Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Twelfth Meeting
March 26-27, 2007
Bethesda, Maryland

Committee Members Present

Reed Tuckson, M.D., Chair
Sylvia Mann Au, M.S., CGC
Cynthia Berry, J.D.
Chira Chen
James P. Evans, M.D., Ph.D.
Andrea Ferreira-Gonzalez, Ph.D.
Kevin FitzGerald, S.J., Ph.D., Ph.D.
Julio Licinio, M.D.
Barbara Burns McGrath, R.N., Ph.D.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Steven Teutsch, M.D., M.P.H.
Huntington F. Willard, Ph.D.
Marc S. Williams, M.D., FAAP, FACMG

***Ex Officios*/Alternates Present**

Gurvaneet Randhawa, M.D., M.P.H. (HHS/Agency for Healthcare Research and Quality)
Muin J. Khoury, M.D., Ph.D. (HHS/Centers for Disease Control and Prevention)
James Rollins, M.D. (HHS/Centers for Medicare & Medicaid Services)
Steven Gutman, M.D., M.B.A. (HHS/Food and Drug Administration)
Denise Geolot, Ph.D., R.N. (HHS/Health Resources and Services Administration)
Francis S. Collins, M.D., Ph.D. (HHS/National Institutes of Health)
Alan Guttmacher, M.D. (HHS/National Institutes of Health)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Anand Parekh, M.D., M.P.H. (HHS/Office on Public Health and Science)
Michael Carome, M.D. (HHS/Office for Human Research Protections)
Martin Dannenfelser (Administration for Children and Families)
Michael Amos, Ph.D. (Department of Commerce)
Scott McLean, MC, USA (Department of Defense)
Peter T. Kirchner, M.D. (Department of Energy)
Matthew Daynard, J.D. (Federal Trade Commission)
Amy Turner, J.D. (Department of Labor)
Sherrie Hans, M.D., Ph.D. (Department of Veterans Affairs)
Peter Gray, J.D. (Equal Employment Opportunity Commission)

Executive Secretary

Sarah Carr, NIH Office of Biotechnology Activities

MONDAY, MARCH 26, 2007

Welcome and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, Chair of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), welcomed those in attendance and stated that the public was made aware of the meeting through notices in the Federal Register, as well as announcements on the SACGHS website and listserv. Dr. Tuckson introduced the newest Committee member, Dr. Marc Williams. Dr. Williams is a board certified clinical geneticist and Director of the Intermountain Healthcare Clinical Genetics Institute in Salt Lake City, Utah. He chairs the Committee on the Economics of Genetic Services for the American College of Medical Genetics (ACMG) and is Editor-in-Chief of the Manual on Reimbursement for Medical Genetic Services. Dr. Tuckson welcomed two members of Secretary Michael Leavitt's key staff, Sheila Walcoff, Counselor to the Secretary for Science and Public Health; and Dr. Greg Downing, Program Director of the Secretary's Personalized Health Care (PHC) Initiative. Dr. Tuckson also welcomed Robert Kolodner, the Interim National Coordinator for the Office of Health Information Technology, and Ms. Jodi Daniel, the Office's Chief of Policy and Research.

Dr. Tuckson described the original priorities decided upon by the Committee in 2004 and provided an update on relevant achievements and activities. In the area of genetics education and training of health professionals, the Centers for Disease Control and Prevention (CDC) began an initiative known as Genetics for Early Disease Detection and Intervention (GEDDI) designed to educate the public and providers about genetically based disorders that, if detected early, could lead to interventions that improve outcomes. The American Nurses Association (ANA) and the International Society of Nurses in Genetics (ISONG), in collaboration with other nursing groups, published a set of core competencies for the nursing community. The National Coalition for Health Professional Education in Genetics (NCHPEG) was targeting their efforts toward speech language pathologists and audiologists and developing new programs for physician assistants and dieticians. NCHPEG was also developing a database to provide concise, clinically relevant genetics information to nongenetics professionals at the point of care.

In 2006, the Committee transmitted a report and recommendations to the Secretary on coverage and reimbursement of genetics tests and services. In June, Dr. Tuckson and Ms. Cindi Berry had briefed Mark McClellan, then-Administrator for the Centers for Medicaid & Medicare Services (CMS), on key issues in the report. Mr. McClellan and his staff expressed a strong interest in advancing the report's recommendations.

In 2005 and 2006, SACGHS wrote letters to the Secretary on direct-to-consumer (DTC) marketing of genetic tests. These efforts led to enhanced collaboration among the Food and Drug Administration (FDA), CDC, CMS, the National Institutes of Health (NIH), and the Federal Trade Commission (FTC). In July 2006, FTC issued a consumer alert on at-home genetic tests. Dr. Tuckson stated that, according to Matt Daynard, FTC *ex officio*, web hits on the alert on the FTC website totaled 6,461. In addition, almost 12,000 copies of printed brochures that included the alert were distributed. The consumer alert was widely covered in the media, with stories disseminated through the Wall Street Journal, the New York Times, U.S. News and World Report, Contra Costa Times, American Healthline, the FDA News, Medical Device Week, and on National Public Radio.

Dr. Tuckson announced that the report, *Policy Issues Associated with Undertaking a New Large U.S. Population Cohort Study of Genes, the Environment, and Disease* had been transmitted to the Secretary earlier in the month. Copies of the printed version were made publicly available. Dr. Tuckson extended thanks to Dr. Hunt Willard, Chair of the Task Force on Large Population Studies, and to the entire Task Force for guiding the effort through a long and difficult fact-finding and consultative process. He also thanked the many experts who helped broaden the Committee's understanding of the issues involved, the members of the public who provided comments, and the staff members who brought the report to fruition.

The draft report and recommendations on pharmacogenomics (PGx) was released for public comment the previous week to coincide with the Secretary's roll-out of the PHC Initiative. Progress was also being made on the study of the impact of gene patents and licensing practices on patient access to genetic technologies. Dr. Tuckson reminded the Committee that a meeting of the Gene Patents and Licensing Task Force was scheduled for that evening.

Dr. Tuckson stated that t the November 2006 meeting, after several presentations and extensive discussion about the oversight of genetic testing, the Committee was left with many questions about the adequacy of the Federal oversight framework and they decided to engage in further fact-finding. Since then, he learned that HHS had formed an internal working group to examine the roles of Federal agencies related to analytical and clinical validity and to determine where gaps lie within the Federal Government. He stated that Ms. Walcoff would be speaking momentarily and would give SACGHS a specific charge on oversight on behalf of the Office of the Secretary (OS).

Dr. Tuckson noted that the Committee would end the meeting the following day by considering whether to take on one or both of two new priorities: an investigation of the economic consequences of genomic innovations, as proposed by Dr. Steve Teutsch, and an evaluation of real-world outcomes of gene-based applications, as proposed by Dr. Muin Khoury and Dr. Gurvaneet Randhawa.

Dr. Tuckson acknowledged the death of Dr. Joseph Hackett, who had participated in a number of SACGHS meetings and task forces on behalf of FDA. He extended condolences to Dr. Steve Gutman of FDA for the loss of a valued colleague and friend.

Dr. Tuckson noted two OBA staff changes, including the addition of Ms. Tara Hurd to help with administrative tasks and the departure of Ms. Amita Mehrotra. He noted that a search was underway for subject matter experts to support the committee's analytical work. After Executive Secretary Sarah Carr reviewed the Committee's conflict of interest responsibilities, Dr. Tuckson turned the floor over to Ms. Walcoff.

Update on the Secretary's Personalized Health Care Initiative

Sheila Walcoff, J.D.
Counselor for Science and Public Health
Office of the Secretary
U.S. Department of Health and Human Services

Ms. Walcoff presented an update on the work of the Department of Health and Human Services (HHS) in accelerating personalized health care (PHC). She stated that Secretary Leavitt outlined the PHC Initiative to the Personalized Medicine Coalition the previous week and she recapped his remarks, stating that PHC is one of the Secretary's top 10 priorities. He believes that advances in medicine, biomedical science, and

technology present opportunities for health care practices to become increasingly patient-specific. The desired outcome is the effectiveness and safety of medical practices and increased value and transparency for patients using modern tools, technologies, and information. The PHC Initiative emphasizes a health care strategy that incorporates new methods of genetic analyses to better manage a patient's disease or predisposition to a disease and facilitates the discovery and clinical testing of new products.

Some of the long-term goals for the next 5 to 10 years are to promote connectivity through a national system of health care information networks; assess the need for new policies, technologies, and oversight approaches; develop incentives across the health care system to use genetic information; foster new business models for the pharmaceutical and diagnostic industries; encourage consumer participation in medical decisionmaking, health care management, and prevention through new information-based tools; increase consulting support and incentives; and provide real-time decision support for disease management strategies using health information technology systems.

Some of the short-term goals are to present the American Health Information Community (AHIC) with recommendations for genomic medical testing and family medical history data adoption in electronic health records (EHRs). The Initiative is also developing policies and programs to strengthen consumer and health care provider trust in parallel with infrastructure and technical capacity development, encouraging development of validated clinical genomic testing capabilities, and establishing networks of interactive data sources.

Ms. Walcoff displayed a pyramid-shaped diagram of the overall vision. Health information technology and knowledge development (expansion of the science) form the base of the pyramid. These elements include electronic systems, clinical databases, and knowledge repositories that are based on a common set of definitions and standards. The next level of the pyramid is intervention development and review. Ms. Walcoff said there is an increasing need for and value placed on integrated data sets and high-quality information about efficacy and safety outcomes. The ability to assimilate and relate experiences using integrated databases is enabling incredible predictive power for outcomes in disease management. As technological capabilities develop across the health care system, better information, based on individual differences, will aid in future medical product evaluation and postmarket assessments of safety and efficacy. An expanded set of health measurement tools will foster research and development for conditions for which there are currently few successful health interventions or preventive approaches. The top of the pyramid represents translation into clinical practice. Ms. Walcoff stated that the key players in this transformation are health care providers and she said that better bridges are needed between research and health care delivery. Currently, the field lacks the infrastructure and analytical strategies for data management and knowledge development across biomedical research and health delivery enterprises. There are barriers to standardized formats that would allow information exchange among willing partners in health care. The PHC Initiative is attempting to create a health care system with a continuum of transformation that builds on knowledge management to support the integration of discovery, development, and delivery in the health care enterprise and paves the way for a modern doctor-patient relationship in which value for the patient is the ultimate objective. Ms. Walcoff said the Secretary's role in the Initiative is to facilitate technology development and the formulation of policies to support the appropriate use of genetic information.

Technology goals include the establishment of an interoperable public/private data partnership of networks that facilitate the appropriate use of research and clinical data. The President's Fiscal Year (FY) 2008 budget included $15 million for the Initiative to begin building this network, which will ultimately link genomic and clinical data to add efficiencies to therapy development, identify clinical best practices,

and provide better methods for tracking adverse events. Ms. Walcoff said this effort was just starting and would be based at the Agency for Healthcare Research and Quality (AHRQ). The technology track also includes the establishment of standards for the incorporation of genomic health information and personal family history into EHRs.

The goal of appropriate use of genetic information includes protecting individuals from genetic discrimination through legislation, providing oversight of genetic testing to assure analytical and clinical validity through regulation of testing platforms and systems and proficiency in practices for performing tests and data interpretation, and standardizing access policies to federally funded databases of genetic information. Current policies for accessing these genomic databases are not entirely consistent.

Ms. Walcoff noted that AHIC established a PHC work group to advise on these issues. The group is composed of a broad cross-section of stakeholders from Federal agencies; industry; health plans; laboratories; consumer organizations; and experts on ethical, legal, and social issues. The specific charge to the work group is to make recommendations to AHIC on establishing standards for reporting and incorporation of common medical genomic tests and family medical history data into EHRs and to provide incentives for adoption across the country, including Federal agencies. If such standards are not widely accepted, a patchwork of different systems of EHRs will impede interoperability and the exchange of useful health information. It is also important that primary care physician acceptance and understanding of this new medical technology catches up with the rapid pace of genetic research.

Secretary's Charge to SACGHS on the Oversight of Genetic Testing.

Ms. Walcoff noted that the Secretary's office was aware of the deliberations of SACGHS on the oversight issues and had recently reviewed the July 2000 report, *Enhancing the Oversight of Genetic Tests*, prepared by the Committee's predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT). The Office of the Secretary (OS) was also closely following the information-gathering efforts of a broad cross-section of stakeholders in other forums to better understand the issues and to discuss internally how the Department should coordinate oversight in this complex area.

Ms. Walcoff indicated that because the oversight issues are critical to the Secretary's PHC goals, the Secretary wanted SACGHS to extend its efforts on the topic. Ms. Walcoff then presented the Committee with a specific charge involving the development of a comprehensive map of steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. The map would consider and address the following questions:

> Generally, what are the existing pathways that examine the analytical validity, clinical validity, and clinical utility of genomic tests? What organizations are currently responsible for each of these aspects and what are they doing to address the issues? What are the potential pathways to communicate clear information to guide test and treatment selection by providers? OS also wanted input on the analytical validity and clinical validity of genetic tests, including: What evidence of human harm exists regarding genetic tests? Is that harm attributable to analytical validity of the tests, clinical validity, and/or clinical utility? If evidence does not exist, what threats exist that currently are not being addressed by regulatory oversight? What distinguishes genetic tests from other laboratory tests for oversight purposes? What resources, such as standard reagents or materials, are needed to develop proficiency testing (PT) requirements? What is currently available in terms of PT kits for genetic tests and what information is provided by PT? What new approaches or models for private and/or public/private sector engagement could

demonstrate clinical validity and utility for developing effectiveness measures for use of genetic tests? What should be considered and why? Where and how would additional revised Government oversight add value for patients?

Dr. Tuckson thanked her for conveying the charge and noted that the public's anxiety concerning privacy and confidentiality is the sister issue to oversight. He said the PHC movement would not go far if the public does not have trust in the regulatory process. He recognized that the Secretary was interested in seeing results in a timely manner and asked the Committee to think about what product could be delivered in a short time frame. Dr. Tuckson said the Committee would return to a discussion of the charge later in the meeting.

Dr. Andrea Ferreira-Gonzalez asked Ms. Walcoff if the Secretary wanted SACGHS to look at the roles of the Federal Government, the States, and the private sector in the oversight of genetic testing. Ms. Walcoff said the charge was purposefully crafted to be broad so that the information SACGHS gathers will reflect input from the variety of stakeholders that SACGHS represents. She indicated that the charged is focused primarily on the Federal side since OS can make an impact primarily in that area, and the intersection of Federal efforts with the private sector, including public/private partnerships. She stated that OS would continue to work with the Committee as the charge was refined and asked the group to work on an accelerated timeline.

Dr. Tuckson introduced Dr. Robert Kolodner and Ms. Jodi Daniel of the Office of the National Coordinator (ONC) for Health Information Technology.

Briefing on the Activities of the Office of the National Coordinator for Health Information Technology and the American Health Information Community

Robert M. Kolodner, M.D.
Interim National Coordinator
Office of the National Coordinator for Health Information Technology (ONC)

Jodi G. Daniel, J.D., M.P.H.
Director, Office of Policy and Research
Office of the National Coordinator for Health Information Technology (ONC)

Dr. Kolodner stated that there are multiple challenges to the advancement of genomics, including discrimination on the basis of genetic information. Genetic information is unique to the individual, predictive of a person's future health, and immutable once it is disclosed. Genetic information also provides information about other family members. When genetic information is linked with data from non-covered entities, violations of privacy can occur. Trust in the privacy and security of genetic information is fundamental its use.

Health information technology (IT) can add value to genomics by enhancing adoption by front-line clinicians. Dr. Kolodner described a number of drivers for health IT adoption, including the rising cost of health care in the U.S. and the fact that consumers are not currently receiving the value of the dollars they invest. If costs continue to rise at the current rate, the U.S. economy will be undermined. There are other drivers for health IT adoption. Consumers and the economy are beginning to receive substantial benefits. Some organizations are taking the lead in demonstrating how health IT can improve care. The leadership of the Administration, both in the Executive Branch and on the Hill, was providing bipartisan support for

the health IT agenda. There was also strong endorsement from industry and commercial leaders, who would benefit from global competitiveness.

Dr. Kolodner said the key health IT components are electronic health records, personal health records, public health information, technical and security standards for data, and an interoperable Nationwide Health Information Network (NIHN). He said the President established the Office of the National Coordinator (ONC) through an Executive Order in April 2004. The charge to the Office was to advance the vision for developing a nationwide interoperable health IT structure and achieve widespread adoption of electronic health records by 2014. ONC is providing leadership to achieve this goal and to improve the quality and efficiency of health care through the National Health IT Agenda. Health IT is seen as a critical component for a transformation in individual and population health.

The framework for health IT adoption builds on the 2004 charge. By 2014, Dr. Kolodner said there will be widespread use of electronic health records, personal health records, the public health infrastructure, home telehealth, and continuous monitoring of one's own health in real time. ONC developed four goals to support the charge: 1) informing health care professionals, 2) interconnecting health care, 3) personalizing health management, and 4) improving population health. Dr. Kolodner pointed out that SACGHS and ONC have several common goals.

The Federal advisory committee for ONC is AHIC, or "The Community," and is chaired by Secretary Leavitt. It is a public/private collaboration that provides input and recommendations to HHS on efforts to advance the health infrastructure toward interoperability. AHIC enables market forces by setting certain boundaries, setting targets, removing barriers, and providing incentives for interoperability and transformation of the health arena.

AHIC's work is conducted by seven work groups. In 2006, more than 50 meetings were held involving over 120 experts and stakeholders. The focus of the work groups is developing recommendations for consideration by the full membership of AHIC regarding technical, business, and social issues so that AHIC can make recommendations to the Secretary. In November 2005, AHIC established work groups to address consumer empowerment, chronic care, biosurveillance, and electronic health records. In May 2006, groups were established on confidentiality, privacy, and security issues and on quality. The most recent work group was established in October 2006 to address personalized health care.

Dr. Kolodner said two contracts were entered into to foster organizations that would have ongoing roles in serving the Nation. The first was a health IT standards panel (HITSP). This group was identifying and harmonizing IT standards in a variety of areas. A decision had to be made concerning which standards to use so that systems would be able to communicate with one another. The Certification Commission for Health IT (CCHIT) was analyzing a variety of products and services, including outpatient and inpatient electronic health records, network services, and personal health records, so that certification could be provided. The reasons for certification are twofold: to push forward the adoption of identified standards and to allow front-line providers to rely on certified products, which will reduce risk.

A third contract was established to foster the development of the National Health Information Network (NHIN). In 2006, contracts were issued to technology consortia to develop prototypes and AHIC drew upon the best ideas. Dr. Kolodner said the next step would be to approach the health information exchange communities in local and State regions so they can contract for services. AHIC will define mandatory capabilities, particularly those that allow individuals to control network information.

Other collaborative activities were taking place at the State level, where the most significant actions must occur. Dr. Kolodner stated that although the development of standards and certification can be encouraged at the national level, true implementation will occur locally. The Health Information Security and Privacy Collaboration (HISPC) identifies variations in State laws that create barriers to the movement of information. The State Alliance for eHealth was created through a contract with the National Governors Association and is also a committee within HHS. It established an executive-level advisory body and connects to the Governors and legislative levels in the States to develop consensus solutions for State policy. The State-level Health Information Exchanges (HIE) Initiatives examined established State HIEs and identified leading-edge best practices so that AHIC could learn from the key issues and strategies of the early adopters.

Dr. Kolodner compared these efforts to a tree, with privacy, security, and confidentiality as the basis (e.g. soil) for transforming health care. Health IT activities (e.g., creating standards, fostering interoperability) feed the roots of the tree. He said the real purpose is the foliage and fruit of the tree, i.e., added value to patients and providers, high quality, safe health care at lower costs, and improved public health.

