DEPARTMENT OF HEALTH AND HUMAN SERVICES

Seventeenth Meeting of the
SECRETARY'S ADVISORY COMMITTEE ON
GENETICS, HEALTH, AND SOCIETY
December 1-2, 2008

Meeting Summary

Hubert H. Humphrey Building
200 Independence Ave., SW
Washington, DC

Prepared by the Office of Biotechnology Activities
National Institutes of Health

Participants

December 1, 2008

Committee Members Present

Steven Teutsch, M.D., M.P.H., Chair
Mara Aspinall, M.B.A.
Sylvia Mann Au, M.S., CGC
Paul Billings, M.D., Ph.D., FACP, FACMG (Appointment Pending) [by telephone]
Rochelle Dreyfuss, M.S., J.D.
James P. Evans, M.D., Ph.D.
Andrea Ferreira-Gonzalez, Ph.D.
Kevin T. FitzGerald, S.J., Ph.D., Ph.D.
Julio Licinio, M.D.
Barbara Burns McGrath, R.N., Ph.D.
Paul Steven Miller, J.D.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Marc S. Williams, M.D., FAAP, FACMG
Paul Wise, M.D., M.P.H.

Ex officio Members/Alternates

Michael Amos, Ph.D. (Department of Commerce/National Institute of Standards and Technology)
Col. Scott D. McLean, Medical Corps, U.S. Army (Department of Defense)
Dan Drell, Ph.D. (Department of Energy)
Michael A. Carome, M.D. (HHS/Office for Human Research Protections)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Steven Gutman, M.D., M.B.A. (HHS/Food and Drug Administration)
Alan E. Guttmacher, M.D. (HHS/National Human Genome Research Institute)
Lisa Kalman, Ph.D. (HHS/Centers for Disease Control and Prevention)
Charles N.W. Keckler, M.A., J.D. (HHS/Administration for Children and Families)
Gurvaneet Randhawa, M.D., MPH (HHS/Agency for Healthcare Research and Quality)
Barry M. Straube, M.D. (HHS/Centers for Medicare & Medicaid Services)
Thomas Alexander, J.D. (U.S. Department of Labor)
Douglas Olsen, Ph.D., R.N. (Department of Veterans Affairs)
Naomi Earp, J.D. (Equal Employment Opportunity Commission)

SACGHS Staff

Sarah Carr, Executive Secretary, NIH Office of Biotechnology Activities
Cathy Fomous, Ph.D.
Darren Greninger, J.D.
Kathi Hanna, Ph.D., Consultant
Yvette Seger, Ph.D.
Linda Silversmith, Ph.D., Consultant

Special Guests/Consultants

Shubha Chandrasekharan, Ph.D. (Center for Genome Ethics, Law & Policy, Duke University)

Robert Cook-Deegan, M.D. (Center for Genome Ethics, Law & Policy, Duke University)
John LeGuyader (Department of Commerce/U.S. Patent and Trademark Office)

Maryellen de Mars, Ph.D. (Critical Path Institute)
Debra Leonard, M.D., Ph.D. (Weill Cornell Medical College/New York Presbyterian Hospital)
Ralph Martel, Ph.D. (Critical Path Institute)
Lori Pressman (Independent Consultant)
Mark L. Rohrbaugh, Ph.D., J.D. (HHS/Office of Technology Transfer, National Institutes of Health)
Brian R. Stanton, Ph.D. (The REDANDA Group, Inc.)

Speakers

James P. Evans, M.D., Ph.D. (SACGHS Task Force on Gene Patents and Licensing Practices)
Michael Amos, Ph.D. (National Institute of Standards and Technology)
Willie May, Ph.D. (National Institute of Standards and Technology)
John Butler, Ph.D. (National Institute of Standards and Technology)
David Bunk, Ph.D. (National Institute of Standards and Technology)
Karen Phinney, Ph.D. (National Institute of Standards and Technology)
Steven Gutman, M.D., M.B.A. (Food and Drug Administration)
Jeff Cossman, M.D. (Critical Path Institute)

Public Commenters

Michael S. Watson, Ph.D. (American College of Medical Genetics)
Debra Leonard, M.D., Ph.D. (Association of Molecular Pathology)
Guido Brink (Agendia BV)
Carol R. Reed, M.D. (Clinical Data, Inc.)

December 2, 2008

Committee Members Present

Steven Teutsch, M.D., M.P.H., chair
Mara Aspinall, M.B.A.
Sylvia Mann Au, M.S., CGC
Paul Billings, M.D., Ph.D., FACP, FACMG (Appointment Pending) [via telephone]
Rochelle Dreyfuss, M.S., J.D.
James P. Evans, M.D., Ph.D.
Andrea Ferreira-Gonzalez, Ph.D.
Kevin T. FitzGerald, S.J., Ph.D., Ph.D.
Julio Licinio, M.D.
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Marc S. Williams, M.D., FAAP, FACMG
Paul Wise, M.D., M.P.H.

