of genetics from their inception. She cited recent campaigns on obesity, cardiovascular disease, and women's health, and said future programs could involve a commitment to fund genetic studies and keep the public aware of the significance of genetics. Dr. Guttmacher suggested that the Committee might be better served by calling the importance of large population studies to the Secretary's attention, but felt they should hold back from recommending specific study design issues. He

said the emphasis should be on the potential value of these studies and on general design issues that would make a study effective. He agreed that the issue of community consultation is key.

Dr. Khoury stated his belief that the Committee was well situated to recommend an initiative to the Secretary that takes the Human Genome Project to the next level. He said that his Office tries to integrate the messages of genomics into every project, in the manner Ms. Berry suggested. He expressed the opinion that the Committee should encourage HHS to develop agency-wide collaborations to determine how the human genome influences health and to address the number of studies that should be conducted.

Dr. Tuckson noted that a letter to the Secretary must be specific concerning the study's aims, coordination of resources, and planned deliverables, and he asked the group to comment on the level of detail that should be included. Dr. McCabe said he believed multiple studies would be necessary, but the question of how many studies and how they should be prioritized must be examined. He suggested, and Dr. Tuckson agreed, that the letter address the idea of a public/private partnership and would like to see an investment up front from the private sector. Dr. Winn-Deen recommended a three-phase approach: review the valuable work that has already been done, find knowledge gaps, and fund studies to fill the gaps, funded by the Government or possibly through a public/private partnership. Dr. Willard asked what level of information Dr. Winn-Deen would like to see in the review of the studies. She replied that she was referring to state-of-the-art information pulled together in one coherent document. Dr. Willard suggested reviewing the NIH Working Group document rather than creating a new document. He said the Committee could then take into account ongoing activities within NIH and CDC, which might inform their thoughts on an HHS-wide initiative.

Dr. Tuckson returned to Dr. Fitzgerald's question about public participation. Dr. Fitzgerald said that efforts to engage the public could be considered one of the gaps that must be further addressed. Dr. Willard emphasized that the American people may not be ready to trust that their sensitive medical and genomic information would be handled with appropriate confidentiality. He said the public should be extensively involved in any plans to conduct a study that could enroll a million or more Americans from many different racial and ethnic groups. Dr. Leonard also voiced concerns that the American people may lack trust in scientists and the Government. Dr. Fitzgerald returned to the idea of the need for town hall and focus group meetings as a way of creating a dialogue with the public to build trust.

In summarizing the discussion, Dr. Tuckson said the Committee feels strongly that this initiative should move forward and that a letter should be written to the Secretary. The task force could generate a first draft of a letter that describes support for the three-phased approach proposed by Dr. Winn-Deen. The letter could emphasize that one of the identified knowledge gaps is public input and the need to gain the trust of the American people. It also might call for the use of both public and private dollars, while addressing the relationship between the public and private sectors.

Continued Discussion on Coverage and Reimbursement of Genetic Tests and Services

Dr. Tuckson asked the Committee to consider billing and reimbursement of genetic counseling services. He asked the Committee to consider whether to make a recommendation stating that genetic counseling providers should be able to bill independently. In addition, he asked them to consider whether this would apply to all payers or only to public insurance. He said that if the Committee supported this

recommendation, the next issue would be the method for implementation, i.e., whether direct billing should be allowed only in States in which licensure is available. And, in States in which licensure is not available, should certification by ABGC or GNCC be used as the standard for direct billing? As an alternative, he asked, should the Secretary establish a body to oversee certification of non-physicians providing genetic counseling? Dr. Tuckson added that if the Committee were to decide against a recommendation for direct billing, would to the Committee recommend creation of a body to conduct further analysis and research on the matter.

Dr. Tuckson asked the Committee to vote on the recommendation. Dr. Leonard, Ms. Harrison, Dr. Kimberly Fries, Ms. Masny and Dr. Fitzgerald supported direct billing. Ms. Berry agreed with the recommendation but pointed out that the Secretary does not have authority to allow providers to bill Medicare without first working with Congress to change legislation. Dr. Rollins, Dr. Telfair and Dr. Willard believed stronger evidence is needed that demonstrated non-physicians can make determinations more effectively than other groups.

Once all Committee members weighed in on the issue, Dr. Tuckson led the group in crafting wording for the draft recommendation. He stated although there were differences in the Committee members' opinions, they all agreed that the Secretary should be involved in the matter and that more information should be gathered. Dr. Fitzgerald suggested that they could recommend multiple steps. First, genetic counselors and nurses certified by ABGC or GNCC could serve as the starting point for those who can bill directly. Dr. Tuckson added that the Secretary could then use his influence to establish a body with the appropriate knowledge and training to develop the requirements, conditions, and processes for those who are not credentialed. The certification processes currently in place could inform this body's work.