Dr. Kolodner stated that AHIC had achieved some specific milestones, but a number of activities lay ahead. The issue of privacy would be critical in shaping policies and principles. In addition, AHIC would be transitioning to a public/private entity. A Federal advisory committee would remain in place, but governance would move to an entity in the private sector.

Dr. Kolodner said that health IT can facilitate knowledge management and help organize information to improve safety, quality, and efficiency in the health care sector. This will be accomplished through common standards that pervade the electronic health records, databases, and repositories that will be created. Systems must be managed to generate knowledge on individual differences, evidence development, postmarketing assessments of safety and efficacy, and tracking and reporting of adverse events. Systems must move from collecting health information for billing or reimbursements to automating the core processes of health care. Health IT will support the physician and other care providers by keeping them up-to-date with medical information, making sure they have all the information they need to provide better care and improve diagnoses, providing decision support at the point of care, and allowing for improved predictions about disease course and outcomes. Health IT supports researchers by making health measurement tools available and by providing access to a wealth of information in databases that go beyond randomized controlled studies. Health IT supports the consumer by providing safer, higher quality personalized health care. Dr. Tuckson thanked Dr. Kolodner and introduced Ms. Jodi Daniel.

Ms. Daniel said patients and providers must trust the systems that share electronic information. She stated that technology adds greater risks, e.g., if an error occurs, larger amounts of information could be disclosed. Yet health IT can protect data in ways that are more secure than methods for protecting information on paper. One of the goals set forth in the Executive Order that established ONC relates to privacy and security, stating that a nationwide interoperable health information technology infrastructure must ensure that patients' individually identifiable health information is secure. Ms. Daniel said privacy policies must be created in parallel with the development of new technologies. The trial implementations of the NHIN were allowing opportunities for privacy policies to be created at the same time as the architecture standards.

Ms. Daniel stated that the Health Information Portability and Privacy Act (HIPAA) provides the foundation for health privacy in the U.S. HIPAA allows for State protections that are greater than Federal

protections in the area of genetic information. As new privacy and security policies are developed, both Federal and State policies must be taken into account. Health IT may pose additional privacy or security risks that might not have been considered by HIPAA, such as opportunities for greater data sharing and aggregation. There are also new types of regional health information exchanges that are not directly covered by HIPAA. They may be covered indirectly through contracts with the entities involved. However, these emerging situations create challenges, since entities that hold genetic information in databases may not be covered directly by Federal or State privacy laws. Some of these issues were being raised by a privacy and security solutions contract at the State level. ONC was also working with the HHS Office for Civil Rights on these issues.

Ms. Daniel addressed the Health Information Security and Privacy Collaboration (HISPC), which examines State privacy laws and business practices in 34 States and territories. It identified variations in privacy and security policies and laws, State solutions to problems, and various implementation plans. They planned to bring States with similar challenges together to foster regional or multi-state collaborations. Because the HISPC identified the need for cross-State collaboration, it was one of the drivers for the State Alliance for eHealth. This effort by the National Governors Association works with the National Council for State Legislatures, the National Association of Attorneys General, and the National Association of Insurance Commissioners to build consensus by State leaders. The State Alliance is made up of Governors, legislators, Attorneys General, insurance commissioners, staff from State health agencies, and technical advisors who are working toward harmonization of policy decisions. Three task forces focused on privacy and security were providing information to the State Alliance. One is the Health Information Protection Task Force. Their efforts would build on information from the HISPC to identify opportunities for cross-state collaboration on privacy policies.

At the Federal level, a major source of policy development is the Confidentiality, Privacy, and Security (CPS) Work Group of AHIC. The charge to this group is to make recommendations to the community on the protection of personal health information to secure trust and support appropriate interoperable electronic health information exchange. They made five recommendations describing how entities can make patients identity-proof, which were advanced by AHIC to the Secretary. CPS was in the process of addressing the fact that some participants in electronic health information exchanges are not subject to existing Federal and State privacy and security laws and was trying to ensure appropriate protections to ensure consumer trust. They were focusing on personal health record privacy policies because some of these records are not covered by Federal or State laws.

Ms. Daniel said CPS Work Group information was feeding the certification activities for electronic health records and networks, the State Alliance, the NHIN trial implementations, other AHIC work groups, and Federal policy development. Ultimately, the goal is to have a nationwide health information network that brings together policies and technology.

Dr. Tuckson asked how SACGHS could ensure that genetics is a priority in the electronic health records committees. He asked the Committee think about the natural linkages between SACGHS interests and AHIC's work concerning anti-discrimination, because people with genetic diseases have complex illnesses that require extensive interaction with the health care system. Dr. Tuckson suggested that the Committee receive a formal update from the PHC Work Group at every SACGHS meeting.

Dr. Kolodner agreed that the PHC Work Group should interact with SACGHS, and he recommended that the Committee work closely with Greg Downing of OS. Dr. Williams noted that he and Dr. Teutsch were members of the PHC Work Group and said they would keep the Committee informed of Work Group

activities. Dr. Tuckson felt it was important to have a connection to CCHIT as well. Ms. Daniel said the CPS Work Group was open to adding more members and was interested in integrating privacy and confidentiality issues more closely with genetic information issues.

Dr. Francis Collins noted that the charge to the PHC Work Group was heavily focused on the use of genetic laboratory tests as a means of ensuring that information is properly standardized and incorporated into the electronic health record. He was surprised that there was no reference to family history, given that family history is a strong driver of whether a genetic test will be conducted. He stated that this information is an independent predictor of potential future risk and is free, yet it is poorly represented in any electronic form in most medical records. Dr. Kolodner replied that family history was an important area of focus for the PHC Work Group and stated that a recommendation in this area would be forthcoming. Dr. Williams added that significant harm could be prevented if family history information was put into usable form.

Ms. Daniel addressed a question on consumer trust by stating that personalized health records will allow consumers to gather their own health information and have greater control over its dissemination. She stated that consumers are involved in all of AHIC's collaborative efforts and are engaged up front as policies are developed.

Ms. Chira Chen asked how electronic records would be shared. Dr. Kolodner said the heart of their agenda was to standardize information so it would be usable across providers. This was currently happening on a small scale and they were attempting to foster widespread use. They were working with the Health Resources and Services Administration (HRSA) to make sure they did not increase gaps in care for the uninsured.

Dr. Joseph Telfair asked about methods for maintenance and sustainment of the system being developed and asked what method was in place for monitoring the policy and work group processes and ensuring that they were moving in the same direction. Dr. Kolodner said they planned to enable market forces so that electronic and personal health records would be self-sustainable within the provider setting. Employer-based, insurer-based, and individual-based personal health records would also be self-sustaining. AHIC was moving into a public/private process that would oversee and foster these outcomes. Ms. Daniel added that almost all the contracts they entered into required sustainable business models, e.g., the NHIN prototype contracts.

Dr. Muin Khoury commented that the ultimate utility of personalized health care resides not only in establishing standards, but in connecting the information obtained from providers and patients. He said the day's discussion had addressed three areas in genetics: genomic and genetic tests, family history, and the GEDDI initiative. He suggested that AHIC merge the results of genetic tests with the results of family history and disease signs and symptoms so that health care providers could make early diagnoses and intervene effectively (i.e., a code that will allow signs and symptoms to become evident in the medical records). In addition to the results themselves, Dr. Khoury said physicians and other health care providers need decision support to help them determine the meaning of the results. He encouraged Dr. Kolodner to include coding that would prompt referrals for genetic testing. Dr. Kolodner agreed and said these types of prompts exist on a small scale and will increase.

Session on Genetic Discrimination

Mr. Brian Petersen
Deputy Legislative Director
Office of Representative Judy Biggert

Ms. Kristine Bradsher
Legislative Analyst
Office of the Assistant Secretary for Legislation, HHS

Ms. Michelle Adams
Legislative Director
Office of Representative Louise Slaughter

Mr. Brian Petersen, Ms. Kristine Bradsher, and Ms. Michelle Adams spoke to the Committee via teleconference to provide an update on the Genetic Information Nondiscrimination Act (GINA). The speakers were at the center of Congressional efforts related to GINA. Dr. Tuckson stated that enactment of Federal legislation to prohibit genetic discrimination in health insurance and employment had been the Committee's highest priority since it was established. GINA was introduced in the House and the Senate as H.R.493 and S.358, respectively, and it was predicted that after a decade of effort, this legislation would soon be passed by Congress and enacted into law.

Ms. Bradsher stated that the Administration favored enactment of legislation to prohibit the improper use of genetic information in health insurance and employment. The Senate was working out several remaining issues. The House was attempting to reconcile three versions of the bill, with the goal of having one bill after recess. The three versions were from the House Education and Labor Committee, the House Energy and Commerce Committee, and the House Ways and Means Committee, each of which had jurisdiction over parts of the bill. Ms. Bradsher stated that the Secretary was pleased with the progress made by SACGHS on this issue. Ms. Adams added that after the three versions of the bill were consolidated, it would go to the Rules Committee for floor action. Mr. Petersen said they were continuing to push forward with a strong bipartisan effort in the House, with Representative Louise Slaughter's and Representative Judy Biggert’s leadership.

Dr. Tuckson opened the floor for questions. Dr. Williams referred to the language of the bill concerning the term “genetic test” and asked if a cholesterol test or blood pressure measurement could be interpreted by some as detecting a genotype. Mr. Petersen stated that there was an effort by a number of Republicans to narrow the definition of genetic test in a way that would be problematic and would force HHS to develop a master list. This would create a regulatory burden for HHS. Ms. Adams clarified that these attempts to change the definition were defeated and Dr. Collins commented on the negative consequences that would have occurred if the definition had been limited.

Dr. Tuckson asked Ms. Sharon Terry to comment. She stated that she was satisfied with the progress of the bill. Her main concerns going forward related to reconciling the three sets of issues in the committees. She emphasized the need for the bill to go forward in order for the PHC initiative to be effective.

Discussion of the Secretary's Oversight Charge

SACGHS members engaged in further discussion of the charge with Gregory J. Downing, D.O., Ph.D., Project Director, PHC Initiative, who accompanied Ms. Walcoff. In response to a question from Dr. Ferreira-Gonzalez about organizations referenced in the charge, Dr. Downing replied that it included organizations involved in the systems being examined, e.g., Federal regulatory agencies, regulated industries and providers, research organizations, and professional organizations. He said there are conduits of information aggregation and analysis that could be useful and that the Secretary would like to see a categorization of the types of information needed at various steps.

Dr. Teutsch noted that the charge seemed focused on clinical issues. He asked whether it also included public health and population health utility of laboratory tests. Some genetic information used for population health may be related to toxic exposures in the environment or recommendations for nutrition policy and some tests might have a population health impact for specific ethnic or geographic groups. Dr. Downing clarified that both clinical individual patient use and tests used in population-based environments are part of the Committee's charge.

Dr. Tuckson referred to Dr. Khoury's statement that the effort would primarily be a fact-finding activity, since much work had already been done. All the domains of organizations that might be relevant should be included, whether in the academy, private sector initiatives, or Government regulatory agencies. The charge was to lay out a road map that indicates all the relevant organizations and entities involved in the oversight of genetic tests.

Dr. Ferreira-Gonzalez asked how SACGHS should focus its efforts, in light of work already under way in the Secretary's Office to review the oversight issues within Federal agencies. She asked whether the Committee should focus on the private sector. Dr. Downing said HHS internal efforts were exploring the different authorities of each agency and their intersections to determine where they do or do not align in order to identify gaps and overlaps of policies and regulations. This effort would help agency communications, interactions, and deployment of policies. Dr. Downing added that many different types of technologies had evolved since previous reports on genetic testing were developed in 2000 and 2001. He suggested that SACGHS look at specific requirements for different types of genetic tests, whether polymerase chain reaction (PCR) or multigene array analyses, to see whether the information developed has differences in terms of clinical and analytical validity. The interpretation and defining of genetic tests should take into consideration the methodologies and types of information that are developed, processed, and presented as data to be utilized for clinical applications or in population-based health.

Refinements to the charge were made to reflect Dr. Downing's statements and the Committee's discussion. One of the changes emphasized the point about a legitimate role for public/private partnerships as a solution to problems with oversight.

Dr. Downing said OS was interested in the key analytical questions that must be framed and answered in order to develop the information necessary to use tests in a way that allows transparency about the implications of their results. He said a number of models and discussions had been recently published about what would be needed in terms of organization and science, medical, and health systems input to deploy these technologies and the information necessary to create a process in which information continues to accrue. He spoke about the refinement of those tools and their applications. He said OS did not have a specific concept in mind, but thought that the path forward would require more than just the Federal Government's role. He said SACGHS work should be focused on the public/private partnership

role for clinical validity and utility and the use of tests in clinical practice. The Committee should address the question: Where do those responsibilities currently fall and what are some better ways to accrue information moving forward?

Dr. FitzGerald noted that the pharmacogenomics report identifies clinical outcomes as an important part of the formula and asked if they should be included in the oversight report. Dr. Downing said they would be useful if the Committee had the insight and expertise to address the issue. If not, the evidence OS was looking for in the short term related to analytical validity in the oversight of the test kits themselves and the performance of those tests. Those issues were the prominent concerns of SACGHS and had been discussed in previous meetings. OS was interested in more clarity on those concerns.

Dr. Tuckson summarized by stating that the Committee was being asked to describe the pathways that exist now for analytical and clinical validity and clinical utility and define the organizations with responsibility and accountability for those pathways. They would also need to look at the appropriate role for public/private efforts. He stated that once the road map was laid out, the Committee could look at whether roles should change to include not only Government oversight, but public/private partnerships.

Dr. Randhawa asked for clarification on "developing effectiveness measures." He asked whether this meant developing new measures or collecting known measures and synthesizing them appropriately. In response, Dr. Downing said the term "evidence development" could be substituted—i.e., how do we know that a test is providing information that clinicians, health care providers, and consumers want, need, and can reliably use, and under what parameters is it useful? He said that if the Committee was already thinking about new ways to develop that information, it would be useful to include it in the report.

Dr. Randhawa asked whether the Committee should consider efficacy as part of effectiveness or focus only on effectiveness. Dr. Downing said he would combine the two approaches, although he wanted to give the Committee latitude in framing the issues. Dr. Tuckson said Dr. Randhawa raised an important question. In addition to the actual oversight of tests, the idea of measures of effectiveness was being introduced. The Committee needed to think about whether to address that issue.

Dr. Tuckson opened discussion on the aspect of the charge that addressed "potential pathways to communicate clear information to guide tests and treatment selection by the provider." Dr. Ferreira-Gonzalez asked Dr. Downing if this meant SACGHS should look not only at how testing is differentiated, but how different technologies are viewed and information is relayed to physicians and how that information is interpreted and leads to testing. Dr. Downing said OS was not looking for a complete inventory of every test that could be categorized as a genetic test, but for a framework for understanding those cases in which the result is not just a positive or a negative, but instead required interpretive skills and analysis. How will those results be interpreted and what information is passed on to those making decisions with it? He said the earlier reports focused predominantly on test performance and that was still an important issue. However, the field is moving into more complex areas, and OS wants to know what is new in cases where interpretation is required. How is information gauged? What is the level of evidence that the test results are benchmarked against? And if that includes utilizing other data sets, how is that process performed and what are the cognitive capabilities needed to make accurate determinations? Dr. Downing suggested that expertise might be needed on an *ad hoc* basis from outside SACGHS.

With regard to the question in the charge about the evidence of harm related to genetic testing, Dr. Tuckson noted that it would be important to identify real or potential harms through the development of case scenarios. Dr. Downing agreed and suggested that case studies might provide transparency on how

information is gathered and used, which would inform processes to deal with new information as it unfolds.

Dr. Downing noted that in the context of legislation, "genetic information" has a very broad definition and it should be left to the Committee to decide how to define this concept for the report. Regardless of the definition, information with a genetic origin is used for many different types of decisionmaking processes. The levels of risk in play when making decisions about test results have bearing on the level of oversight needed and the kinds of questions and evidence necessary. He said "harm" does not necessarily mean that someone has to be harmed; it includes analytical work not being done or being done incorrectly. How are genetic technologies and tests different from other types of medical tests? What is unique and definable about genetic tests that causes concern?

Dr. Collins said the Committee should not only look for evidence of harms or potential threats, but for instances in which public benefit has been slowed or limited, so that benefits are not accruing as rapidly as they might. Dr. Downing agreed that "harm" should be broadly defined, but still apply specifically to genetic tests.

Dr. Tuckson asked Dr. Downing to explain the aspect of the charge concerning resources needed for PT.

Dr. Downing replied that OS was looking for answers to questions such as: What are the models for PT with well-characterized specimens and processes for splitting or sharing samples? Are there unique and common reagents or things that are used to test and provide common results from different laboratories performing those tests, particularly as new tests evolve and roll out? Are those things commonly available, and what are the implications of that on the laboratory for everything from costs to availability? He said that a "perfect" framework would not work in the real world if the necessary reagents to conduct testing are not available. If there is a menu of commonly available materials necessary to provide analytical validity requirements in a framework that addresses different types of genetic tests, it would be helpful to know what they are.

In response to a question from Dr. Tuckson about the part of the charge that includes guidance to Government, Dr. Downing said that OS was asking SACGHS to be creative and think outside the box in terms of methods and approaches.

Dr. Downing was also asked whether a literal map or diagram of pathways and communications was being requested or whether the Committee should simply address each question in a logical fashion. Dr. Downing clarified that OS wanted a tool that would help a layperson visually and graphically understand the oversight process, the technologies that are developed and performed, and the information flow that enables the physician and clinical providers to obtain the right information. Dr. Tuckson said the map should lay out what exists today and what does not exist and indicate where the gaps lie. It should show where the responsibility lies for the Food and Drug Administration (FDA) and the Center for Medicare & Medicaid Services (CMS), and where no one has responsibility.

Dr. Scott McLean asked how the Committee should conceptualize treatment (e.g., management, genetic counseling, pharmacologic interventions). Dr. Downing said treatment in this context should be defined broadly, in terms of either wellness decisionmaking processes or others. He said the context was that of someone taking a test and making a decision that will alter a process or health function.

Dr. Williams said that much of what was being discussed related to decision support algorithms. He said the Committee would need to be explicit concerning oversight in this area because there had already been talk in other venues of clinical support algorithms that were being scrutinized under the rubric of a device. He suggested that advice for the Government might mean elimination of some functions, not necessarily the addition of something.

Dr. Tuckson closed the discussion by stating that the group would subpopulate the outline for responding to the charge in the afternoon session. The Committee was not limited by what the Secretary's office asked for. Dr. Tuckson thanked Dr. Downing for guiding SACGHS so that the Committee's efforts fit in with HHS's overall efforts. Dr. Downing said they were agnostic about the manner in which the response was prepared, but he emphasized that time was of the essence.

Public Comment

Deborah Kloos
Gentris Corporation

Ms. Deborah Kloos represented Gentris Corporation, a pharmacogenomics company in Research Triangle Park, North Carolina, which manufactures products for predictive genetic testing, including reference controls and *in vitro* diagnostics (IVD). She stated that Gentris has always been directed by FDA to achieve clearance on all products, which ensures that consistently reproducible reference controls, obtained from properly consented patients, are available to meet the Clinical Laboratory Amendment Act (CLIA) testing requirements. They received clearance in December 2006 for six human genomic DNA reference controls for testing of the P450 CYP2D6 gene.

Gentris chose reference controls for their first 510(k) product submission based on the fact that there was one FDA-cleared platform for CYP2D6 testing, the Roche AmpliChip CYP450 test. They agreed with FDA that it would be helpful to the genetic testing industry to provide reliable, cleared companion controls for this cleared platform. Ms. Kloos informed the Committee that non-compliant material from other sources is also being used for the same purpose, which calls for action on the part of those in a position to effect change.