Ex officio Members/Alternates Present

Dan Wattendorf, on behalf of COL. Scott D. McLean (Department of Defense)
Dan Drell, Ph.D. (Department of Energy)

Peter T. Kirchner, M.D. (Department of Energy)
Michael A. Carome, M.D. (HHS/ Office for Human Research Protections)
Robinsue Frohboese, J.D., Ph.D. (HHS/ Office for Civil Rights)
Denise Geolot, Ph.D., R.N. (HHS/Health Resources and Services Agency)
Steven Gutman, M.D., M.B.A. (HHS/Food and Drug Administration)
Alan E. Guttmacher, M.D. (HHS/National Human Genome Research Institute)
Charles N.W. Keckler, M.A., J.D. (HHS/Administration for Children and Families)
Muin J. Khoury, M.D., Ph.D. (HHS/Centers for Disease Control and Prevention)
Gurvaneet Randhawa, M.D., MPH (HHS/Agency for Healthcare Research and Quality)
Jeffrey Roche, M.D. (on behalf of Barry Straube) (HHS/Centers for Medicare and Medicaid Services)
Thomas Alexander, J.D. (U.S. Department of Labor)
Ellen Fox, M.D. (Department of Veterans Affairs)
Kerry Leibig (Equal Employment Opportunity Commission)
Matthew Daynard, J.D. (Federal Trade Commission)

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Debra Leonard, M.D., Ph.D. (Weill Cornell Medical College/New York Presbyterian Hospital)

Speakers

Paul Wise, M.D., M.P.H. (Chair, SACGHS Task Force on Priority Setting)
Marc S. Williams, M.D. (SACGHS Task Force on Priority Setting)
Barbara Burns McGrath, R.N., Ph.D. (SACGHS Task Force on Priority Setting)
Kevin T. FitzGerald, S.J., Ph.D., Ph.D. (SACGHS Task Force on Priority Setting)
Sylvia Mann Au, M.S. (SACGHS Task Force on Priority Setting)
Joseph Telfair, Dr.P.H., M.S.W., M.P.H. (SACGHS Task Force on Priority Setting)
Mara Aspinall, M.B.A. (SACGHS Task Force on Priority Setting)

Public Commenters

Sue Friedman, Ph.D. (Facing Our Risk of Cancer Empowered)
Amy Miller, Ph.D. (Personalized Medicine Coalition)

December 1, 2009

Opening Remarks

Dr. Steven Teutsch, Chair of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), welcomed other SACGHS members, the public, and webcast viewers to the 17th meeting of this Committee. He then invited members of the public to sign up to speak during the meeting's public sessions, listed the meeting's goals, summarized the highlights of the previous meeting, and cited some other recent developments. Dr. Teutsch also welcomed new Committee members, thanked those members for whom this is their last meeting, and mentioned his own change of professional position.

Goals. The meeting's main goals were:

(1) to review a draft report that explores the question of whether gene patenting and licensing practices affect patient access to genetic tests and to determine whether the report is ready to be released for public comment,
(2) to take an in-depth look at some of the important federal initiatives to enhance quality and innovation of genetic technologies through standards development,
(3) to continue to discuss and refine future study priorities and plans, and
(4) to discuss a draft progress report to the incoming Secretary of Health and Human Services (HHS).

Letter to the Secretary. At their July 2008 meeting, SACGHS members decided to write a letter to the then current HHS Secretary Michael Leavitt to thank him for giving a high priority to policy challenges and strategies related to genetic technologies and to highlight several issues that SACGHS members viewed as needing critical attention over the remainder of his tenure. [A copy of this letter is available at http://oba.od.nih.gov/oba/SACGHS/reports/letter_to_Sec_08-18-08.pdf.]

Ongoing activities. The Food and Drug Administration (FDA) is working on the co-development guidance for pharmacogenomic drugs and diagnostics—one of SACGHS's concerns—and, Dr. Teutsch expects a letter soon from Secretary Leavitt on coverage and reimbursement issues. Secretary Leavitt released two weeks ago a report on "Personalized Health Care: Pioneers, Partnerships, Progress." The report touches on issues relevant to the SACGHS charter. [The Department's website for its personalized health care project is http://www.hhs.gov/myhealthcare/ , and the new report is available at http://www.hhs.gov/myhealthcare/news/presonalized-healthcare-2008.html.] Also, the Surgeon General's Office has released a new version of its family history tool (see https://familyhistory.hhs.gov/fhh-web/home.action), and rulemaking is in process to implement the Genetic Information Nondiscrimination Act of 2008 when the Act takes effect next year.