Ms. Berry described the model by which registered dieticians were able to obtain coverage under Medicare to provide medical nutrition therapy for some indications. Ms. Berry suggested that the Committee could ask the Secretary to direct NAS or another health research organization to fund a similar study on genetic counseling services. Dr. Feetham suggested building this effort on the 3-year study of the genetic workforce funded by HRSA and NIH. The Committee agreed that this would be an expeditious approach.

Dr. Tuckson stated that the following draft recommendations would be included regardless of the Committee's decisions about the above issue:

1. The Secretary should direct Government programs to reimburse prolonged service codes when determined to be reasonable and necessary.

2. Further, HHS, with input from the various providers of genetic counseling services, should assess the adequacy of existing CPT E&M codes and their associated relative values with respect to genetic counseling services. Any inadequacies identified should be addressed as appropriate.

3. Non-physician health providers who are currently permitted to directly bill any health plan, whether public or private, should be eligible for a National Provider Identifier.

4. The Secretary should direct CMS to allow non-physician health professionals who are

qualified to provide genetic counseling services and who currently bill incident to a physician to utilize the full range of CPT E&M codes available for genetic counseling services.

The Committee moved on to discuss the final two draft recommendations. The first states that the medical workforce needs ongoing training in genetics and genomics to adequately care for patients and reiterates SACGHS' recommendations made to the Secretary in 2004 encouraging HHS to work with State, Federal, and private organizations to provide tools to health providers to ensure such education and asks that HHS incorporate genetics and genomics in its initiatives. The Committee unanimously agreed to this draft recommendation.

The final draft recommendation recognizes the insufficiency of reliable knowledge available to the public to help them make medical decisions related to genetics and genomics. It recommends that such information be developed so that patients and health providers can make responsible decisions. It also recommends the development of performance and efficiency measures to evaluate the quality and safety of genetic tests and services. The Committee amended the language to recommend to the Secretary that more guidance and education on genetics, genomics and family history be made available to the public through Government websites.

Ms. Berry said that Committee members could continue to provide input via email for a period of time. Dr. Tuckson suggested that comments developed after the meeting should be emailed to all members of the Committee so that the members would be aware of each other's edits. He also reminded the Committee that the reimbursement report would go out for public comment prior to the June meeting. Additional changes will be made once feedback is received from the public.

Public Comments

Susan Manley, M.S., CGC
National Society of Genetic Counselors

Ms. Susan Manley, Chair of the Professional Issues Committee of the National Society of Genetic Counselors, stated that NSGC represents over 2,000 genetic counselors who practice in various medical specialties, as well as in academia, research and biotechnology activities. She stated that Masters-trained genetic counselors make up more than 50 percent of practicing genetic specialists and therefore provide the majority of these types of services. She acknowledged that more studies are needed to define the value and cost-effectiveness of genetic counseling services; however, she said that many examples of this value were provided in the previous day's invited testimony. Ms. Manley stated that reimbursement is critical, particularly for Masters-trained counselors, as lack of reimbursement will continue to prevent access to quality services nationally and compromise public health. She stated that NSGC strongly encourages the Committee to continue to develop recommendations that support the recognition of non-physician genetic service providers. She also hoped SACGHS would advocate for the development of CPT coding specific to genetic counseling, for third-party payers and CMS recognition of the importance of reimbursement, and for studies that assess the value and cost-effectiveness of genetic counseling provided by non-physicians. Dr. Tuckson encouraged her to work with her colleagues to provide detailed suggestions on these matters to inform the public discourse.

Stephanie Mensh

Consultant to the Advanced Medical Technology Association (AdvaMed)

Ms. Stephanie Mensh stated that AdvaMed represents manufacturers of diagnostic and genetic tests and other medical devices. She said her organization believes that Medicare's policy on genetic tests will have a significant impact on access. She noted the Medicare Modernization Act (MMA) addresses how new tests are paid for under the Medicare Clinical Laboratory Fee Schedule and lays outs plans for a thoughtful and transparent process. AdvaMed has offered in its policy statement on this issue suggestions for additional regulatory provisions. Ms. Mensh stated that the notice of proposed regulation on implementation is expected to come out in late spring or early summer. She requested that the Committee document their support for these new provisions.

Maureen Smith, M.S., CGC
NUgene Project, Center for Genetic Medicine, Northwestern University

Ms. Maureen Smith spoke on behalf of the NUgene Project, a genetic banking study in Chicago that began in 2002. It is a population-based initiative that is developing a diverse collection of samples and information to facilitate biomedical research on the genetic and environmental factors that contribute to health and disease. NUgene combines a centralized genomic DNA sample collection and storage system with the ability to regularly update participants' health status and retrospective and prospective data from electronic medical records. It was initially funded by Northwestern, and its health care partners include five hospitals and numerous outpatient clinical sites throughout the Chicago area. They have IRB approval and a certificate of confidentiality from NIH. Although their experience has been that the public is interested in participation in studies of this type, Ms. Smith said the investigators continuously examine ethical, legal, and social issues. They served as the site for the Department of Energy-funded study of informed consent for population-based genetic research and are now in the process of publishing that data. She said their work has begun to demonstrate the value of large collections of data for research. Ms. Smith stated that her institution believes that U.S.-based population repositories should be further developed into a national, not-for-profit consortium.