She stated that there are three main resources for laboratories to obtain genetic testing controls: leftover patient specimens, with or without direct informed consent; commercially available research use only (RUO) or research-grade products, obtained most frequently from the Coriell Institute for Medical Research; and FDA-cleared IVD controls manufactured by companies such as Gentris and Maine Molecular Quality Controls, Incorporated. Materials sold as RUO are not required to be manufactured under good manufacturing practice (GMP) regulations, so they have virtually no regulated quality assurance requirements and are not subject to FDA audits. Their performance characteristics have not been established and they are not to be used for diagnostic procedures. In contrast, a small company such as Gentris dedicates large resources of time, money, and personnel to perform clinical trials, submit products for FDA clearance, maintain stability data, and manufacture products in a GMP environment. They can find no justification for lowering the bar for reference controls, which are an indispensable component of pharmacogenomic testing. Until recently, only RUO products and residual patient materials were available to laboratories. However, laboratories now have alternatives for many controls because companies such as Gentris are ready to meet the higher standards for producing IVD controls. Yet research-grade products or leftover patient samples are being put into clinical practice without the safeguards required for IVDs. As long as laboratories are permitted to use them, they have no incentive to

use FDA-cleared product control. Ms. Kloos said this disparity must be resolved before companies lose their incentive for manufacturing IVD controls. Manufacturers will not want to produce a regulated product when alternatives are available at lower cost.

Ms. Kloos urged the Committee to recommend to the Secretary of HHS that the Department seek Congressional legislation or another means to create parity for manufacturers and harmonize the oversight of this area of genetic testing. She stated that the regulatory infrastructure had not caught up with state-of-the-art technology. She said that FDA was doing its best to enforce the ASR rule to ensure that only FDA-cleared products are used in situations in which there are life-threatening consequences, however, she stated that FDA was seriously underfunded. Ms. Kloos asked the Committee to recommend to the Secretary that his Office seek increased FDA funding for oversight of this issue. Dr. Tuckson thanked Ms. Kloos and asked her to provide staff members with greater specificity on the issue she raised.

Ann Cashion
President, International Society of Nurses in Genetics (ISONG)

Ms. Ann Cashion stated that ISONG is a specialty nursing organization dedicated to caring for people's genetic health through excellence in the provision of genetic health services by fostering the professional and personal growth of nurses in human genetics. She said the nursing workforce holds great potential for caring for people's genetic health. ISONG has, in conjunction with the ANA, developed and promulgated the scope and standards of genetics clinical nursing practice. In addition, ISONG is one of over 40 endorsing organizations of the Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics. Ms. Cashion said ISONG was eager to work with SACGHS as the Committee examined the impact of gene patents and licensing practice on patient access to genetic technologies. Dr. Tuckson asked ISONG to send the Committee a thoughtful analysis on the status of professional education in genetics and their opinion on whether enough is being done in the private sector.

Kathy Hudson
Director of the Genetics and Public Policy Center, Johns Hopkins University

Ms. Kathy Hudson stated that her organization previously expressed concern about the inadequacies in genetic testing oversight. She commented that little had changed over the previous year and she reviewed CMS activities on the issue. In June 2006, CMS was planning to create a genetic testing specialty under CLIA. Less than 3 months later, the agency said no specialty area would be developed. Ms. Hudson stated that CMS gave many explanations for this policy reversal, including the statement that there is no evidence of a problem. Ms. Hudson’s organization was not in agreement. They conducted a survey of laboratory directors and asked them about their participation in existing formal proficiency testing (PT) programs. It was found that one-third of laboratories were not participating in such programs. Ms. Hudson said that when Congress passed CLIA in 1988, it was gravely concerned about the failure of laboratories to perform PT and the consequences for patient health. Therefore, Congress directed the Secretary to require that laboratories participate in PT unless the Secretary determined that an appropriate PT program cannot be implemented. Ms. Hudson said that CMS was following neither the spirit nor the letter of the law. CMS’s position was that the lack of a mandate for PT has no practical effect because there are so few formal PT programs available. Ms. Hudson stated that although the number of tests far exceeds the number of formal PT programs, if CMS required laboratories to participate in formal programs, the number of programs would increase.

CMS characterized the survey findings as identifying pre- and post-analytic errors in genetic testing, which Ms. Hudson said was an inaccurate representation. Thirty percent of the most common errors identified by laboratories were analytic errors. A strong predictor of whether a laboratory's most common error is an analytic error is the level of PT performed by the laboratory. She said the message was that PT matters and many laboratories are not performing it.

Ms. Hudson said that when enacting CLIA, Congress directed the Secretary to make the results of PT testing available to the public and she stated that CMS had not done this, making it impossible for an external body to assess the quality of laboratories. Ms. Hudson also stated that CMS asserted that only a few organizations wanted the agency to issue a genetic testing specialty, when, in fact, over 100 organizations and individuals representing industry, laboratories, patients, and health care providers called on CMS to move forward. In September 2006, the Genetics and Public Policy Center, the Genetic Alliance, and Public Citizen filed a petition for rulemaking with CMS requesting that a specialty be created. Six months later, they had received no response.

She asked SACGHS to focus on several issues, including: moving quickly on PT, providing transparency so the public can have confidence that laboratories are performing adequately on PT and have the expertise to ensure accurate testing, and developing a coherent regulatory framework to ensure that all tests are clinically valid before they're offered to patients.

Sharon Terry
Coalition for 21st Century Medicine

Ms. Sharon Terry stated that the Coalition for 21st Century Medicine was founded in late 2006. It represents 22 of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and over 30 patient advocacy groups, including the Genetic Alliance's coalition of 600 advocacy organizations, linked together with the common mission of developing advanced diagnostics that improve the quality of health care for patients. The Coalition shares HHS's focus on personalized medicine and the goals of Congress and FDA in assuring that treating physicians and their patients have access to safe, accurate, and reliable information to assist in decisionmaking. They support striking a balance between regulation and innovation.

The Coalition met with FDA leadership in December 2006 to exchange ideas about their initiatives concerning *in vitro* diagnostic multivariate index assays (IVDMIAs) and analyte specific reagents (ASRs). They presented at FDA’s February 8th public hearing and submitted dozens of formal comments on specific draft guidances. The Coalition was concerned that, if implemented in their present form, ambiguities in the draft guidances for IVDMIAs and ASRs could result in adverse, unintended consequences. They urged FDA and HHS to continue a dialogue with patients, providers, and innovators that could influence Congress's heightened interest in enacting a new law in this sector. Ms. Terry said that Congressional action and the resulting novel or substantially modified statutory authority could ultimately supersede the draft guidance in important ways.

Ms. Terry noted that various legislative initiatives were being introduced and could be enacted that would establish different regulatory provisions. Chairman Kennedy and Senator Smith introduced the Laboratory Test Improvement Act. Although the Coalition provided input on the legislation and shared Chairman Kennedy's interest in safeguarding laboratory tests, they were concerned about specific elements of the bill. They believed it could hinder innovation by regulating all laboratory-developed tests

(LDTs) as Class II medical devices subject to potential premarket review, which would present enormous difficulties for some laboratories and for the FDA. The legislation would be a burden for smaller laboratories that service underserved communities of patients, particularly those with rare diseases.

The Coalition also worked with Senator Obama and his staff on the Genomics Personalized Medicine Act. They encouraged the development and use of high quality LDTs, including genetic tests, and supported the flexible approach to regulation introduced in Senator Obama's bill. The Coalition planned to continue to emphasize the importance of CLIA in ensuring that patients and physicians have timely access to these diagnostics.

The Coalition had requested, through a letter to Dr. Tuckson, that Secretary Leavitt convene a meeting to engage key stakeholders, members of Congress, and agency officials to ensure that a wide range of views would be heard and considered and that appropriate coordination would be achieved among these initiatives before any final decisions relating to a new regulatory provision were put into place. Dr. Tuckson asked that Ms. Terry continue a dialogue on these issues with Dr. Ferriera-Gonzalez, Chair of the Oversight Task Force.

David Mongillo
Vice President for Policy and Medical Affairs, American Clinical Laboratory Association

David Mongillo, representing the American Clinical Laboratory Association (ACLA), focused his comments on recent activities related to the regulatory and legislative oversight of laboratory-developed tests. FDA had recently proposed new guidance on IVDMIAs and had held a meeting on February 8th, 2007 to hear public comment on the draft document. More than 300 representatives attended the meeting and over 30 comments were submitted from clinical laboratories, manufacturers, Government officials, academia, and others. Some common themes emerged from these presentations, including the belief that all laboratory tests should be safe, clinically valid, and effective. FDA was also told that the draft guidance, as proposed, raised concerns and questions that needed further clarification and stakeholder involvement.

Mr. Mongillo noted that two important bills had been introduced in the Senate: Barack Obama's Genomics and Personalized Medicine Act and Edward Kennedy's Laboratory Test Improvement Act. Both bills addressed issues associated with molecular and genetic testing oversight. ACLA was one of 25 organizations that sent a March 16th letter to Senator Kennedy requesting additional time for analysis and discussion of the bill. The sign-on organizations represented professionals and entities comprising virtually the entire spectrum of laboratory and medical interests, including genetic disorder patient groups, genetic and molecular practitioners, genetic-oriented policy groups, pathologists, laboratory technologists, and clinical laboratories. They were united in the opinion that any new legislative initiative in this area should be carefully crafted to focus on specific areas of concern and not be so broad as to encompass laboratory tests that are clinically established or that are serving a valuable purpose for rare disease groups and public health needs. Mr. Mongillo said ACLA wanted to avoid rushing to solutions without thoughtful deliberations on all the issues associated with the need for increased genetic testing oversight. ACLA asked that SACGHS communicate their wish to provide input on these issues before they were finalized.

Session on Oversight of Genetic Tests

Framing the Session
Reed Tuckson, M.D.
Andrea Ferreira-Gonzalez, Ph.D.

Dr. Tuckson recapped the activities of the November 2006 SACGHS meeting relating to oversight. He stated that Judy Yost and Tom Hamilton of CMS reported that a Notice of Proposed Rulemaking (NPRM) on a genetic testing specialty would not go forward as planned. CMS had decided to explore other avenues for strengthening genetic testing oversight that would be faster to implement and, in their view, equally effective—i.e., improving the CMS Web site, providing technical training to surveyors on genetic testing, and collaborating with the Centers for Disease Control and Prevention (CDC) to publish educational materials. Dr. Ann Willey, Director of Laboratory Policy at Wadsworth Center, New York State Department of Health, described the New York State program and conveyed some concerns about gaps in the oversight system. Steve Gutman of FDA described two new draft guidances relating to oversight of certain types of genetic tests. The first clarified that when analyte-specific reagent s (ASRs), the active ingredients in genetic tests, are marketed in combination with other products or with instructions for use in a specific test, they are considered test systems and are not exempt from pre-market notification requirements. The second draft guidance targeted the class of devices known as *in vitro* diagnostic multivariate index assays (IVDMIAs), which use an algorithm to calculate a patient-specific result. The IVDMIA guidance clarifies that these tests must meet premarket and postmarket device requirements appropriate to their level of risk.

Dr. Tuckson further recalled that at the November 2006 meeting, the Committee heard conflicting perspectives from presenters about gaps in the oversight of genetic testing and concluded that it was not clear where the gaps were or who was responsible for addressing them. The Committee decided to probe these issues more fully, and Andrea Ferreira-Gonzalez agreed to chair a task force to organize a fact-finding session and to discuss preparation of a letter to the Secretary expressing concerns about oversight.

Dr. Ferreira-Gonzalez provided an overview of the day's sessions, which were designed to address the oversight roles of Federal, State, and private sector entities in the analytic and clinical validity of genetic tests, followed by presentations on New York and other State laboratory systems. The final presentations would focus on private sector responsibilities for clinical laboratory accreditation, standard setting, and the development of clinical practice guidelines for genetic testing. Dr. Ferreira-Gonzalez introduced Dr. Wylie Burke, who presented via videocast.

Primer on the Oversight of Genetic Testing
Wylie Burke, M.D., Ph.D.
Chair, Department of Medical History and Ethics
University of Washington School of Ethics

Dr. Burke said the reasons for concern about the oversight of genetic testing have been discussed for a decade. Some stem from the fact that many new genetic tests are resulting from the Human Genome Project. They involve many different technologies, complexities in determining who to test, and difficulties in interpreting test results. In addition, many clinicians have a limited knowledge of genetics and are uneasy about using genetic tests. Dr. Burke emphasized four areas in which action can be taken on oversight: statutory regulation, public leadership, decisions about health care funding, and professional leadership.

Statutory regulation of genetic testing at the Federal level comes primarily from Clinical Laboratory Improvement Amendments of 1988 (CLIA) certification of laboratories and the role of FDA in premarket review. The CLIA system provides certification for laboratories that provide test results for clinical use. It provides oversight regarding laboratory procedures and documentation, standards for training laboratory personnel, and the credentials needed for test interpretation. At issue was whether a genetic testing specialty was needed under CLIA.

Dr. Burke discussed the work of the National Institutes of Health (NIH) and Department of Energy Task Force, which published a report on genetic testing in 1997 that found that genetic tests need more attention to ensure a sufficient evidence base before entering clinical practice and called for evidence-based entry of new genetic tests into clinical practice. The Task Force also called for criteria to identify the tests for which special measures should be taken to require validation and clinical utility data before entering the marketplace. The Task Force envisioned that the process would involve an independent review of tests prior to market entry and that professional organizations as well as FDA might play important roles. The Task Force also recommended the establishment of a Secretarial level advisory committee to study this issue further.

As a result, SACGT was established in 1998. In a 2000 report, SACGT recommended that all genetic tests, including laboratory-developed tests, should be subject to FDA oversight. The committee also developed a tool, a data template, to help streamline the review process for what is known and not known about each test in terms of analytic validity, clinical validity (which is often limited when a test comes to market), and clinical utility (information is extremely limited). The Secretary of HHS accepted the Committee's report, which made several other pertinent recommendations, and asked FDA to consider what would be involved in its implementation. SACGHS also tried to develop a simple formula for determining when a test should receive higher scrutiny but decided in the end that there was no simple way to categorize genetic tests because most genetic tests have multiple uses, there are different definitions for terms such as "predictive" and "diagnostic," and test manufacturers would likely seek review under the least problematic test category.

Ultimately, Dr. Burke stated that recent activities of FDA related to oversight indicated that they had identified two areas of priority: pharmacogenomics and test complexity. She stated that test complexity is a more functional way to think about tests that need higher scrutiny than the diagnostic/predictive categorization used by SACGT. She said that FDA had recently issued several draft guidance statements related to this, focusing on the voluntary collection and submission of data and creating a "safe harbor" in which to explore interesting data that could inform manufacturers and the public about appropriate development and use of drugs. FDA also made a statement about its intent to change the clinical pharmacology section of the drug label to include pharmacogenomic information when it is relevant to the use of the test. In the past several years, FDA approved several genetic test kits—e.g., Roche AmpliChip, Invader UGT1A1, and HER2 molecular assays. The agency issued a draft guidance proposing the extension of oversight to IVDMIAs, tests that utilize both laboratory data and analytic tools to generate results, such as gene expression profiles that might predict cancer prognosis and guide the use of chemotherapy.

Dr. Burke said it was an open question whether different kinds of statutory regulation were needed for direct-to-consumer (DTC) tests. She noted that a Government Accounting Office report on nutrigenetic testing raised questions about whether Web sites offering nutrigenetic tests were misleading consumers.

On the topic of genetic discrimination, Dr. Burke said that the role of the Americans with Disabilities Act (ADA) in providing protection against genetic discrimination was unclear. Based on the courts' interpretation of ADA claims in nongenetic cases, it seemed that ADA would provide protection only when people's lives are actively interrupted. Genetic susceptibility is not likely to meet that standard. The other opportunity for oversight concerning genetic discrimination was legislation at the Federal level.

At the State level, statutory regulation plays an important role in genetic testing. Some States have more stringent laboratory oversight than is called for by CLIA. Many States enacted genetic nondiscrimination legislation, although it had not yet been tested in the courts. Newborn screening is also under the oversight of the States.

Dr. Burke said the role of statutory regulation in the oversight of genetic tests was not clear. However, at FDA, there was an ongoing concern about whether there should be more regulation concerning performance of genetic tests in laboratories and uncertainty about measures that should be taken to protect consumers from DTC tests. Statutory regulation was a potential vehicle for standardized reporting and labeling of information about genetic tests, but, in her opinion, not a route for establishing a standard of practice around the use of genetic tests. Dr. Burke felt that other mechanisms were more likely to be effective, as described below.

She said Federal agencies, in addition to regulatory responsibilities, have the opportunity to provide public leadership in a variety of ways. These include promoting best practices and supporting education and training, practice guidelines, and research. Dr. Burke cited the example of the Division of Laboratory Sciences at CDC. The Laboratory Practice Evaluation and Genomics Branch within this Division is providing leadership for quality control and quality assessment in the development of technology and practice improvement. Other activities include education and training, research activities, and policy development (e.g., interaction with CLIA on standard setting).

Dr. Burke stated that public leadership extends to such areas as guideline development, stating that the Evaluation of Genomic Applications in Practice and Prevention project (EGAPP) is an important initiative of CDC and AHRQ. In addition to providing guidance on the use of some genetic tests, EGAPP was working on establishing methodologies for evaluating genetic tests and addressing the level of evidence sufficient for claiming that a particular genetic test is ready for clinical use. The U.S. Preventive Services Task Force had also provided some important guidelines, notably around BRCA testing. The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was very active in the area of newborn screening.

Dr. Burke noted that public leadership could contribute to the translational pathway, which begins with research on the genetic contribution to disease and ultimately leads to improved health outcomes. Federal research support is critical in the early part of that pathway, such as that provided by NIH, AHRQ, CDC, and the Health Resources and Services Administration. There is great potential for enhancing oversight through Federal research support for educational research and interventions (helping providers and patients use genetic testing appropriately), for a focus on clinical utility (starting with clarifying the term and determining what kind of evidence would be needed to support clinical utility for different kinds of tests), and for research into ethical, legal, and social implications and policy options. Dr. Burke said it was an open question whether more Federal support should be provided in specific areas.

Dr. Burke said that future decisions about health care funding will have a powerful impact on whether a test is used, even when it is available for clinical use. Challenges include determining when genetic

counseling is essential and who should provide it, inflexible reimbursement rules, and inequitable access to genetic services because they are underfunded or because people lack insurance.

Professional leadership and collaborations by organizations could play a powerful role in creating standards of practice. Professional organizations could help identify the importance of genetics issues for their members, whether in national meetings or stand-alone educational programs. They can also play an important role in laboratory oversight, working within the context of CLIA to set standards and create PT programs. They develop practice guidelines, which are a trusted source of information for doctors. Dr. Burke said the problem with practice guidelines is that they are "all over the map." Many different bodies provide guidelines using different processes, some of which are more transparent and evidence-based than others. Professional, personal, or financial interests sometimes affect the process, and methodologies vary and are not always disclosed. Even if the processes used are good ones, the evidence may be lacking. Public and professional leadership is important in ensuring that research is being conducted to gather evidence and that practice guidelines follow rigorous procedures so they can provide legitimate guidance. Dr. Burke said it is necessary to acknowledge that "standard of practice" is an evolving concept. As new data emerge, guidelines must be revised. In the field of genetics, technology is evolving rapidly and the quality of evidence is increasing over time. Case law also influences what is meant by standard of practice.