The *ex officio* members of SACGHS will soon receive a survey, due at the end of January, from the Committee's Genetics Education and Training Task Force. This Task Force also invites comments on the draft competency statement (Tab7, meeting briefing book) that emphasizes the importance of understanding genetics and genomics as they relate broadly to public health. The competency statement will be submitted to the Council on Linkages Between Academia and Public Health Practice, which is revising its core competencies for public health practitioners and academicians (due date for comments, December 15).

The SACGHS charter was extended for two years in September (a copy is in the meeting briefing book and at http://oba.od.nih.gov/oba/SACGHS/sacghs_charter.pdf). The main url for SACGHS's new website is http://oba.od.nih.gov/SACGHS/sacghs_home.html.

Rules review. Ms. Sarah Carr, SACGHS Executive Secretary, next reviewed with Committee members governmental rules on conflicts of interest and lobbying as they apply to special governmental employees.

Draft letter to incoming HHS Secretary. Dr. Teutsch invited Committee members to review the draft letter to the next administration's HHS Secretary and be prepared to comment on it the next day.

Gene Patents and Licensing Practices

Review of the SACGHS Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests

Dr. James Evans, Chair, SACGHS Task Force on Gene Patents and Licensing Practices, led the review of the Task Force's draft report, with contributions also by Dr. Debra Leonard, past Task Force Chair.

History. Dr. Evans commented on the breadth and depth of the draft report as well as its long history. SACGHS made gene patents and licensing a priority in March 2004, then waited for the March 2006 National Research Council (NRC) report, which was commissioned by the National Institutes of Health (NIH). SACGHS agreed with the thrust of the NRC's 13 recommendations but wanted an additional emphasis on clinical and patient access issues; consequently, the Committee established a Task Force in June 2006 and has had relevant topic briefings on its meeting agendas several times since then. The Task Force also has benefited from the literature review and case studies developed for SACGHS by Dr. Robert Cook-Deegan and his team at Duke University's Center for Genome Ethics, Law & Policy. (Dr. Evans later introduced Dr. Cook-Deegan and Dr. Shubha Chandrasekharan, a postdoctoral fellow at the Center.)

Purpose. Dr. Evans indicated that the Task Force wants SACGHS not only to review its draft report today but also to discuss a range of policy options for public consideration. After a 60-day public comment period, the Task Force will develop its final draft report and recommendations for discussion at the October 2009 SACGHS meeting.

Intellectual property. A reason to define and protect intellectual property is to promote progress in the sciences and arts, investing in ideas. This protection allows and encourages openness, and discourages secrecy, as a stimulus to further development. It also rewards innovation. The types of intellectual property that can be protected include trademarks, copyrights, trade secrets, and patents. Basic requirements for patents are that they be useful, novel, and not obvious. Patents become limited-time monopolies.

Some landmarks with human materials leading to the patenting of genes and life forms were the patenting of adrenalin in 1911, insulin in 1923, prostaglandins in 1958, and a genetically engineered bacterium for eating oil in 1980. For most of the world, patents for isolated genes and life forms were a logical next step. There are, however, moral and practical problems affecting various stakeholders (the public, patients, industrial researchers, academic researchers, clinicians, small innovators, and ethics-based groups). The interests of these stakeholders can overlap, and individuals in all other categories can potentially become patients.

Perceived problems. There are several arguments in opposition to patents on genes. Some make a moral argument that genes have an inherent value and, no one should own human genes. Others focus on purported negative effects of gene patents, arguing that gene patents hinder research and patient access to genetic tests. Problems in access to tests are seen as occurring through pricing effects or because there is only one provider. The presence of only one provider in the marketplace can cause other problems. For example, other laboratories cannot verify the test. In addition, the lack of competition can affect a sole

provider's ability and willingness to carry out robust proficiency testing which may limit efforts to improve upon the test. Gene patents have also caused concerns about the future of genetic testing, as patent thickets may develop.

Benefits. Just as there are moral arguments against gene patents, there are moral arguments for them—for example, the argument that inventors have a natural right to their inventions, including discovered genes. There are also arguments that patents, including gene patents, have positive effects. For example, patents are credited with attracting post-invention investment needed for commercialization of an invention. Patents prevent what is called the "free rider" problem; that is, if inventions could not be protected by patents, copiers of the invention—free riders—could compete against the inventor and lower the inventor's return on his or her investment. Others suggest that patents empower the "little guy" to invent. The 2006 NRC report concluded that gene patenting was not currently a significant barrier for biomedical research, but it did not focus on clinical and patient access to genetic tests. The SACGHS Task Force, on the other hand, has focused on positive and negative effects of current gene patenting and licensing practices on patient access to genetic tests.