Mary Steele Williams
Director of Scientific Programs, Association of Molecular Pathology (AMP)

Ms. Mary Williams spoke on behalf of the Association for Molecular Pathology, an international not-for-profit education society that represents more than 1,200 physicians, doctoral scientists, and other professionals from both the public and private sector who perform molecular and genetic testing. She stated that AMP strongly supports the draft recommendation in the coverage and reimbursement report that requests CMS to review and revise reimbursement practices for molecular CPT codes. She said that as the number of available genetic tests increase, laboratories will not be able to continue absorbing the losses associated with those tests. Ms. Williams also reported that AMP is strongly supports limiting the definition of a genetic test to heritable germline variations, i.e. not including somatic variations. She said that if a genetic test is broadly defined as any molecular biology-based test, a distinction will need to be made between the ethical, social, and regulatory issues that apply to heritable genetic tests and those that apply to testing for somatic mutations. Dr. Williams also stated that AMP also supports the ability of genetic counselors and medical geneticists to directly bill for services. She concluded by asking SACGHS to give full consideration to the negative impact of exclusive licensing and enforcement

practices for gene patents.

Summary Report from the Conference on Promoting Quality Laboratory Testing for Rare Diseases: Follow-up and Future Activities

D. Joseph Boone, Ph.D.
Assistant Director for Science, Division of Laboratory Systems, CDC
Stephen C. Groft, Pharm.D.
Director, NIH Office of Rare Diseases (ORD)

Dr. Joseph Boone reported on a conference held in May 2004 on quality laboratory testing for rare diseases, held jointly by CDC, NIH, HRSA, Emory University, and several professional genetics organizations. He said that, for many rare conditions, testing is available only in a foreign laboratory or from research laboratories. The conference addressed the quality of these laboratories. Primary concerns included patient testing conducted without a Clinical Laboratory Improvement Amendments (CLIA) certificate and the translation of genetic research findings into clinical practice. Dr. Boone noted that the U.S. is falling behind in the development of genetic tests.

One result of the conference was the formation of the North American Laboratory Network for Rare Disease Genetic Testing. The network is comprised of laboratories that are CLIA-certified. They will be working collectively to increase the development of new tests. In addition, the American Society of Human Genetics and OHRP agreed to provide education to researchers and IRBs. A second conference is planned in September 2005.

Dr. Stephen Groft stated that a number of discussions have taken place since the May conference to identify the major concerns of the target audiences attending the September meeting, He noted that the key groups that need to be involved in the effort have come together. Efforts are underway to prioritize the development of genetic tests for rare diseases and expand the intramural research program at ORD. The Office is looking for partnership opportunities within the NIH system so that the development of genetic tests can be expanded.

Dr. Groft said they hope to achieve better health outcomes, including improved follow-up and support for the individuals tested, as a result of increased access to rare disease tests. They define success, in part, as recognition by the health care system in terms of private and public payers being willing to cover the expenses of genetic testing. They hope to evaluate their successes through pre- and post-surveys of laboratories, consumer and advocacy groups, and CMS and other payers. They also will be monitoring the quality of the new tests that become available.

Discussion

Dr. Willard asked how priorities will be established for the development of testing for rare diseases. Dr. Groft said they hope to start with research that is already taking place and move these efforts forward to clinical applications. Dr. Boone said the private sector is very involved, is receiving funding from the

rare disease communities, but does not have enough capacity to develop new tests as quickly as the public would like. Dr. Groft added that their group will not be entirely responsible for developing priorities for test development. They are looking for a cooperative effort that involves patient advocacy groups, laboratories, NIH, CDC, and other Government agencies.

Dr. Zellmer asked if the barriers to the development of new tests are primarily the lack of laboratory capabilities, financial constraints, or both. Dr. Groft said there are numerous factors contributing to the barriers and it would be hard to pinpoint them.

Closing Remarks

Dr. Tuckson summarized the status of various Committee activities prior to adjournment:

- Concerning the tasks related to genetic discrimination, he stated that the DVD script was approved and he had completed the narration. The public comments for the Secretary were being collected and would soon be ready to move forward. A letter to the Secretary will ask for a stakeholder meeting to broker differences on the topic of genetic discrimination.

- Concerning the health information infrastructure, the Committee would be sending a letter to thank Dr. Brailer and to remind him of the importance of family history issues and genetics and the need to incorporate them in EHRs.

The meeting was adjourned.

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.

Reed V. Tuckson, M.D.
SACGHS Chair

Sarah Carr
SACGHS Executive Secretary