Dr. Burke stated that health professional education has the potential to enhance other efforts by enabling health care providers to make good judgments in gray areas. However, there are many challenges. Traditional methods of holding conferences and lectures do not have much impact on physician practice. Many genetics curricula are collecting dust. Dr. Burke said it would be important to talk to individuals in need of genetics education to determine what would be most relevant to them.

Dr. Burke closed by stating that different approaches to the oversight of genetic testing have the potential to be complementary. She said it would be a challenge to think through what should be expected through statutory regulation, public and professional leadership, the research agenda, better practice guidelines processes, and education.

Dr. Ferreira-Gonzalez opened up the floor for questions. Dr. Marc Williams asked Dr. Burke to address postmarket data collection and surveillance. Dr. Burke stated that if there is not much evidence available when a test enters the clinical arena, even more evidence will be needed postmarket. Some questions, such as the clinical validity of a test, can only be answered over time. Dr. Burke raised the idea of a premarket review that has requirements for certain kinds of postmarket data collection. She also asked what kind of partnerships should be put in place to maximize the quality of the information obtained postmarket, such as the laboratories offering the tests, large health care systems that have a stake in the proper use of these tests, and appropriate public participation through funding. These partnerships might create systems in which there is prospective planning for gathering data on the uptake, outcome, and ultimate clinical effects of new tests.

Dr. Williams asked if Dr. Burke felt the Collaboration, Education, and Test Translation (CETT) model of translation for rare diseases could be applied for common disease-based genetic tests. The model has incentives built in to translate knowledge into the clinical arena and it requires transparency, educational materials for patients and providers, and data collection for five years after a test is in clinical practice. Dr. Burke said that the questions would be the same, but pointed out that some of the logistics issues would be more complex, such as the need to collect data more broadly and to collect comparative data.

Dr. Ferreira-Gonzalez asked Dr. Burke for her view on genetic exceptionalism. Dr. Burke replied that genetic tests have extraordinarily high predictive value compared with other medical tests. The idea that genetic tests require a different approach to oversight is based on that fact. In addition, genetic tests raise questions about family members that are not raised by other tests. There is greater cost effectiveness if family members at risk are identified, but this leads to unique issues concerning confidentiality and privacy. Dr. Burke stated that since our society accords tremendous power to genetic information, people are concerned about discrimination. However, she cautioned against pushing the concept of genetic exceptionalism too far.

Dr. Julio Licinio asked whether there should be special protections when the genetic contribution to disease is very small (e.g., 3 percent in the case of a common, complex disease). He pointed out that a specific variant associated with depression, diabetes, or arthritis does not mean that an individual will have the disease. Dr. Burke said this was a tremendously important issue, and she worried that a variant that predicts a small increased risk of type II diabetes would be viewed as having the same power as a test for a Mendelian disease. She suggested that public and professional leadership and those involved in health professional education craft the right kind of messages about multifactorial disorders.

New York State's Clinical Laboratory Evaluation Program
Ann M. Willey, Ph.D., J.D.
Director of Laboratory Policy and Planning
Wadsworth Center
New York State Department of Health

Dr. Willey said that New York State has had statutory regulatory authority concerning clinical laboratory oversight since 1964, which predates CLIA. The 1964 statute was passed to limit the practice of laboratory medicine to laboratories physically in the State of New York, which infringed on interstate commerce. The statute was challenged in the Federal courts and overturned in its ability to restrict business to laboratories in New York. However, the same court said that the State could apply its standards to any laboratory doing business in New York. Thus, the New York State regulations now apply to other States as well as laboratories around the world, including Iceland, the United Kingdom, and Hong Kong. If a specimen is drawn in New York State and shipped to a laboratory anywhere in the world, the laboratory is subject to New York licensure requirements. Dr. Willey clarified that New York does not regulate manufacturers of kits, devices, or reagents—only laboratories.

The New York statute says that "a laboratory shall perform only those assays that have been validated or verified at the site where the assay will be performed." This statute applies primarily to multisite, large commercial entities that want to validate an assay at one site and then transfer it to other sites. They must reproduce the validation data at any site at which they intend to offer the test or ship all the specimens for that assay to one site. A laboratory must hold the appropriate permit category for the test. New York State has 26 specialties, with 70 different categories in which they issue permits. Every test falls into one or more of those categories. The laboratories must meet all other requirements related to personnel, PT, and onsite inspection. New York State review of the validation of a laboratory-developed assay or an assay using certain commercial reagents is part of an integrated program, and inspectors are familiar with the types of personnel required in the laboratories. Every category must have an Assistant Director or Director holding specified credentials. They must be doctoral-degreed individuals with a minimum of four years postdoctoral clinical laboratory experience and a minimum of two years in the specialty. All other personnel must meet relevant training experience. The laboratories are physically inspected every two years for their quality assurance program, quality control, reagents, equipment, and physical location.

They are required to participate in New York State's PT program and encouraged to participate in any other relevant proficiency tests.

Dr. Willey listed assays that require specific validation review for approval prior to offering the test. These include commercially distributed assays labeled for research use only (RUO) and those using ASRs. Other assays that require validation review include FDA-approved assays or investigational use only assays that have been modified from their intended use or investigational device exemption approval from the FDA, and any in-house developed assays. Dr. Willey stated that a change in an intended use is a change in the specimen type, the type of analysis (e.g., qualitative or quantitative), the purpose of the assay (e.g., screening, diagnosis, prognosis, monitoring, confirmation), or the target population, as specified by the FDA or outlined in the package insert.

The materials submitted for validation review must include the assay name; the manufacturer of any reagents other than those they make themselves (the majority of laboratories obtain reagents from manufacturers); if using manufactured components, the commercial designation (e.g., RUO, ASR); the method or scientific principle behind the assay; the New York State permit category; the specimen type (e.g., blood, tissue, bone marrow); the target population(s); the purpose (e.g., diagnostic, prognostic, screening, predictive); whether it is qualitative or quantitative in intent; the performance evaluation method (e.g., comparability to an established method or correlation of results to clinical status of test subjects); assay description and complete standard operating procedures; practitioner/patient information, including limitations of the test; specimen collection instructions; the principle of the assay and indication of clinical validity (usually as reported in the literature); equipment list; reagents and their sources; controls; means of calculating or interpreting the result; interferences and limitations; copy of test requisition; for germline genetic tests, policy and compliance documents relevant to informed consent; sample reports for both normals and abnormals, including all necessary disclaimers; scientific references; analytical validation data; analyte and specimen matrix stability; reagent source and quality, particularly for RUOs; and performance characteristics of the assay (e.g., accuracy, precision, reportable ranges, sensitivity, and specificity).

In cases where performance evaluation is based on the clinical outcome of test subject status, additional information is needed on protocols to establish clinical status, protocols to blind specimen evaluation from clinical status, how discrepant results are resolved, and how predictive value calculation is done. New York State standards also require that cytogenetics and genetics laboratories report with an interpretation suitable for a nongeneticist physician, reference ranges (e.g., the heterozygote and homozygote results for germline genetics of single gene disorders), and whether the assay predicts disease state. Also required are the assay data for representative runs, the quality assurance plan, and the internal PT design. New York State has its own cytogenetics proficiency test and occasionally tests the ability of a laboratory to perform fluorescence *in situ* hybridization (FISH). All laboratories must have some form of proficiency assessment twice a year for every analyte. They must develop their own blinded proficiency assessment, usually using materials derived from previous specimens. When surveyors visit, they ask to see the data and the design of the assay.

Dr. Willey provided some statistics on the program's workload since 1995. During that year, they looked at eight assays, all of which were for genetics. In 2006, they looked at 586 assays. The majority was for genetics and included genetic testing, biochemical genetic testing, deoxyribonucleic acid (DNA)-based genetic testing, cytogenetics, preimplantation genetic diagnosis, forensic DNA technologies, paternity identity, histocompatibility, and oncology molecular markers.

Dr. Willey said they are often asked about the impact of the New York State program on testing in this country. She said they have 70 cytogenetics laboratories in the country, five of which are preimplantation genetic diagnosis laboratories. There are 32 laboratories that perform biochemical genetic assays and 71 molecular genetics laboratories, including four that perform preimplantation genetic diagnosis. The impact of the New York State validation review program is that all major reference laboratories solicit and receive specimens from New York and are subject to New York clinical laboratory permit requirements, including approval of in-house developed assays. It has been estimated by others that as much as 75 percent of all cytogenetic and genetic testing performed in the United States (numbers of specimens tested, not number of laboratories) is subject to New York State oversight. GeneTests estimates that more than 300 laboratories are subject to New York requirements. Dr. Willey stated that tort law medical malpractice cases have not looked favorably on laboratories subject to New York State standards that apply less stringent standards to the testing of specimens from other jurisdictions. Concerning other States, Dr. Willey said that 26 have some degree of statutory authority for oversight of the practice of clinical laboratory medicine. Washington is the only other State that has CLIA-exempt status, and they do not have specific standards for genetic testing. California, through its Genetics Disease Branch and newborn screening and prenatal screening program, has rigorous review of those types of assays. That oversight does not generally extend to other genetic testing. New Jersey applies some personnel standards of the American Board of Medical Genetics to laboratories that perform genetic testing. Dr. Willey said she knew of no State that requires review of validation data for individual assays, other than in the context of a physical onsite inspection which, for most State programs, does not involve peer review.

Dr. Willey explained how the New York State program addresses harms. She stated that if specimens are sent from New York to a laboratory that offers unvalidated assays or assays that the State believes are problematic, New York is aggressive in sending the laboratory a cease-and-desist letter, warning that they can be fined $2,000 a day for continued operation or $2,000 a specimen. She gave the example of a laboratory in New England that offered to predict the gender of fetuses at 5 weeks but had never submitted validation materials to the State to indicate analytical validity. Other laboratories have offered to conduct single nucleotide polymorphism (SNP) profiles and provide them to patients' clinicians on a compact disc (CD), claiming that the physicians will be able to interpret the data and predict medical needs. The laboratories have not been able to document clinical validity for the vast majority of those SNPs. There have also been serious challenges from laboratories that wish to perform nutrigenomics (i.e., profiling SNPs that they claim are linked to genes that may predict responses to nutritional products). These laboratories have not proven clinical validity. Some entities offer profiling for ancestry and paternity. In New York State, consumers cannot legally order laboratory tests other than those that have been approved by the FDA for over-the-counter self-testing. The laboratories cannot accept any of those tests without the written consent of the person being tested. Laboratories in violation are told they must cease and desist.

Dr. Willey said the greatest challenge of the New York State program is its expense. The costs for personnel and expertise to conduct the reviews are significant. The cost to the laboratories is also high, and there is a lawsuit pending because some laboratories did not want to pay for that part of the program. It is time-consuming for laboratories to prepare documentation for these validations in a format that can be readily reviewed by State staff. The major criticism of the New York State program is turnaround time. The program tries to complete reviews within 45 days, but some packages wait for a year or more. Often, the packages go back to the laboratories more than once for more information before being approved. The largest contributing problem is that laboratories frequently ignore previous critiques and their submissions

are poorly organized. Dr. Willey noted that the State also has an active program for investigating complaints.

In New York, if a physician wants to order a test that is not offered in an approved laboratory or is offered only in a laboratory whose documentation is awaiting review, a specific request can be made for a non-permitted laboratory approval based on medical necessity. The permit granted is for a one-time test for a specific patient in a specific laboratory. A letter is sent to the doctor stating that the laboratory is not approved for the test and that the State cannot guarantee the results. There is a 24-hour turnaround time for those requests.

Dr. Ferreira-Gonzalez asked if the program examines clinical utility. Dr. Willey replied that it does not and clarified that when she used the term "clinical outcome" she meant whether the patient is symptomatic of the disease for which the test is being established (i.e., clinical validity). Dr. Ferreira-Gonzalez also asked how they identified DTC laboratories. Dr. Willey said this occurs through the Internet, general health care, pharmaceuticals, and laboratory entities soliciting the submission of specimens. She said several companies have established themselves as test facilitators. They market to consumers at high costs, often 10 times what a laboratory would charge, and they do not perform the tests themselves. Sometimes they use legitimate laboratories for legitimate validated assays. Dr. Willey noted that New York State requires the laboratory to bill patients directly.

Dr. Williams asked if the program had begun to develop standards concerning what information laboratories should be reporting back on variance of unknown significance for DNA. Dr. Willey said the laboratories have to be able to describe how are they going to resolve the issue—Are they going to sequence the gene? Are they going to send it to another laboratory? How are they going to report it?

Dr. Tuckson thanked Dr. Willey and asked her to help the Oversight Task Force as they move forward with the Secretary's charge. Dr. Ferreira-Gonzalez introduced Dr. Gail Vance.

Accreditation of Genetic Testing Laboratories
Gail Habeggar Vance, M.D., FCAP
College of American Pathologists

Dr. Gail Vance said she would be speaking on the College of American Pathologists (CAP) accreditation program as it pertains to molecular pathology, cytogenetics, and PT. The goals of the CAP accreditation program are to assure that tests are analytically and clinically valid and that there is patient safety, patient access to testing, and innovation and improvement of laboratory-developed tests. The accreditation program is designed to assure that high-complexity laboratory tests are provided by high-quality laboratories that assure analytic and clinical validity of their tests, have patient safety plans in place, and have incremental improvement and innovation in testing and that testing is not impeded.

CAP is a professional organization composed of approximately 16,000 board-certified pathologists. The accreditation program is CMS-approved and, like New York, holds to a higher standard than the CLIA regulations require. There are specialized inspector requirements for genetics laboratories, many of which are developed through scientists on the Scientific Resource Committees. Approximately 24 of these committees develop specialty accreditation requirements. In the field of genetics, there are hybrid committees composed of both College members who are pathologists and laboratory scientists who are members of the American College of Medical Genetics (ACMG). Laboratories enrolled in the

accreditation program are required to report and update their testing menu continuously. This effort allows CAP to know what the laboratories are testing for and provide the required PT.

The CAP accreditation program began in 1961, predating CLIA, and was initially voluntary. The first Cytogenetics Checklist and inspections were offered in 1976, and a Molecular Pathology Checklist was created in 1993. Laboratory members of the accreditation program are required to undergo inspections by a team of external reviewers every two years. The team is usually composed of peer inspectors who are actively practicing scientists in the specialty they inspect. The inspection tool used is the checklist, which allows laboratories to understand the standards to which they are being held. CAP offers approximately 18 checklists consisting of about 3,500 discipline-specific laboratory requirements. Over half of these requirements, approximately 1,700 questions, are in addition to CLIA minimal standards. Some of the special disciplines not covered by CLIA include forensic testing, autopsy, histology processing, embryology, and molecular pathology. Sections within traditional disciplines that go beyond the CLIA standards include PT for nonregulated analytes, laboratory computer systems, laboratory safety and hygiene, prenatal screening, and sweat chloride testing.

CAP inspectors are actively practicing molecular scientists familiar with the checklist to be utilized and possessing the technical and interpretive skills necessary to evaluate the quality of the laboratories' performance. Inspector training includes live training seminars or online interactive training modules. There are also audio conferences for discipline-specific areas. As of July 2006, every Team Leader must have completed mandatory training and must renew that training every two years. Regulations were being put in place for a requirement for retraining of team members every two years.

Standards that apply to genetics and exceed CLIA requirements include clinical validation, use of universal and proper nomenclature, correlation with clinical information and other studies, recommendations for genetic counseling and further studies, and turnaround time requirements. Examples of how CAP standards exceed CLIA are found in two of the questions from the Molecular Pathology Checklist: "Are the clinical performance characteristics of each assay documented, using either literature citations or a summary of internal study results? Does the final report include an appropriate summary of the methods, the loci or mutations tested, the analytical interpretation, and clinical interpretation, if appropriate?"

The CAP Molecular Pathology Checklist covers most aspects of clinical molecular testing, including not only inherited genetic testing, but also acquired genetic testing. It includes oncology, hematology, infectious disease, inherited disease, histocompatibility typing, forensics, and parentage applications. Any testing that involves DNA, ribonucleic acid, or nucleic acid probe hybridization or amplification constitutes molecular testing. Techniques covered by this checklist include requirements for extraction and purification, amplification, restriction endonucleases, sequencing, detection, real-time PCR, arrays, and *in situ* hybridization, all of which exceed CLIA requirements. CAP is piloting a test for comparative genomic hybridization arrays in the Cytogenetics Resource Committees and hopes to offer that as a proficiency test in the future.

The CAP Cytogenetics Checklist covers cytogenetic testing, including both standard G-banding and molecular cytogenetics. It covers chromosome analysis of amniotic fluid and chorionic villi, non-neoplastic blood and fibroblasts, and neoplastic blood and bone marrow. Techniques with specific compliance requirements include the establishment and maintenance of cultures, cells counted, karyotypes, band levels of resolution, and FISH.

Dr. Vance described how the accreditation process is conducted. She said that if a deficiency is cited during an inspection, the laboratory must respond to CAP with a corrective action plan within 30 days. A two-tier review process by a CAP technical staff analyst and a practicing pathologist designated as a regional commissioner to CAP determines the adequacy of the action plan and the laboratory's ability to maintain sustained compliance. However, the ultimate decisionmaking resides with the Accreditation Committee of the Council on Accreditation, which is composed of laboratory experts. On alternate years, when the laboratories are not being externally inspected, they are required to complete a self-inspection and submit the results. These results go into the inspector packet for the next cycle of external inspection.

CAP accredits approximately 6,500 national and international laboratories, including approximately 250 laboratories in the cytogenetics discipline and approximately 700 laboratories with a molecular pathology discipline. CAP accreditation includes 98 of the top 100 hospitals and the majority of large commercial reference laboratories, including LabCorp and Quest.

Some of the most common deficiencies cited in molecular pathology are in response to the following questions: 1) In cases where there is no commercially or externally available PT, does the laboratory at least semiannually (in compliance with CLIA) participate in external PT or exercise an alternate performance assessment system for determining the reliability of analytic testing? 2) Are temperatures checked and recorded appropriately for equipment in which the temperature is critical? 3) Is there a summary statement signed by the laboratory director or designee documenting review of validation studies and approval of the test for clinical use?

Some of the most common deficiencies cited for cytogenetics are in response to the following questions: 1) Are the final reports for tests requiring rapid reporting results available within seven days of specimen receipt in at least 90 percent of cases? 2) Are the final reports for neoplastic bloods and bone marrow analysis provided within 21 calendar days of specimen receipt in at least 90 percent of cases? 3) Are reagents and solutions properly labeled as applicable and appropriate? Dr. Vance explained that there are four or five criteria that must be labeled on the reagent and if only one of those is missing, the laboratory is cited for a deficiency.

CAP offers external PT for genetic laboratories, allowing them to evaluate their performance regularly and improve the accuracy of their results. Each laboratory is provided with unknown specimens for testing. They are told the category, but not the specimen. The participants analyze the specimens and return the results to CAP for evaluation. The results are evaluated by the Scientific Resource Committees or their peer groups from a comprehensive database of laboratories. CAP's proficiency tests in genetics are among the few in existence. Some of the products available include chromosomal abnormality identification, FISH using chromosome-specific DNA probes, biochemical genetics for metabolic diseases, and molecular analysis of lymphoma and leukemia. Dr. Vance displayed an algorithm that indicated what it looks like when there is a PT failure in a laboratory. If a laboratory receives an unsatisfactory PT evaluation on one PT event, it is issued a warning for testing for that analyte. They are also provided with educational materials on how to improve. The laboratory is monitored and if there is one unsatisfactory report for the next two PT events, the laboratory is given a choice: cease testing for that analyte or document a plan for corrective action. If a corrective action plan is submitted and considered acceptable, the laboratory is allowed to continue testing for that analyte until the next PT event, although at maximum for six months. If the next PT is satisfactory, the laboratory is monitored for another PT cycle. If their results are good, they are allowed to continue testing. If, on the following PT event for that analyte, they again receive an unacceptable response, they are required to cease testing for

that analyte. The laboratory must sign a cease testing form and document a plan of action for that analyte. The earliest that the laboratory could test for that analyte again is six months.

Dr. Vance displayed a summary of the PT performance results for 2006. The analytes tested included Factor V Leiden, prothrombin, prothrombin interpretation, methylene tetrahydrofolate reductase, fragile X mental retardation, Prader-Willi syndrome, hemochromatosis, Duchenne muscular dystrophy, and hemoglobins S and C. Laboratory performance on these analytes was generally good in 2006.

Dr. Vance said the CAP laboratory accreditation program can serve as a model for improving the quality of laboratory-developed tests. The CAP accreditation process improves patient care and protects the public's health, but does not stifle or impede test development, innovation, and improvement. CAP's recommendation to SACGHS was that private organizations, including CAP and laboratories, should build on the work of CLIA that has been successful over the previous 15 years. CAP believes that the goal of assuring analytic and clinical validity for all high-complexity laboratory tests could best be achieved through the CLIA inspection process. Dr. Vance concluded by stating that, to achieve this goal, statutory changes to CLIA may be needed.

Dr. Ferreira-Gonzalez thanked Dr. Vance and introduced Dr. Carolyn Sue Richards.

Clinical Laboratory Standard Setting
Carolyn Sue Richards, Ph.D.
Professor of Molecular and Medical Genetics
Director of the DNA Diagnostic Laboratory
Oregon Health and Science University

Dr. Richards said she is involved in standards development with a number of groups but was speaking primarily as a representative of ACMG. Through ACMG, there are multiple mechanisms for setting professional guidelines, including the Laboratory Quality Assurance Committee, the Professional Practice and Guidelines Committee, and ACMG special projects for commissioned guidelines.

There are three types of ACMG statements that can be viewed as standards: policy statements, which are often responses to a single issue that must be addressed immediately; a practice guideline, which is a clinical guideline on the testing that should be done in specific settings but often does not specify how testing should be performed; and laboratory standards and guidelines, which address how laboratories should perform particular tests. The purpose of ACMG standards and guidelines, which are voluntary, is to provide an educational resource to assist medical geneticists in providing accurate and reliable diagnostic genetic laboratory testing consistent with current technologies in clinical cytogenetics, biochemical genetics, and molecular diagnostics.

The ACMG Laboratory Quality Assurance Committee is dedicated to evaluating new technologies, monitoring accreditation requirements, and, through CAP, monitoring laboratory PT. Committee representatives attend meetings of the CAP Resource Committee to monitor laboratory performance. They use this information as a trigger for developing new standards and guidelines. For example, if there is an analyte for which laboratories are performing poorly, the Committee addresses the problem with a guideline. The guidelines therefore change continually over time. They also include model laboratory reports. Since 2000, ACMG has issued disease-specific guidelines.

The Laboratory Quality Assurance Committee functions as a resource for education, including for the nongenetics communities. When new guidelines are developed, ACMG reaches out to different professional groups and organizations and conducts workshops. They believe all health professionals will have a role in the genetic testing process and, as such, need to be conversant with test quality issues and the communication of test results interpretation. Three working subcommittees, composed of clinical laboratory geneticists certified by the American Board of Medical Genetics, address molecular, cytogenetic, and biochemical genetics. A biostatistician helps with validation questions and statistical work. Outside experts are frequently used for selected topics.

Some Laboratory Quality Assurance Committee representatives are involved in the Clinical and Laboratory Standards Institute (CLSI) and some work with EGAPP projects. ACMG has a pulse on activities in genetic testing and tries to address new issues as they arise. Dr. Richards said that standards ensure the quality of genetic testing by setting a standard of practice in the field. They are used to develop laboratory inspection checklists for CAP as a regulatory requirement for accreditation. They are also used to develop PT challenges and test interpretations through the CAP process and as an educational resource.

Dr. Richards provided an example of how ACMG professional guidelines have intersected with Government projects. The CDC and NIH sponsored meetings about promoting quality laboratory testing for rare disease in 2004 and 2005 to address quality, availability, and accessibility of genetic testing for rare disorders. The CETT project, a laboratory guideline developed by ACMG on technical standards, and guidelines for molecular genetic testing for ultrarare disorders resulted from this work.

Dr. Richards said there is a need for guidelines and standards to ensure quality assurance for genetic testing, and ACMG believes they can play a major role in their development and they were interested in working with SACGHS to answer questions about technologies, personnel, test validation, quality control, quality assurance, and test interpretation. They address preanalytical, analytical, and postanalytical test issues and pitfalls that could be involved in genetic testing. A number of guidelines were in development through the various ACMG working groups. “Quality Watch” is a program for reporting and following up on adverse events that might be caused by laboratory products or reagents that impede accuracy in genetic testing. Quality Watch was to be launched on the new ACMG Web site in May 2007.

Dr. Richards described how standard development is supported. Committees are composed of unpaid volunteers and are supported from public and private sources, including industry. Costs can range from $100, 000 (e.g., the pharmacogenetics standard and guideline) to $1 million (newborn screening documents). Costs include meeting costs, evidence-based reviews, and administrative costs.

Standard development begins when a need is identified. Approval is sought from the Laboratory Quality Assurance Committee, and a leader and working group of five to six members are appointed. They develop documents through conference calls and e-mails. They hold two face-to-face meetings a year, and the remaining work is done behind the scenes with no funding. If a guideline is fast-tracked, it can reach draft form within six months. Many guidelines take much longer. There is a thorough review process that is similar to the CLSI consensus document review process. Several rounds of revisions include comments from the full Laboratory Quality Assurance Committee, the Board of Directors, experts in the field, and others who review the document online on the ACMG website. After all comments are addressed, the draft is sent to the Board of Directors for approval. If approved, the document is posted on the Web site and published in *Genetics in Medicine*. There is an ongoing renewal and revision process that ensures that the document keeps pace with advances in knowledge in technology. Although adherence is voluntary,

the standards are used for developing accreditation standards and PT models and are therefore indirectly enforced through CAP.

The ACMG standards exceed CLIA requirements, have incorporated some of New York State's requirements, and are attentive to their European and Australasian counterparts. ACMG has a strong focus on nomenclature standards and reporting standards.

Dr. Richards said standard-setting organizations interact with and involve the Government in various ways. They respond to the Government on guidance statements and legislative proposals and include Government representatives in the committee work that develops the standards and guidelines. She acknowledged that there are, and always will be, gaps in current standards because professional organizations cannot keep pace with test development.

Dr. Richards closed by suggesting that SACGHS address issues related to gene patents and licensing that are affecting test validation. She said that exclusive licensure of testing to a single entity will not allow for the expertise needed to develop standards or support PT. She concluded her remarks by stating that the ACMG guidelines are available on the Web site www.acmg.net.

Dr. Ferreira-Gonzalez thanked Dr. Richards and introduced Dr. Alfred Berg, who presented via teleconference.

Development of Clinical Practice Guidelines
Alfred Berg, M.D., M.P.H.
Professor and Chair
Department of Family Medicine
University of Washington

Dr. Berg described clinical practice guidelines as recommendations issued for the purpose of influencing a decision about a health intervention. They have been in existence as long as medicine has been practiced. In the past, many guidelines were well intentioned but were proved incorrect in practice. Dr. Berg noted that there is renewed attention to guidelines because medical literature is increasingly complex, which makes it difficult for an individual clinician to understand a given clinical topic. Patients are increasingly interested in participation in medical decisions, including guidelines. There is also legal pressure to define standards in medicine. He said there are now better methods to generate guidelines than there were in the past.

Clinical guidelines are needed because clinicians cannot keep up with the large volume of emerging medical literature. Guidelines help make sense of thousands of articles on a given clinical topic. They help clinicians deal with complex decisions, improve the quality of decisionmaking, and provide justifications to patients, payers, and the legal system about why decisions are made. Guidelines are useful for transmitting medical knowledge, assisting with patient and physician decisions, setting clinical norms, contributing to quality improvement projects in hospitals and group practices, and privileging and credentialing, and they can be used for payment, cost control, and medicolegal evaluation.

Dr. Berg stated that in the past, most guidelines were constructed using "global subjective judgment." This technique had clinicians meet together to develop guidelines based on their own judgment. The process was not transparent. Now guidelines are increasingly explicit and evidence-based. The hallmarks of evidence-based guidelines are that they are clearly laid out, transparent, and publicly accountable. Dr.

Berg listed the characteristics the Institute of Medicine specifies as important to clinical guideline development: the guideline should be extremely clear about the clinical condition addressed; the health practice or intervention proposed; the target population; the health care setting (e.g., whether a specialist setting or primary care setting); the type of clinician (e.g., nurse, physician, nurse practitioner, or physicians assistant); the purpose (e.g., to improve clinical care); and the source of the guideline and sponsorship (e.g., who is funding guideline development).

AHRQ has also specified a number of process characteristics for clinical practice guidelines. These include: How was the panel selected and what were the screens for potential conflicts of interest? How was the problem specified? How was the literature search strategy devised, how was the analysis conducted, and how was the evidence summarized? How does the evidence link to the recommendations made? What are the clinical outcomes? Dr. Berg said the process should be sensitive to cost and practicality. AHRQ's attributes of a guideline are that it be valid, reliable, practically applicable, flexible, clear, multidisciplinary, peer-reviewed before publication, and well documented. AHRQ's specific characteristics of validity include clear projected health outcomes, projected costs, and any policy rationale. It should be evidence-based, including a rigorous literature review and literature evaluation. Dr. Berg stated that there is growing availability and promotion of genetic tests and that clinicians need authoritative advice. Although evidence-based processes for clinical guidelines have evolved, there are challenges in using these methods for genetic tests. Many conditions in genetic testing are uncommon or exceedingly rare, and the interventions and clinical outcomes are not well defined. The technologies for interventions and test characteristics are changing so rapidly that there is not enough time to thoroughly examine the clinical outcomes. Many genetic tests have inadequate sensitivity and specificity in the general population. Many tests are proposed and marketed based on descriptive evidence and pathophysiological reasoning, not evidence from clinical trials. A number of advocacy groups from industry and patient special interests are concerned about these challenges.

Dr. Berg focused specifically on EGAPP, for which he is a panel member. EGAPP has a nonregulatory, multidisciplinary panel composed of independent, nonFederal employees. The panel underwent an exhaustive conflict of interest review to ensure that no participants had biases about genetic testing or had financial interests at stake. The panel's process is evidence-based, transparent, and publicly accountable. The goal is to establish and evaluate a systematic and sustainable mechanism for premarket and postmarket assessment of genomic applications in the United States. The first two years focused on the methodology, which includes topic selection, an analytic framework for literature search strategies and assessment of the evidence, attention to analytic and clinical validity, and a way to specify clinical outcomes. Many of the clinical outcomes in genetic testing are different from clinical outcomes in other domains of medicine. The project made significant progress in advancing the field of clinical outcomes and was developing a manuscript for publication that outlines four general categories: health information impact, therapeutic choice, impact on patient outcomes, and impact on the family and society.

The work plan steps are to select topics, define relevant clinical outcomes, conduct reviews and make recommendations, and test methods. The first topics examined were cytochrome P450 (CYP450), hereditary nonpolyposis colorectal cancer (HNPCC), and ovarian cancer screening. EGAPP is experimenting with brief reviews when the data are limited. Since they may not be able to cover all the components in a full clinical practice guideline, the scope is narrow. The first review was a UGT1A1. Dr. Berg said they were midway through the third year of a three-year project that was extended to four years and might be extended to five years. They hope to conduct three to five major reviews and two to three brief reviews, to publish their methods, and to conduct a rigorous evaluation.

Dr. Berg walked through the clinical scenario for the EGAPP topic of CYP450 testing, which was fairly advanced, to give the Committee a sense of how the panel works. The question asked was: Does testing for CYP450 polymorphisms in adults entering selective serotonin reuptake inhibitors treatment for nonpsychotic depression lead to improved outcomes or are testing results useful in medical, personal, or public health decisionmaking? It was hoped that the results would provide useful advice to clinicians and patients. They started by developing an analytic framework. Out of that framework, they extracted a series of key questions and conducted an explicit search using a standard abstract, full text, and two reviewers. They assessed the quality of evidence, and when there was enough information to put into a table (which was not often), they created evidence tables.

The overarching question was: Does testing improve outcomes? Derivative questions were: What are the test characteristics? What are the correlations of the tests with efficacy and adverse effects? Are there any known effects on management, clinical outcomes, or decisionmaking? Are there harms associated with testing? The preliminary observations for CYP450 testing found that there are some data on sensitivity and specificity, but no studies directly linking testing to clinical outcomes. The studies they found were small, poor-quality cohort studies. No studies directly compared alternative testing strategies, and many of the studies failed to account for the relevant genotypes, making it difficult to combine the studies and develop a single clinical recommendation.

Dr. Berg summarized the apparent gaps in genetic testing evidence, including gaps in knowledge about the prevalence of these abnormalities in the general population, a gap in evidence regarding the penetrance of the abnormalities into something that is clinically recognizable, an absence of clinical trials that compare testing and intervention strategies, an absence of studies that fully assess all relevant outcomes, a lack of attention to harms, and very little literature on the cost and feasibility of these technologies. His personal observations were that a large and growing number of tests are marketed to clinicians and consumers in the United States, and the national attitude seems to be that "more is always better" and "technology is always good." This environment is relatively hostile toward regulation. There is potential to use these technologies for both benefits and harms, but unfortunately there is limited evidence. Dr. Berg stated that he was surprised that the EGAPP topics had so little evidence because they were chosen based on the belief that they had the most data.

Roundtable Discussion

Dr. Tuckson reviewed the charge given to SACGHS earlier in the day. Dr. Ferreira-Gonzalez asked Dr. Vance if she could account for the apparent discrepancy between the public comments from the Genetics and Public Policy Center (GPPC), which stated that two-thirds of laboratories are involved in PT testing and a third are not, and Dr. Vance's data indicating that in 700 molecular pathology laboratories, the most frequent deficiency on the PT program accounted for 3.9 percent of laboratories. Dr. Vance replied that not all laboratories adhere to CAP standards, as it is a voluntary program. She added that the numbers are dynamic because small laboratories are often bought by larger laboratories and new laboratories open frequently. She said it is very difficult to track the laboratories and make sure that they are involved in a CLIA or CAP inspection process.

Dr. Berg stated that a number of tests are promoted as single-source tests, which presents a problem because the data relevant to their usefulness in practice are proprietary. In addition, there is very little information in the peer-reviewed literature on these tests. They are also not subject to PT mechanisms that are in place for other kinds of tests.

Dr. Tuckson asked Dr. Berg to help the Task Force develop some case studies that show the continuum of activities from analytic and clinical validity and clinical utility all the way through to the point where tests are chosen for use by a clinician. He said Dr. Berg's description of CYP450 might be one example and he asked him to think of others.

Dr. Ferreira-Gonzalez asked Dr. Vance whether CAP reports the results of its PT to CMS. Dr. Vance said yes, but she could not address what CMS does with that information. Dr. Ferreira-Gonzalez also asked who is responsible for checking on laboratories that fail the PT program to make sure they follow the required steps. Dr. Vance replied that CAP has become more involved and recently spent $9 million to bolster its accreditation program, particularly with regard to monitoring, and they created a new council called the Council on Accreditation. One of its subcommittees is called the Continuous Compliance Committee, which has responsibility for monitoring PT results and sending cease-testing letters. There is a two-pronged review: monitoring the laboratory testing menus to ensure that laboratories are enrolled in required PT and making sure they are performing PT successfully. The inspectors look at PT results and plans of action if the laboratories have been previously unsuccessful.

Dr. Steve Teutsch asked Dr. Berg about the complexity of getting guidelines translated into practice. Dr. Berg said that those who work in primary care have been happy to see the NIH Roadmap leading toward T2 translation (bedside to the community). He hoped that more groups will address that process.

Dr. James Rollins asked the EGAPP panel members present how the EGAPP initiative will result in positive outcomes at the population level, decreased cost, or better management of patients. Dr. Berg emphasized that EGAPP is committed to issues of clinical utility.

After concluding the question-and-answer session and with input provided by Clinical Laboratory Improvement Advisory Committee (CLIAC) chair Dr. Lou Turner and Joe Boone, Associate Director for Science in the Division of Public Health Partnership of CDC, Dr. Ferreira-Gonzalez reported on the February 2007 CLIAC meeting's discussion of CMS's decision not to go forward with the NPRM for a genetic testing specialty under CLIA. CLIAC heard from CMS about its plans for strengthening genetic testing oversight, and CLIAC members generally expressed support for these efforts. However, several members of the committee expressed concerns about CMS's decision not to go forward with a genetic testing specialty and questioned the agency's rationale. They pointed to concerns in the genetic testing community about laboratory quality, particularly regarding the qualifications of laboratory personnel and the interpretation of genetic test results. They said these two important measures of quality are not being captured in CMS survey data, because CMS surveys do not routinely inspect genetic testing laboratories.

In summarizing the session, Dr. Tuckson said he was concerned about the testimony from GPPC regarding the relationship between the specialty designation and PT. The GPPC representative stated that one-fourth of laboratories are not doing PT as they should be. Dr. Williams pointed out that because participation in CAP and other accreditation programs is voluntary; laboratories have the choice to opt out. Dr. Tuckson stated if the CLIAC committee did not explicitly deal with the frequency of PT, the issue should be added to the SACGHS charge. He also said that SACGHS should determine whether the results of PT performance are being made available to the public.

Dr. Ferreira-Gonzalez led the Committee in a discussion of the questions in the oversight charge from HHS OS. The Oversight Task Force had also developed a list of questions prior to the meeting, and Dr. Ferreira-Gonzalez asked the group to compare the two lists and determine whether any issues should be added to the charge. She felt that the Task Force's question 5 should be added to the charge from the

Secretary. It read: “What would be the impact of these solutions on the accuracy and quality of genetic testing, investment and innovation, availability and cost of genetic tests, and patient/consumer health and health care decision-making? How might these effects vary for different categories of genetic tests, for example, direct-to-consumer, predictive, diagnostic, pharmacogenomics? What would be the effects of leaving the system as it is?”

Dr. Joseph Telfair pointed out that the oversight charge from OS contained a number of compound questions that should be rewritten to be more discrete. He also suggested looking at existing information, such as the work of CDC, to draw upon the efforts that are already under way.

Dr. Ferreira-Gonzalez noted that public comments from Gentris Corporation addressed the use by some entities of reference controls that are not FDA-cleared. She suggested adding this issue to the discussion of PT materials. Dr. Williams said this issue had come up frequently in the CETT process. He asked whether, if all controls were required to be FDA-cleared, there would be a system for controls for all tests—even ultrarare disorders that rely on patient samples—or whether there would be certain exemptions. He felt this was a relatively narrow view of the control issue. Dr. Ferreira-Gonzalez agreed, stating that not only are there a limited number of FDA-cleared controls, but there is a cost associated with running the controls, complicated by a lack of reimbursement. She added that there might be exceptions allowing the use of already characterized specimens from patients that have been run with FDA-cleared testing. She said this was an issue for further examination.

Dr. Tuckson ended the day by thanking the Task Force for arranging the sessions on oversight and adjourned the meeting.

TUESDAY, MARCH 27, 2007

Welcome and Opening Remarks

Dr. Reed Tuckson

Dr. Tuckson opened the meeting by thanking Dr. Hunt Willard for leading the Task Force on Large Population Studies and guiding the development of an excellent report. He asked if any Committee members wanted to create a first draft of the comprehensive map on oversight requested as part of the Secretary’s charge and provide it to Dr. Ferreira-Gonzalez before the meeting’s end. Dr. Muin Khoury stated that he was working on a draft of the map.

Dr. Tuckson noted that the Gene Patents and Licensing Task Force, led by Chair Jim Evans, had been very active since the previous meeting. He turned the meeting over to Dr. Evans to facilitate the gene patents session.

Session on Gene Patents and Licensing Practices

Overview of Session
Jim Evans, M.D., Ph.D.
Task Force Chair

Dr. Evans explained that the session included a series of educational talks from leaders in the field of gene patents and licensing. He stated that the Gene Patents and Licensing Task Force was collaborating on the study with Duke University's Center for Genome Ethics, Law, and Policy, led by Dr. Robert Cook-Deegan and Dr. Christopher Conover. The Task Force met the previous evening to receive an update from the Duke team.

Dr. Evans reviewed the history of activity on the gene patents and licensing issue since it was identified as a priority by SACGHS in 2004. Work was initially deferred pending the findings of a National Academy of Sciences (NAS) study. In October 2005, after the NAS report was released, a small group of SACGHS members reviewed it and concluded that more information was needed on the topic of patient access to genetic tests. In June 2006, SACGHS held an informational session on the topic and decided to move forward with an in-depth study. The Task Force on Gene Patenting and Licensing Practices and Patient Access to Genetic Tests was established, and work began on development of the study's scope and work plan. The scope and work plan were refined over time and finalized in December 2006. Dr. Evans noted that the scope encompassed both the positive and negative effects of current gene patenting and licensing practices on patient access to genetic technologies. In January 2007, the team from Duke was enlisted to conduct a literature review, develop relevant case studies, and provide other assistance. The study would focus on gene patents for health-related tests, including diagnostic, predictive, and other clinical purposes. Dr. Evans explained that the study was examining both clinical access (i.e., a provider's ability to order tests for patients) and patient access. The Task Force was also considering the effects of gene patents on translational research; i.e., factors that block the ability of new technologies to reach the clinical setting.

Dr. Evans displayed a diagram of the three components of the study plan, which would ultimately result in a report to the Secretary. Part 1 would consist of data gathering and analysis, e.g., a literature review, expert consultations, case studies, and possibly, additional research. Part 2 would involve gathering public perspectives. Part 3 would provide insight on international perspectives on gene patents. To the extent possible, the components of the study would be addressed in parallel.

Dr. Evans described the goals of the day's sessions as basically educational; i.e., a primer on gene patenting and licensing practices that would assist in the development of the study. Topics included various forms of intellectual property, the use of gene patents and licenses by the Federal and private sectors, and the history and changing landscape of gene patent policies. Dr. Evans introduced the first speaker, Dr. Jorge Goldstein.

Primer on Intellectual Property
Dr. Jorge Goldstein
Director, Biotechnology Chemical Group
Stern, Kessler, Goldstein & Fox

Dr. Goldstein addressed the origin of the concept of intellectual property. He stated that patents were first used in Venice in the 15th Century to attract and retain artisans from the Middle East so that they would

teach the Venetians the arts of canal building, ammunitions, and silk weaving. Patents gave them exclusive rights as long as they remained in Venice and taught. Patents protect ideas and expressions, promote investments, and encourage disclosure of new ideas. Dr. Goldstein stated that the source of intellectual property protections in the United States is the Constitution. Article 1, Section 8 promotes the progress of science and the useful arts by securing for limited times (i.e., 20 years from filing) the exclusive right to writings and discoveries. This includes the right to have copyrights and patents.

Dr. Goldstein discussed trade secrets as a type of intellectual property and cited the example of the formula for Coca Cola, which is kept in a vault in Atlanta. A trade secret is knowledge that confers advantages to an entity. The advantage lasts as long as the knowledge is kept secret; however, secrets are hard to keep. A trade secret does not prevent someone else from independently discovering or inventing it. The disadvantage to the public is that the knowledge is not placed in the public domain. Trade secrets are enforced in State court, not in Federal court.

Trademarks are another type of intellectual property. A trademark can be a word, a sound, a color, or a type of building, such as the design of McDonald's restaurants. It distinguishes the goods and services of one company from those of another. The advantages are that trademarks last as long as they are used, and others can be prevented from using similar marks. There is an advantage to the public because they can connect the source with a product. However, if a trademark is not used, it is lost.

Copyrights are a different form of intellectual property. They are legal protection for an expression, protecting not an idea, but the idea’s style and format. The expression must be independently created and not unique, and must be capable of being fixed in a tangible medium. Things that can be copyrighted include literary works, musical works, sound recordings, dramatic works, choreography, pictorial graphic and sculptural works, motion pictures, and architectural works. Software can also be copyrighted although, the most efficient way to protect software is to protect its ideas and the flow of information, which is best achieved through patents. Dr. Goldstein said he did not believe gene sequences could be copyrighted. The law does not allow a copyright to protect the function of the object.

A patent is a right of limited duration, granted by the government, to exclude others for a limited period of time from making, using, selling, offering for sale, importing, or exporting an invention, in exchange for the patentee disclosing the invention or design to the public. If it is not fully disclosed or disclosed fraudulently, the patent is invalid. Even though the Patent Office grants it, a patent may not hold up in court. Litigators frequently go to court to try to prove that a particular patent was granted by mistake. Classic patents are utility patents, which last 20 years from the date of filing. The invention must be useful, novel, and not obvious in light of what has been done before. Design patents protect decorative designs or articles of manufacture and last 14 years. Plant patents are for asexually reproduced plants and last 20 years from the date of filing.

Dr. Goldstein focused his remaining comments on utility patents and the things that can be protected by them, including processes, methods of producing compounds and using them in therapy and diagnosis, instrumentation, machines, manufactures, and software. Methods of doing business can now be patented, which is relatively new and causing consternation in the financial industry, which faces lawsuits from sole inventors of patented methods for calculating bond fund balances. Abstract ideas cannot be patented, nor can mathematical equations, algorithms without any use, or laws of nature. The “laws of nature” issue has become controversial in cases concerning correlations between metabolites and diagnosis. In a metabolite case that was tested, the Supreme Court said cert should not have been granted. It was unclear what would happen with diagnostic correlation patents.

The advantages of patents are that they encourage disclosure and investments. They can prevent others from using an invention as a trade secret. Dr. Goldstein noted that case law indicates that an inventor must choose either trade secrecy or patents; an inventor can't patent a trade secret after 25 years. The disadvantages of patents are that thorough public disclosure of an invention makes a product easy to copy, patents are expensive to obtain and litigate, patents may need to be sought in many countries, and they may be of limited value if technology evolves quickly.

Patents on genes claim isolated and purified molecules within a given DNA sequence, not their natural form in the chromosomes. Dr. Goldstein cited extensive legal precedent on the issue. One case often used as a precedent is the 1980 Chakrabarty case, in which General Electric made a recombinant bacteria that was able to grow and metabolize a set of hydrocarbon fractions. After they tried to patent it, the case went to the Supreme Court, which ruled that, "Anything under the sun made by man…" can be patented.

Dr. Goldstein stated that a gene patent ultimately is a gene claim. Describing Kirin-Amgen's erythropoietin (EPO) patent, he said a purified and isolated DNA sequence was claimed. It was a statutory requirement that the sequence be purified and isolated. They also claimed DNA sequences that hybridize under stringent conditions to the DNA sequences defined in the patent. This expanded the human gene to a family of similar isolated orthologous EPO genes and to mutational variants of the basic human genes.

Dr. Goldstein asked: Who owns your genes? From a legal point of view it depends on whether they are in your body or not in your body. If they are in your body, the genes are yours. However, if your blood has been extracted, the law is clear that the genetic material belongs to the hospital or laboratory. It is possible to arrange with the laboratory to preserve ownership of your genes after isolation. However, if someone else has a patent on your isolated genes, you can't commercialize them. Although you own the tangible, personal property, the other party owns the intangible, intellectual property.

There are a number of standards in the Patent Office for obtaining a gene patent. Utility has a very high standard, as it must be substantial, credible, and specific. There must also be a written description of the gene and its variants. The applicant must meet the standard of "enablement," i.e., the ability to reproduce the invention. The gene must be novel (not previously published in isolated form) and non-obvious. The standards are very high for utility and written description and lower for non-obviousness. The European standards for non-obviousness are higher and there is extensive criticism in the academic literature about the direction U.S. courts have taken on this issue.

The essence of a patent is the right to exclude others from commercializing anything within the scope of the claims. The right to exclude encompasses the right to an injunction, the right to extract damages for lost profits, and the ability to leverage the possibility of injunction/damages to license technology. In the U.S., the right to exclude has been historically broad, although a recent Supreme Court case, MercExchange v. eBay, cut it back. But until very recently, any activity that furthered an institution's legitimate business objectives was considered an infringement and could be enjoined. Dr. Goldstein noted that the experimental use defense is essentially non-existent in the United States. He stated that clinical use of a drug that is generating data that will go to the FDA under 271(e)(1) is exempt from patent infringement. If a pharmaceutical company is doing clinical work using a patented drug, they are free to do so until the clinical work ends and they go to market.

Dr. Goldstein reiterated that the right to exclude was recently cut back and injunctions are no longer automatic. Patent holders that do not manufacture (i.e., are not in the marketplace with the infringer) may not readily obtain injunctions. Health is a major public policy concern, so patent holders in the health

sciences who do not work or license their inventions may not be able to obtain injunctions. This opens the door for the first time in the U.S. to compulsory licenses, which are forced on the patent holder against his or her will by order of the court. Large corporate interests in the U.S. have opposed compulsory licenses for decades.

Dr. Goldstein stated that the economic and social foundations of any patent system encourages full disclosure of otherwise secret technology in exchange for time-limited exclusivity, encourages capital formation for technologies with risky outlook, and privatizes technology that would otherwise be in the public domain to help promote investment.

Although the law doesn't make a distinction, there are patents in different industrial sectors. The synthetic drug sector, like the pharmaceutical industry and the biopharmaceutical industry, is the “poster child” for a strong patent system. Major investments are needed, there are long delays in the development process with a high risk of failure, and products have a very long life. At the other end of the spectrum are business methods, which don't require high-risk investments and product lives are relatively short. The semi-conductor industry is in the middle. Investments are needed and copying is still a risk, but there is a thicket problem. It is estimated that if you want to put a DVD player or a miniature MP3 player on the market, you will need thousands of patent licenses. For a complex, high definition television set, you might need 19,000 or 20,000 licenses. This is the industry that created patent pools, because without them, a product could not be put on the market.

Dr. Goldstein posed the following questions: Are isolated human genes more like synthetic drugs or like business methods? What role do gene patents play? He said the answers depend on the function and use of the genes and who the potential defendants might be. He suggested thinking about gene patents in three different categories. First are DNA patents that encode therapeutic proteins, such as tPA, EPO, and interferon beta. The defendants tend to be biopharmaceutical companies. At the other end of the spectrum are patents for DNA sequences that encode molecular targets and receptors, such as CCR5, and DNA sequences encoding molecular receptors used for drug screening. The potential defendants in this category tend to be academic institutions and small research companies doing high throughput screening. In the middle are diagnostic probes. These are not DNA sequences that encode any protein; instead, they are short gene fragments that are used as probes for detection of full-length genes, e.g., the BRCA1 gene. The potential defendants are mixed, and might include diagnostic companies that are marketing kits or the medical community, whether involved in clinical work or research.

Dr. Goldstein discussed DNA encoding protein drugs, using the gene for tissue plasminogen activator (tPA) as an example. From the standpoint of patenting, he said these drugs have more similarities to synthetic drugs than business methods. Commercial applications are higher and research applications are lower. The risk is high; case law suggests that the patent on tPA has been construed so narrowly that subsequent generations of tPA are not covered by the original patent. Dr. Goldstein stated that DNA-encoding receptors, such as the erythropoietin (EPO) receptor, are at the other end of the spectrum. Research applications are higher and commercial applications are lower, because the EPO receptor is used as a high throughput screening tool, i.e., a research tool. The development risks and costs are not very high. Enforceability is questionable for these types of research tool patents and preclinical use may be exempt. They can be used abroad and the data can be imported. It would be very difficult to determine damages, which might be limited to reach-through royalties on sales of products outside the patent scope.

NIH opposes exclusive licenses of research tools because they delay research and impede dissemination of the tools. In addition, pharmaceutical companies do not like stacked royalties, and their view carries

significant weight. DNA-encoding diagnostic probes fall in the middle, because the commercial and research obligations are in tension. Worldwide manufacturers and distributors of kits and rapid tests want patent protection. The patent owner may have to enforce against end users, not just manufacturers, as with protein drugs. There is debate in the literature and some evidence that incremental improvements in genetic tests may lead to large fragmentation of the patent field, as with semi-conductors. Limits on who can perform genetic tests might interfere with good medical practice and inhibit others from finding new mutations.

Dr. Goldstein stated that a number of academic research and law groups have examined the issue of patent pooling. In August 2005, Dr. Goldstein published a paper in the scientific journal *Nature Biotechnology* titled, "Patent Pools and Standard Setting in Diagnostic Genetics." It said that, following the model of consumer electronics, one could create patent pools for DNA-encoding diagnostic genes using internationally recognized diagnostic medical standards (e.g., the American College of Medical Genetics standard for cystic fibrosis) to define essential patent pools. He stated that pools are not a panacea for solving problems with patents and must be thought through very carefully.

Dr. Goldstein concluded by stating that no one other than you owns your genes, although others may own patents on isolated versions of your genes. Such gene patents provide commercial exclusivity for a limited period of time. However, there are different categories of patents and they should be thought of in different ways. He stated that health-based compulsory licenses may become a reality in the near future. Concerning patent pools in the diagnostic field, he said it will be important to start working with international health organizations to create universal standards for genetic diagnostics. It will also be important to better define experimental and preclinical research exemptions without undermining all research tool patents.

Federal Sector Role
Claire Driscoll
Director, Technology Transfer Office
National Human Genome Research Institute (NHGRI)

Ms. Driscoll stated that she would explain how NIH handles the patenting and licensing of genomic inventions, including gene patents. NIH is concerned about the possible negative health repercussions of broad, exclusive licensing of gene patents for diagnostic applications. She stated that interventions should take place at the level of licensing; not at the level of patents. The policies she discussed applied only to the NIH intramural program. Grantees in the extramural program can voluntarily adhere to these policies, but there is no mandate that they follow them.

Generally, the NIH intramural program will patent if there is a high public health priority, if patenting will facilitate access to technology, or if it is necessary for investments in R&D. The intramural program will not pursue patents if: no further research and development (R&D) is needed (e.g., research tools), there is a low public health priority and/or a lack of commercial interest, or patenting will hinder technology transfer or access to inventions. NIH's intramural licensing principles focus on public health benefits first, with royalty income and financial benefits as the lowest priority. NIH never gives a license for a broader scope than a company realistically needs to develop an invention and they use specified fields of use and enforceable benchmarks. To optimize the number of new products that will reach the market, NIH allows non-exclusive or narrow exclusive licenses. The agency also insists on the availability of technology for research; licensees must permit research uses by not-for-profit and governmental institutions.

Ms. Driscoll described the technology transfer mechanisms used by NIH. A Cooperative Research and Development Agreement (CRADA) gives the CRADA collaborator an option to exclusively license any inventions, an anomaly, because NIH usually grants non-exclusive licensing options. However, NIH is very careful to ensure that the scope of the license matches the scope of the research plan. Most NIH patent commercialization licenses are non-exclusive (80 percent), some are co-exclusives, and a few are exclusives, in areas such as therapeutics or vaccines, and are quite narrow (by field of use, by disease indication, or by technology platform). NIH rarely gives broad exclusive licenses. In contrast, academic institutions usually grant exclusive licenses.

Extramural grantees may generally do as they wish when it comes to patenting and licensing. Under the Bayh-Dole Act of 1980, investigators control their own inventions and may commercialize them as they see fit. However, NIH may enact some restrictions, such as asking for acceptable intellectual property sharing plans. Grantees are also asked to adhere to the guidance document, "NIH Best Practices for the Licensing of Genomic Inventions," although it is not a requirement. The guidance was released by NHGRI so that the public would know how NIH handles the licensing of gene patents. NIH rarely makes a “declaration of exceptional circumstances” (DEC), by which grantees are told that they have no Bayh-Dole rights, however, for some projects, it is necessary that the end products, such as full-length cDNAs from humans, rats, and mice, are available to the research community without restrictions.

Ms. Driscoll stated that the academic research enterprise is the source of many of the platform technologies and new products commercialized by industry. In many cases, the universities control how intellectual property is licensed and are responsible for writing the license agreements. She made the point that there are probably ways to conduct licensing agreements that would avoid monopolies or problems with pricing because one company has a lock. She stated that many academic and clinical researchers disagree with the intellectual property strategies employed by Athena Diagnostics and she displayed a lengthy list of patents owned or exclusively licensed to Athena from the company’s website. Athena Diagnostics created a large collection of patents for various neurological disease conditions. These patents come mostly from academic institutions, not companies. Only three of the patents end-licensed by Athena were developed in house; the rest were licensed from other research entities, mostly with exclusive licenses. They have a policy of not sub-licensing, therefore if someone wants to run one of these many tests, they must send their samples to Athena.

Ms. Driscoll cited a licensing survey conducted by Robert Cook-Deegan and his colleagues at Duke that was published in *Nature Biotechnology* that looked at ownership of DNA patents. Number one was the University of California and number two was NIH. Many of the top 30 DNA patent holders were universities. Ms. Driscoll said a white paper recently came out of a premier technology transfer organization, the Association of University Technology Managers (AUTM), and some of the universities that hold the largest number of gene patents signed on in agreement with its principles. “In the Public Interest: Nine Points to Consider in Licensing University Technology,” was considered by Ms. Driscoll to be sensible, balanced, and technology neutral. It mentions diagnostic tests, but deals with licensing of inventions in general, i.e., how best to serve the public and encourage commercialization. It states that licenses should not hinder clinical research, professional education and training, use by public authorities, or independent validation of test results, even if there is patent coverage. It states clearly that licensing of a single gene for a diagnostic may be counterproductive. The universities that signed it were not afraid to lose some money by being willing to do non-exclusive licensing. It has been endorsed by several groups, including the American Association of Medical Colleges, and it was hoped that more would sign on. Ms. Driscoll felt the universities, who had been receiving a great deal of criticism, took this voluntary step before NIH or legislation forced them to change the way they do business.

Ms. Driscoll observed that the issue of gene patenting has become mainstream, citing an article in Parade Magazine in November 2006 and Michael Crichton's recommendations in the back of his latest book. Crichton called for an end to the patenting of human genes and a reversal of the Bayh-Dole Act. Ms. Driscoll stated that this would halt many industries that base their businesses on inventions coming from universities.

Ms. Driscoll walked through a timeline of significant events in the history of gene patenting in the U.S. Highlights included the completion of the Human Genome Project in 2003, the National Academies' report on the patenting and licensing practices of genomic inventions in 2005,and the NIH best practices document in 2005. The recommendations of the National Academies emphasized non-exclusive licensing, paying attention to fields of use, and retaining a research use provision that includes all parties. Ms. Driscoll stated that several other papers and reports reached similar conclusions, resulting in a convergence of opinion. The American College of Medical Genetics (ACMG) is also in line with these policy documents. Ms. Driscoll stated that people should stop worrying about gene patents and focus on access, because the licensing of key patents is what really matters. She felt it was unlikely that patents on genetic sequences would be revoked or prohibited and it was important to develop alternative, feasible strategies to ensure maximum access and use of inventions by clinical laboratories, research laboratories, and companies.

Ms. Driscoll summarized NIH's 2005 "Best Practices for the Licensing of Genomic Inventions" policy document, which extramural grantees are not required to follow. It emphasizes commercial development and monitoring and enforcement of license terms. If a company does not appropriately commercialize, their license must be taken back. A company must be forced to sublicense if they are not developing tests in a timely manner.

Proposed remedies to gene patenting and licensing problems include: legislation for compulsory licensing of DNA/gene-based inventions for all diagnostic uses, a true research exemption in U.S. patent law for non-commercial uses of genetic inventions, and patent pools. Other possible remedies include encouraging cross-licensing or establishing clearinghouses for genetic inventions, and adopting an open source approach to biological licenses, which work well in the IT industry. Ms. Driscoll stated that in her opinion (not necessarily that of NIH), the best possible remedy would be to ask Government grantees to put in place new guidelines governing appropriate licensing policies for these types of inventions. She acknowledged that grantees would resist the idea. She stated that data is needed to determine the extent of the problem. Adoption of the recommendations in the NIH Best Practices document or the AUTM white paper by grantees would help address the problem.

Ms. Driscoll concluded by stating that policy had moved forward and some common principles emerged, but it took 20 years. She expressed concern that by the time new policy or legislative fixes were put in place, many of the gene patents that were licensed will have expired or the proposals would apply only to new licenses, which would not address the significant legacy problems.

Dr. Evans introduced Dr. Lin Sun-Hoffman, a senior patent attorney from Applied Biosystems. She provides intellectual property counseling and works with research tool products. Dr. Sun-Hoffman worked at Celera Genomics managing patent preparation and prosecution on gene patents, as well as other gene-related diagnostic and therapeutics patents. She also worked as a patent examiner at USPTO in the biopharmaceutical group.

Private Sector Role
Lin Sun-Hoffman, Ph.D., J.D.
Senior Patent Attorney, Applied Biosystems

Dr. Sun-Hoffman stated that her comments represented her personal views, not those of Applied Biosystems. She said that typical claims in gene patents are for nucleic acids, proteins, methods for detecting a gene, methods for making proteins, and methods for screening and making antibodies. A claim also cover a method for diagnosing a disease by monitoring a gene (mutation) or protein expression or a method for treating a disease by targeting a gene using an antibody or small molecule.

Pharmaceutical companies use gene patents when they need a target for screening small molecules. Biotechnology companies need targets for large molecule therapies or for antibody or protein treatment. Examples include erythropoietin, human growth hormone, Rituxan, and Herceptin. Diagnostic companies use genes for disease association studies, such as for BRCA1 and BRCA2. Research companies, such as Applied Biosystems, use genes as probes, primers, and arrays. The majority holders of gene patents are academic institutions and the U.S. Government. Other patent holders include biotechnology and pharmaceutical companies.

Companies want access to patents so that they have "freedom to operate." They conduct searches to determine whether specific genes have patents issued, and the majority are either patented or in the public domain. If there is no freedom to operate, they seek a license, design around, or try to negotiate deals with patent owners. The licensees are usually downstream developers; the majority of biotech companies and research companies obtain their first research information from academics or NIH (usually non-exclusive). Some biotech companies own the gene patents and either out-license them or develop them internally.

Types of agreements include straight license agreements, which tend to be non-exclusive and are usually from genomics companies or academic institutions, and collaboration agreements, which are used by large pharmaceutical companies or biotech companies to co-develop a product. The diagnostic area typically has non-exclusive licenses that can be licensed for different indications for one type of disease, or licensed to various companies. In the therapeutics area, companies prefer exclusive licenses for different components of disease.

Payment can be through royalties only or annual licensing fees. Other payments can be made through achievement of milestones, up-front payment, or a combination of both. Payment type depends on the stage of development of the product. Small companies tend to have fewer up-front payment systems and a greater use of royalties. The determination of royalties can be complicated and depends on the stage of development, the type of technology, the strength of the IP, and the size of the market for the gene.

The field of diagnostics tends to ask for lower royalties, amounting to about 2 to 3 percent. There are usually multiple licenses required to enable one technology, similar to royalty stacking. The cumulative royalty can reach 30 percent. In the therapeutics arena, however, the revenue is high, so the royalties may reach 5 to 8 percent.

Dr. Sun-Hoffman presented a summary of the considerations for royalty determination. For in-licensing, companies look at IP position (whether the claim scope is large or narrow) royalty stacking (how many licenses they have to obtain), potential revenue, and whether it is a diagnostic or a therapeutics area. For out-licensing, they also look at company size (they probably want more money from large companies),

market size, the disease to be treated (whether an orphan drug or for use in a big field, such as oncology), the terms of use, and diagnostic versus therapeutics use.

The gene patent owner believes they have the right to own genes, but it is difficult from the company point of view to determine who is using their genes. Gene patent users are usually in the early stages of research and development, which makes them hard to find. The companies don't worry about academics using their genes and it is not very common for a company to sue an academic. The revenue for a gene patent is usually very low, but depends on the product.

The non-patent owner has concerns about the strength of the IP, the scope of the gene patent, the inconsistency of the patent office standard, the fact that some patents are difficult to search, and the stage of use for the gene (early stage or product development stage).

In her concluding statements, Dr. Sun-Hoffman noted that the majority of genes are patented; licensing a gene patent is possible, either exclusively or non-exclusively, but companies need to consider royalty stacking; and enforcement of gene patents is difficult until the product is developed.

Dr. Evans opened the floor for questions.

Q&A

Dr. Kevin Fitzgerald asked how the Metabolite case could impact the field of gene patenting. Dr. Goldstein explained that the Supreme Court had been asked to review the case, which claimed that if certain levels were found when testing for a specific metabolite, it could be correlated with a particular disease. A critical issue in the case, which had not yet been decided, was whether the subject matter was so close to being a law of nature that it was not patentable. Dr. Goldstein believed that the problem with the case was a technical difficulty in the way the claim was drafted. If the claim was re-drafted the and the patent re-issued so that it was not just a correlation (i.e., a law of nature) but an actual diagnosis of a disease, the Supreme Court would have no say over it. He felt the case would not go back to the Supreme Court and that pure correlation claims would not be drafted in the future.

Dr. Marc Williams asked how patent law will treat variations from published reference sequence mutations. Ms. Driscoll stated that most mutations in the regulatory sequence are either in the public domain or covered in current patent applications. She said there are probably no genes left that are completely unknown. Dr. Sun-Hoffman added that although gene patents are covered, a new development was emerging having to do with association with certain diseases.

Dr. Williams then asked whether greatly increasing oversight and the costs associated with the development of tests would push companies toward patenting as a way to recover costs, rather than sharing information. Dr. Goldstein agreed that this would be the case.

Dr. Williams also noted that in the rare disease testing area, some foreign laboratories were going through the CLIA certification process so they could run tests offshore under U.S. regulation. He asked how that would impact enforcement of a U.S. patent versus an international patent. Ms. Driscoll said several biotechnology companies were founded with facilities offsite to take advantage of loopholes and avoid infringement or the requirement to pay for licenses.

Dr. Goldstein commented that there is a long history of exclusivity in the biopharmaceutical industry, which means that the companies that own patents do not talk cooperatively with each other about cross-licensing or forming pools. If an international organization, such as the World Health Organization (WHO), were to carefully define patent pools for testing for specific diseases, it could force people in the industry to cooperate with each other.

Dr. Hunt Willard commented that NIH and NHGRI play by a different set of rules than private companies because they don't have a mandate to make a profit. Private institutions have expectations that their technology transfer offices might make money for the institution and he said they can't be expected to adopt a set of standards that encourage open sharing. Ms. Driscoll pointed out that the University of California non-exclusively licensed the Cohen-Boyer recombinant DNA patents and made a great deal of money from licensing. She added that it is unrealistic for every technology transfer office to be a profit center.

Dr. Julio Licinio asked how people were addressing the fact that many microarrays are covered by numerous existing patents and every one of the gene sequences in the DNA microarrays used in high throughput technology must be cleared if they are to be used commercially. Dr. Sun-Hoffman said that her company conducts a freedom-to-operate search on the genes they need and talks with each company that holds patents. Sometimes they are not able to find the genes they need. She stated that the licensing fees are usually low. Dr. Goldstein added that in these situations, the patented sequences must either be licensed or taken out of the array; otherwise the entire project must stop.

Dr. Sherrie Hans asked Ms. Driscoll to explain NIH's legal authority concerning mandatory liberal licensing for grantees. Ms. Driscoll did not think NIH had that overall authority, but the agency but could institute requirements as a condition of a grant.

Dr. Evans closed the patents session and turned the floor over to Dr. Tuckson, who announced the start of the public comment session.

Public Comment

Debra Leonard
Association for Molecular Pathology

Ms. Debra Leonard provided AMP's perspective on three issues. The first was Federal legislation related to the oversight of genetic testing. She described two bills that had been introduced in the U.S. Senate on the regulation of laboratory developed tests: Senator Kennedy's Laboratory Test Improvement Act and Senator Obama's Genomics and Personalized Medicine Act. Although AMP agreed with the intended goal of these bills (i.e., to protect the public health) the organization was deeply concerned that if enacted into law, they might restrict access to genetic testing services by the public and decrease innovation and implementation of novel genetic tests. AMP believed that the same intended goals of the bills could be achieved through strengthened existing laboratory oversight mechanisms and collaboration with the private sector. AMP asked SACGHS to request that the Secretary of HHS convene a meeting with key stakeholders, members of Congress, and relevant regulatory officials to reach a common understanding of the legislation and the best ways to achieve its goals without unintended harmful outcomes. The second issue was coverage and reimbursement of genetic testing services. Although the SACGHS report on coverage and reimbursement made recommendations to the Secretary on this issue, AMP was not aware of any actions taken. Ms. Leonard asked SACGHS follow up on the HHS response to the report. The third

point related to gene patents and patient access. AMP asked that SACGHS continue to give full consideration to the negative impact of gene patent exclusive licensing and enforcement practices on genetic testing.

Dr. Andrea Ferreira-Gonzalez suggested that SACGHS write a letter to the Secretary asking him to engage stakeholders on the issues proposed in the legislation and to coordinate HHS efforts with those of Congress. Dr. Tuckson agreed and asked Dr. Ferreira-Gonzalez to develop a draft of the letter.

Dr. Evans introduced Dr. Bob Cook-Deegan. His team from the Center for Genome Ethics, Law, and Policy at the Duke University Institute for Genome Sciences was assisting SACGHS with the patient access study.

Policy Primer on Patents Related to Genetic Testing

Dr. Bob Cook-Deegan
Center for Genome Ethics, Law, and Policy
Duke University Institute for Genome Sciences

Dr. Cook-Deegan explained that he was overseeing a research group at Duke funded by the National Human Genome Research Institute (NHGRI) and the Department of Energy to study the role of intellectual property and information flow in the innovation process in genomics. The Center was examining the impact of the availability of genetics and genomics information to large numbers of people at relatively low cost. The key focus of their work was on the innovation system and its interaction with the intellectual property system through analysis of seminal technologies patented by small start-up firms. The Center was also assisting SACGHS in their study of patient access to genetic technologies.

Dr. Cook-Deegan presented a primer on intellectual property issues. He described several factors that affect access to genetic technologies, including price, "hassle" (i.e., perturbation in existing service), regulatory approval by the Food and Drug Administration (FDA), and coverage and reimbursement of a test. He stated that patents can control pricing because they prevent others from making, using, or selling an invention. "Hassle" affects access because patent holders can impose conditions on the use of inventions. Regulatory approval and reimbursement and coverage policies affect access by influencing the overall market.

Dr. Cook-Deegan's students were developing several case studies on patents and access as part of the SACGHS study. One case study compared breast cancer with colon cancer testing. Although the tests are clinically similar, the patent landscape for each is very different. Myriad Genetics controls the patents relevant to breast cancer testing, while the intellectual property for colon cancer testing is mainly owned by academic institutions and testing is available through many laboratories. Dr. Cook-Deegan stated that the students' completed case studies would probably not supply crisp, clean information that keys in on access specifically. The information provided might examine utilization only, which Dr. Cook-Deegan said is a loose proxy for access.

He stated that a patent provides the ability to prevent others from making, using, or selling an invention for a specific period of time (20 years is the default). The invention must be disclosed in sufficient detail for others to make and use it. The patent system is enforced through the court system of national governments. Dr. Cook-Deegan described two justifications for patents: the human right to make money

from a valuable contribution to society (a concept described by John Locke and used to develop the U.S. Constitution), and an instrumental right based on the likelihood of fostering innovation.

Patents basically do three things in the biomedical research domain. They are tools to distribute fairly the fruits of invention; they foster investment in R&D, contingent on the ability to carve out some intellectual property and sell it for a profit; and they solve problems and protect investments for inventions that require substantial post-discovery development.

A DNA patent mentions DNA or RNA in its description. There were about 44,000 U.S. DNA patents at the time of Dr. Cook-Deegan's presentation. Approximately 16,000 patents worldwide mention a DNA sequence specifically. Most are in the U.S. Approximately 750 DNA patents have been issued in Europe, and about 500 have been issued in Japan. Dr. Cook-Deegan gave examples of patents related to recombinant DNA, PCR, methods, bioinformatics, promoters, and enhancers. A subset of sequence patents are gene patents. The prototypical gene patent is usually for a complete DNA that is the full length of a messenger RNA, e.g., the vector that contains that DNA and the cell line that would produce the protein product of that gene. There are about 3,000 classic gene patents.

It is generally agreed that patents induce investment in private sector R&D and create assets for start-up firms. The patent system also generates income for some universities. However, the patent system makes research more expensive because of the associated transaction costs and the bureaucracy that is needed for tracking and accounting. Dr. Cook-Deegan referred to these costs as a tax on innovation, which raises the question of whether too much efficiency is lost in the R&D system because of high costs. He stated that some research, such as a full exploration of the environmental uses of PCR, did not take place because the Environmental Protection Agency (EPA) and environmental researchers did not have sufficient funding.

Dr. Cook-Deegan compared the adoption curves of some inventions that were patented and some that were not. They included a polymerase chain reaction that was patented by Cetus, a cloning vector that was not patented, and a Maxam and Gilbert sequencing that was not patented. The graphs depicting their market capitalization curves looked very similar. Dr. Cook-Deegan said that little could be concluded from this data because it was not possible to know if the PCR would have been more widely used if it had not been patented. However, the patent did not have a catastrophic effect, although it did add to the cost of the technology.

Dr. Cook-Deegan displayed graphs of the 2000-2001 financial trends for the top 15 publicly traded genomics firms, in which there was rapid investment in the late 1990s. The market peaked in June of 2000, dropped by a factor of five, and started to come back in 2007. At one point, the value of these companies was almost $100 billion, but it dropped precipitously. However, these 15 firms continued to increase their R&D efforts despite market fluctuations. They also invested in laboratory facilities, equipment, and talented employees.

A slide depicting the number of sequence patents issued around the world indicated that the U.S. has always had a slightly higher number than Japan or Europe. Based on a manual count by the team at Duke, Dr. Cook-Deegan indicated that from 1980 to 1993, 39 percent of these patents were owned by academic institutions, which is a much higher percentage than for other types of patents. More than half of the patents were owned by for-profit firms. He added that the Science Policy Research Unit at the University of Sussex showed in 2005 that the fraction of patents in the private sector went up during each successive 5-year time period from 1980 to 2003. A slide from *Science* magazine taken from a 2005 paper by Jensen

and Murray indicated that 82 percent of genes on which sequence information could be found were not patented. Fourteen percent were privately owned and 3 percent were publicly owned. Another slide indicated that academic institutions do not license about 30 percent of the patents they own. Most (about 70 percent) of these patents were licensed once. Some classic patents were non-exclusively licensed, usually as a source of income, which has not interfered with the innovation process.

Dr. Cook-Deegan addressed the policy landscape for patents and the tools available for change by the Government and other stakeholders. He said patent reform legislation was being driven by the intellectual property interests of the telecommunications, computing, and software businesses. The biotechnology and pharmaceutical constituencies were happy with the status quo.

Examples of attempts at patent reform by statute included the recently introduced Becerra-Weldon bill, which would not allow any additional sequence-based patents. Another bill sponsored in the 108th Congress by Rep. Rivers was *designed to minimize some of the negative impacts of patents on the practice of medicine and the advancement of science*. Dr. Cook-Deegan said there are no research exemptions under U.S. law, but there was talk of creating them. Belgium and France passed substantial research exemptions and they are common in other European countries. These exemptions allow use and research on an invention. Compulsory licensing is allowed in Belgium, France, and India. It is not an absolute right to override patent rights, but it takes the exclusive right away from the patent holder in the interest of public good. The inventor is paid a fee, which is supposed to be fair and reasonable. Some developing countries have built compulsory licensing into their statutes precisely because they want to keep public health at the forefront of their governments' activities. Dr. Cook-Deegan noted that India's compulsory licensing law was being actively litigated.

The U.S. is the only major country that has a rule stating that if there is a dispute between two people who filed patents at the same time, the courts must decide who invented it first through an interference proceeding. In other countries, the patent offices require the inventors to prove their cases. If a case can't be proven, the first person that filed the patent application receives the patent.

There is an opposition process in Europe that does not exist in the U.S. When a patent is published, there is a period of time during which outside parties can state that they think it is too broad and that more information must be taken into consideration. This starts a proceeding to look at the patent again in light of the new information contributed by these parties. This process led to the dramatic narrowing of the BRCA1 patent in the European Union from the entire gene to the mutation that is highly prevalent in some Ashkenazi Jewish families. It is a very narrow patent compared to those issued in the U.S.

The Cohen-Boyer patent went through a similar process when Stanford openly prosecuted their own patent because they thought they would be sued. A great deal of prior art was brought to the attention of the patent examiners just before the decision was made, and the patent office issued the patent anyway. If a court looked at that case, they would have to acknowledge the amount of information considered and the fact that the patent withstood intensive scrutiny.

Dr. Cook-Deegan described various policy tools, such as "push-back" by scientists that oppose specific patents. Examples in which policy was changed in response to scientists' actions include PCR licenses, Oncomouse, and Cre-lox. In addition, the patent office began to increase the general level of scrutiny of all gene patents in response to input from NIH scientists.

Several types of guidelines and rules also serve as policy tools, including the Organisation for Economic Cooperation and Development (OECD) Licensing Guidelines (2006) and the NIH Best Practice Guidelines for Genomic Inventions (2004). The scientific community also imposes rules on itself concerning data and materials sharing that affect intellectual property issues. For example, the SNP Consortium crafted a strategy for keeping variations in the human genome in the public domain by filing patent applications and then walking away from them. NIH's research tool guidelines from 1999 were incorporated into its grants cycle. A university statement was developed jointly by several academic institutions (spearheaded by Stanford). Another tool is the data sharing plan required by large NIH grants. The problem with this policy is one of enforcement and monitoring, because only informal enforcement mechanisms exist and there is no way of knowing who is out of compliance. Dr. Cook-Deegan noted that many of the problems being addressed by SACGHS would not exist if the NIH Best Practice Guidelines were being followed. There is also a legacy problem, i.e., policies regarding the patents and licenses that have already been assigned.

Dr. Cook-Deegan reviewed some empirical data on diagnostics testing and patents. A survey conducted by Mildred Cho, John Merz, and Debra Leonard demonstrated that some laboratories stopped offering tests or decided never to offer certain tests because of the patent situation. He noted that this did not necessarily mean that there was a lack of access, because patients who could afford it could send their samples to large laboratories, such as the clinical laboratory at the University of Pennsylvania or Myriad Genetics. This would represent a pricing problem rather than an access problem, but he said it would be difficult to obtain data for this.

Two additional cases on patents are well known. The BRCA case is considered an example of bad behavior in DNA licensing. In the U.S., the licensing of the patent was the focus of attention because BRCA is only offered as a genetic test by Myriad Genetics; they drove other providers out of the market. This did not happen in any other jurisdiction. In the U.K. and Canada, the national health systems pushed back and would not agree to the terms established by Myriad Genetics. These countries are ignoring the patent and Myriad Genetics has not sued. In Australia, Myriad Genetics licensed to an Australian firm that non-exclusively licenses the test to health systems in the country's provinces. The second well known case is Canavan's disease. According to Dr. Cook-Deegan, a combination of secrecy, betrayal, and overpricing led to a bad outcome and an out-of-court settlement. The test is now available as part of a screening panel.

Dr. Cook-Deegan discussed some factors that he thought would be more powerful than patents in predicting access. These included coverage and reimbursement, FDA regulation, and monopoly (one seller facing many buyers) versus monopsony (one buyer facing many sellers). If clinical utility must be proven by companies before a test can be reimbursed by payers in the U.S. system, it will be very expensive and create a heavy burden. If the FDA creates a regulatory hurdle that everyone will have to go through, either for tests for single-gene Mendelian disorders or for multiplex tests, it will increase costs and increase the importance of the intellectual property associated with the tests, because the free rider problem (follow-on development by companies that have not invested heavily in the primary R&D) will have to be solved. The other significant factor is the monopoly power of a patent holder versus a monopsony, e.g., when the only buyer is a national government. When there is only one other buyer, they control the market.

Dr. Cook-Deegan said that several uncertain trends in gene patenting could influence the content of the SACGHS report. One is the possibility of patents being challenged. There may be push-back by universities. A case before the U.S. Supreme Court or the Court of Appeals for the Federal circuit could

change the rules very suddenly. In addition, experiences with BRCA testing in Canada and the U.K. suggest that patents are not necessarily the most important factor to attend to. Finally, the fact that there are domains of intellectual property that are owned in the West that are not owned on the other side of the Atlantic and in Asia has not yet played out. It could take a 20- to 30-year litigation cycle before the full impact is known.

Dr. Leonard asked for clarification of the Government's march-in rights under Bayh-Dole. Dr. Cook-Deegan stated that there are different aspects of Bayh-Dole in this regard. The first is that an invention derived from Federal funding can be used and sold by grantees without payment of royalties. The second is a declaration of "exceptional circumstances." NIH makes these determinations, but they must also go through the Department of Commerce. This is a possible area for reform, because Federal agencies would have more flexibility in using this provision if they didn't have to go through the Commerce. March-in has been invoked several times, but never acted upon. It states that under certain circumstances, such as a public health need, the Government can step in and take back the intellectual property rights.

Dr. Evans introduced Mr. Christopher Conover, who with Dr. Cook-Deegan, provided an update of their work on the SACGHS gene patents study.

Update on the Status of the SACGHS Study on Gene Patents and Licensing

Bob Cook-Deegan, M.D.
Director
Center for Genome Ethics, Law, and Policy
Duke University School of Medicine

Christopher Conover, Ph.D.
Assistant Research Professor of Public Policy
Terry Sanford Institute of Public Policy
Duke University

Dr. Cook-Deegan explained that his team at Duke had been asked to apply their study tools to the SACGHS investigation of gene patents and licensing. Mr. Conover added that graduate students in the Health Policy Certificate Program at Duke are required to conduct policy analyses and he stated that the SACGHS study provided an opportunity for them to work on real world issues. They were assigned a literature review and a number of case studies.

As they thought about the problem of access to genetic technologies, the Duke team developed a conceptual model of the process of innovation, starting from basic research and ending with the testing of actual patients. They planned to examine price issues and various delays that result in lack of access. Mr. Conover noted that the team was relying heavily on a report written by The Lewin Group on the development of new diagnostics. The students were following the Lewin model, but applying it to the specific case of genetic tests. They were also collecting systematic stories or case histories about topics discussed in the literature (e.g., BRCA). The team was attempting to represent various kinds of diseases and make comparisons about the effects of patents, when possible.

Mr. Conover discussed the student's comparison of breast cancer versus colon cancer, which would allow them to look at test pricing. The case study examining Tay-Sachs versus Canavan's disease would

compare the intellectual property landscape of the tests. The cystic fibrosis case study would address the test's relatively liberal licensing, mainly by the academic institutions that made the gene discoveries. The case study of hemochromatosis involved the sale of intellectual property rights for testing to several companies consecutively over a period of time. Two additional case studies would examine the potential for patent pools to develop in cases where some of the intellectual property for genes was liberally licensed and some was not.

Mr. Conover reported that the students had begun work on identifying the patents for these cases, reading the claims, and determining which pieces were essential. They planned to report back to the Committee in the next couple of months.

Committee Discussion

Dr. Evans led the Committee in a discussion of the gene patents session. He asked if it provided sufficient background information on the basics of gene patents and licensing practices and on key policy developments. He asked the Committee to comment on whether there were gaps in information that needed to be filled at the next SACGHS meeting.

Dr. Willard suggested that the Committee lacked information about the percentage of gene patents that related to disease associations versus those that re-cloned a gene for a specific protein. He said it was important to know whether, out of 3,000 gene patents, there were only a few related to genes and human disease or a large number. He said that a quick examination of the claims could determine whether they described a method for diagnosing disease. If the number was very small, there would be less evidence that patents are having a significant impact. Dr. Leonard pointed out that there will be more patenting in the future, so the status of the current 3,000 patents might not influence the Committee's actions. After some discussion with Dr. Cook-Deegan about building on similar work that his team had already done and using computer technologies to refine the results, the group agreed that the Task Force should consider the cost benefit of this idea.

Dr. Leonard suggested that "availability" be added to the list of factors affecting access. Dr. Cook-Deegan stated that although availability can be seen part of the "hassle" factor, it should be added as a separate factor. The Committee decided that the term "hassle" should be specifically defined as the study moved forward.

Dr. Marc Williams suggested that another way of looking at the impact of patents on access would be to examine how payers contract with specific reference laboratories and with the sole sources of specific tests. He said some payers have written their benefits policies to exclude certain tests from payment.

Dr. Cook-Deegan noted that there was another data resource available to his team through Alexandra Shields at Harvard. She was developing some algorithms that might have the ability to extract utilization data from UnitedHealthcare data, which could serve as a loose proxy for access.

Dr. FitzGerald asked about international trends in gene patents in comparison with the United States. Dr. Cook-Deegan stated that the data he presented earlier indicated that the U.S. is an outlier case in terms of intellectual property, but is also an outlier in terms of access to care. There is limited access to many goods and services in the U.S. for certain subpopulations, e.g., the working poor. He stated that identifying the specific factors that are relevant to intellectual property would be very hard and that the dominant value in U.S. systems of care is innovation, not fairness in access.

Ms. Chira Chen asked if the study team could obtain pricing information for tests in Canada and Europe and Dr. Cook-Deegan said they could in some cases.

Dr. Evans asked if the scope of the study should be broadened to include the impact of pathogens in gene patenting and licensing practices on patient access. His view was that it would be difficult to address the study's scope without also addressing the effect of gene patents on human pathogens. Dr. Williams, Dr. Leonard, and Dr. Willard agreed that this topic should be part of the study's focus and the Committee concurred. Dr. Evans closed the session.

Economic Consequences of Genomic Innovation

Steven M. Teutsch, M.D., M.P.H.
SACGHS Member

Dr. Tuckson stated that he had asked SACGHS members and *ex officios* to identify new study topics for the Committee to consider. He introduced the first of two proposals, submitted by Dr. Steven Teutsch, on the importance of analyzing the economic consequences of genomic innovations. Dr. Teutsch noted that his proposal linked closely with the second proposal, to be presented by Dr. Gurvaneet Randhawa and Dr. Muin Khoury.

Dr. Teutsch said one of the major problems in the U.S. is the extraordinarily rapid rise in the overall cost of health care and that one of the major drivers of the increasing cost is technological innovation. He stated that, so far, genomics had played a small role in these cost increases, but it has the potential to play a much larger role in the future. He noted that very few of these new technological innovations save money in the aggregate. It is hoped that genomics will eventually lead to more prevention and the avoidance of huge health care costs, but that may not be the case if a large number of new therapies are targeted, leading to costs for diagnostics, management, and drug therapy or other interventions. He therefore recommended the development of "rules of the road" for moving forward.

Dr. Teutsch stated that the economic consequences of research in general and genomics in particular had not yet been put in a broad economic context for policymaking. Although genomics may increase health care costs, these technological innovations will benefit society by supporting vibrant research and development enterprises and commercial enterprises, improving health and productivity, and leading to a better quality of life. No other group was looking at the broad economic consequences, and Dr. Teutsch said that SACGHS was an appropriate body to do so. He proposed examining the issue on a preliminary basis, by conducting a scan of the economic consequences environment. The following questions could be considered: Who should pay for innovation and its downstream costs? Who will benefit (e.g., industry, public health, employers, academia, individuals, health care payers)? How can these costs be anticipated and managed appropriately? How will these technologies be paid for when they are developed? For those investing in new technologies, what assurance can be made that insurers will cover them? How can available research monies be allocated to basic versus applied research, the use of technology, and translation into practice? Dr. Teutsch suggested the creation of a small exploratory group to prepare an issue brief for presentation at the next SACGHS meeting. If there was agreement that the Committee should proceed with an investigation of this topic, a white paper for the Secretary could be developed.

Evaluation of Real World Outcomes of Gene-Based Applications

Gurvaneet Randhawa, M.D., M.P.H.
AHRQ *Ex Officio*

Muin J. Khoury, M.D., Ph.D.
CDC *Ex Officio*

Dr. Randhawa presented his case for a new SACGHS priority: integrating genomics in clinical practice. He displayed a diagram that showed phases for integrating a new discovery into practice. It indicated that the process begins with the initial discovery of a link between a gene and a disease, either in biomedical research laboratories, by genetic epidemiologists in academia (funded by NIH), or by CDC's HuGENet program. The link is sometimes causative, but is usually a correlation. A discovery can be made through *in vitro* experiments, animal data, or human data.

The next phase takes place during product development in the private sector, e.g., the pharmaceutical industry and the diagnostics industry, followed by therapeutics research and development in Phase I, II, and III trials. Research on diagnostics is not as well defined, and takes place through observational studies that often have not gone through FDA regulatory approval. In most cases, the discoveries undergo regulatory approval and are available for clinical use.

The next step was called "Outcomes Research," which represented many study designs, including randomized clinical controlled trials, cohort studies, case control studies, and new prospective studies. Information for the studies comes from health plan databases, Medicare and Medicaid claims databases, and electronic health records. Dr. Randhawa described three mechanisms at AHRQ that fund outcomes research: the traditional R01/R03 grant mechanism, the Centers for Educational Research on Therapeutics (CERT) program (co-administered with the FDA), and the new contract-based DEcIDE network. DEcIDE looks at the comparative effectiveness of drugs, devices, and diagnostic tests to develop evidence that will inform decisions about effectiveness.

In the next phase, data obtained from the studies is synthesized. One process takes place through the evidence-based practice center (EPC) program. Dr. Randhawa stated that although there are mechanisms to look at many topics, little evidence exists. The challenge is not how to handle evidence, but how to obtain it in the first place.

The next step was called "Decisionmaking," because evidence synthesis is closely paired with decisionmaking for guideline development and for coverage through Medicare, Medicaid, and health plans. These decisions must ascertain whether there is enough net benefit to introduce something new into clinical practice. Questions that must be addressed include: What are the benefits of this new test or therapy? What are the harms? What is the added value? What are the costs and the cost effectiveness? Decisions are then made on whether to cover a test or therapy or recommend using it. Once these decisions are implemented, the test or therapy moves into the final phase, routine clinical use. Dr. Randhawa added that there could be a feedback loop after routine clinical use to determine whether intended benefits were being achieved (i.e., postmarketing surveillance).

Dr. Randhawa said AHRQ was collaborating closely with the National Office of Public Health Genomics at CDC on a DEcIDE project that was evaluating the strengths and weaknesses of existing databases to

obtain outcomes of genetic tests. He stated that that project could serve as a foundation for recommendations that could be adopted by Federal agencies to improve public/private partnerships.

Dr. Khoury continued the presentation, adding an overlay of the public health perspective to Dr. Randhawa's diagram. He stated that during the previous 10 years, CDC had worked on a population health model for translation of genomics into clinical practice. He noted that biobanks and large cohort studies accelerate gene discovery. Dr. Khoury described the Human Genome Epidemiology Network (HuGENet), which was designed as a collaborative global movement to make sense of gene-disease associations. He added that the EGAPP process focuses on outcomes research in genomic technologies, including analytic validity, clinical validity, and clinical utility of tests; as well as ethical, legal, and social (ELSI) issues.

Dr. Khoury stated that once new discoveries become part of routine clinical use, the following questions are asked: What is the impact? Who is using it? Are there disparities? What are the costs? Are health outcomes affected? He said that, unfortunately, the greatest investments in genomics and population health take place in the early phases shown on the diagram, for "big studies, big science, and big therapeutics." Investment atrophies as products move toward translation. Dr. Khoury described an article from the *Journal of the American Medical Association* (JAMA) about the translation pathway. It said the usual meaning of translation is the movement from the bench to the bedside, i.e., a T1 translation. He said that moving a discovery from the bedside to practice is a post-T1 loop. The JAMA paper also described T2 and T3. T2 is essentially the translation step that leads to guideline development, meta-analysis, and systematic reviews. T3 is conducting the research that disseminates, implements, looks at outcomes, and examines the utilization rate. He noted that there were few studies on the T3 aspects of translation, because there is little funding for it. Dr. Khoury said that he, Dr. Randhawa, and Dr. Teutsch were all interested in seeing SACGHS address overarching concerns about the evidence related to genomic applications, their economic implications, and outcomes research.

Dr. Tuckson thanked the speakers and opened the floor for discussion. He agreed that there was synergy between the two proposals, which allowed for the possibility of integrating them. He noted the importance of these topics, since the health care system was moving toward transparency in the performance of the delivery system, both in quality and in efficient use of health care assets. He summarized the proposals by stating that genomics, as a new field, had not conducted enough research to allow specificity in clinical guideline development or translation into real outcome measures for performance. Dr. Teutsch said it was important to include the concept of economic consequences, so that resources could be allocated in the ways that would most benefit the health of the population.

Dr. Williams said that medical outcomes and cost outcomes are inseparable and he concurred with the idea of integrating the two proposals under the umbrella of one task force. He stated that SACGHS had the opportunity to work on other identified priorities within the health care system, such as pharmacogenomic dosing of Coumadin. His Institute recently completed enrollment of a randomized trial to look at genomically informed Warfarin dosing to see if it makes a difference in medical outcomes. They built a cost outcomes study in parallel with that effort to capture costs along with medical outcomes. Dr. Williams said the study is important from a patient safety perspective because there are 2 million adverse events a year related to the use of Coumadin and Warfarin. He stated that these are the types of targets SACGHS should identify.

Dr. Khoury commented that he used the term "population health" instead of "medicine" or "public health," because population health embodies the health of the population, while public health typically

refers to public health agencies and State health departments. He noted that the Institute of Medicine (IOM) referred to a population health umbrella as including the efforts of medicine, public health agencies, and others in the private sector that come together to improve the translation of science to applications and improvements in the population's health. He said there are very few things in genomics that fall under the public health system in terms of delivery of services, such as newborn screening. However, the implementation of genomics and genome-based technologies will be increasing in the country's fragmented health care delivery system, and a population health umbrella should be developed to measure outcomes. This could take place in primary care or well defined communities, such as HMO-based organizations that could develop the actual measures.

Dr. Tuckson asked Dr. Khoury for examples of health enhancing initiatives the Committee could address that go beyond the level of clinical interventions. Dr. Khoury said prevention encompasses both medicine and public health and it is hoped that personalized interventions will be developed at the therapeutic, diagnostic, and health promotion levels. The use of family history is an example. He advocated for developing an approach that would introduce these things using the best available evidence, measuring success and costs, determining the best way to implement them, and ultimately measuring their impact and utilization by the population. He noted that there are large health disparities in the United States population between the haves and the have-nots, which is a strong impetus for public health to step in. Dr. Teutsch stated that the tools of outcomes research have been used to set rankings for preventive services at the population level based on effectiveness, safety, and cost-effectiveness.

Dr. Randhawa said there should be a focus on both the research enterprise and the health care enterprise, so that a more robust infrastructure can be developed to get at outcomes data. He said obesity is an example of the place where clinical health and public health intersect. Screening for body mass index (BMI) can take place in a clinician's office, but a clinician is ill equipped to provide access to the community interventions available to an obese person, such as exercise options, counselors, and nutritionists. For these situations, there should be an interface with the broader public health community. Dr. Tuckson asked for more specificity on how performance measures would be arrived at that would lead to information on outcomes. Dr. Khoury replied, stating that a number of gene variants that might increase the risk of obesity were recently discovered. Efforts were being made to develop a diagnostic test to reduce the risk. This would lead to clinical trials to determine the added value of the diagnostic test and then to questions about possible gene-based interventions. Once a test is deployed in the population, the following questions would be asked: Who is using it? Is it helping people? Dr. Khoury noted that a genetic test for obesity would not stand alone because of the gene-environment interaction. The manner in which a genetic test for obesity would be introduced on the translation highway would be very complicated and would have to include outcomes research. He stated that he was proposing that the Committee grapple with this translation process. Dr. Randhawa added that the Preventive Services Task Force took on the topic of obesity and found that people with a high BMI need medium to high intensity counseling. Evidence would be gathered by identifying genetic populations that need more intensive interventions than the average risk population and conducting studies in the public health community setting. The evidence would not come from an individual patient provider.

Ms. Chira Chen said that some evaluation of performance could be done immediately for the BRCA1 and BRCA2 tests, because a database exists with some outcomes information, but the data was not being mined.

Dr. Sherrie Hans suggested that SACGHS focus on these questions at the policy level. She suggested a study with four points for consideration. First, the group would make the case for the importance of T3

analyses for public health, clinical care, and the related economics by conducting analyses of specific cases. The second point would be a needs analysis indicating what databases and information exists and what is missing. Third, based on the needs analysis, the questions the Department needs to address would be laid out so that appropriate research could be conducted. The fourth and final step would be getting the various agencies within the Department (CMS, NIH, AHRQ, CDC, and possibly VA) to work together to answer the questions.

Dr. Tuckson and Dr. Khoury noted that this initiative would fit well with the Secretary's personalized health care initiative. Dr. Khoury noted that it would be important to include the T2 phase in the Committee's approach, which includes guideline development, meta-analysis, and systematic reviews. He said that these post-Tl steps are the real translation activities.

Dr. Tuckson stated that Dr. Hans' four points were useful as a point.of departure for organizing the new initiative. He encouraged the Committee to be explicit about the large, population-based issues that fall outside the relationship between the patient and the physician, and he encouraged them to address who is accountable for outcome measures. Dr. Tuckson suggested that Dr. Teutsch chair the subcommittee, with Dr. Khoury and Dr. Randhawa as members. Dr. Williams volunteered to participate and said he would provide a link with the Oversight Task Force. Other members include Dr. Hans and Greg Feero of NHGRI. The new subcommittee was named the "Evaluation Task Force."

Next Steps and **Concluding** Remarks

Dr. Tuckson

Dr. Tuckson led the Committee in a discussion of next steps in the strategic plan. He suggested inviting NCHPEG leadership and representatives of professional organizations in genetics to the next SACGHS meeting to discuss the status of education and training issues. He also asked for an update on coverage and reimbursement issues from CMS and an update on direct-to-consumer marketing from CDC. Dr. FitzGerald planned to provide an update on the pharmacogenomics report, which was out for public comment. The topic of gene patenting would be addressed at the July 2007 meeting.

Dr. Tuckson adjourned the meeting.

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 Tuckson, M.D.
SACGHS Chair

Sarah Carr
SACGHS Executive Secretary