After reviewing the relevant literature, consulting with experts, and reviewing commissioned case studies, the Task Force developed a series of policy options for the full Committee to discuss today.

Among the study questions were:

- What is the role of U.S. patent policy in patient and clinical access to existing and developing genetic tests?
- How does a patent owner's use, enforcement, and licensing of patented genetic information affect patient and clinical access to the genetic test?
- How does legal interpretation of patentability and a patent's boundaries affect patient and clinical access to such technologies?
- How are licensing practices affecting patient and clinical access to genetic information and tests?
- How are licensing practices affecting the ability of industry and academia to develop genetic tests?
- What role do technology transfer programs play in influencing clinical access to genetic tests?
- What kind of evidence have we found, and can we find, to answer these questions?
- Where within the health care system do those barriers exist?
- What elements of the patent system relate to these aspects of the health care system?
- In what ways do gene patents and/or licensing and enforcement practices enhance or create incentives or barriers to the development, implementation, and continued performance of clinical genetic tests?
- What are the economic data, or the studies that analyze the contribution of gene patents to the cost of genetic tests and, ultimately, to patient access and treatment outcomes?
- What is the evidence of positive and negative effects of gene patents and licensing enforcement practices on the cost and the pricing of genetic tests?
- How is the quality of genetic testing affected by the current landscape of gene patents and licensing practices?
- What other measures and approaches could be employed to assess the direct effect of gene patents and licensing practices on patient access to and treatment outcomes from genetic tests?

- Are there feasible alternative models that could be applied to the patent and licensing system to enhance the benefits of the system or to help ameliorate problems that are identified?
- What are the lessons concerning patents from parallel situations in health care and in other areas?

Dr. Evans pointed out that multiplex testing is likely to increase in the future and genome sequencing costs of $1,000 may be a reality in the next few years, and as such there is also a need to consider how gene patents and licensing practices may affect the ability to perform multiple gene tests, panels, and arrays.

Introducing the case studies. Dr. Evans listed the case studies that the Duke University team prepared to help the Task Force analyze a number of issues; he then identified relevant major issues. The subjects of the case studies were breast and colon cancer, Alzheimer disease, spinocerebellar ataxia, hearing loss, hemochromatosis, Tay-Sachs and Canavan diseases, cystic fibrosis, and long QT syndrome. This list provides a broad analysis of patenting and licensing formats for disease genes and includes many of the most frequently ordered clinical tests.

Issues. Some case studies (e.g., breast and colon cancer in one study) provide natural experiments for trying to tease out the role of patents and licensing. Topics examined through the use of case studies include how patents and licenses influence the development, commercialization, and marketing of genetic tests; how patents and licenses impact adoption of a test by clinical providers and testing laboratories; whether patents and licenses affect adoption by third-party payers; and whether patents and licenses affect consumer utilization.

There are multiple parameters of access to a genetic test; these parameters include whether a diagnostic test is available at all, how quickly it is available following discovery of a genotype-phenotype connection, from how many providers the test is available, whether test improvements are available, whether these improvements are available soon after follow-on discoveries are made, and whether the cost of the test is reasonable to both the provider and the patient.

The intellectual property rights associated with a genetic test directly affect the following parameters of access: the number of providers offering a test (because licensing decisions dictate the number of providers); the test price; and the availability of a test following discovery of a particular gene or mutation associated with a disease. Factors only indirectly related to patents and licenses can also affect access to a test; these factors include coverage and reimbursement for testing, the utility of a test for clinical decisionmaking, and the quality of testing services. Fear of genetic discrimination may also prevent a patient from choosing an available test

Case study #1: breast, ovarian, and colon cancers. The breast cancer *BRCA*1 and BRCA2 genes increase an individual's risk for breast and ovarian cancers. Myriad Genetics holds rights to the patents claiming both genes and is the sole provider of full-sequence BRCA testing in the United States. In contrast, the patent rights for two types of colon cancer genes with multiple known mutations are held by nonprofit organizations and licensed nonexclusively, resulting in multiple test providers. The predictive value of the tests for colon and breast cancer is similar (the tests correctly predict their respective diseases 85 percent of the time).

Comparing the costs of genetic testing for breast cancer and colon cancer, Dr. Evans reported similar ranges in overall pricing ($1,150 to $4,760) between the exclusive laboratories of Myriad Genetics and the nonexclusive laboratories offering colon cancer testing. Furthermore, comparing these diagnostic costs by the cost per amplicon (an amplicon is a cloned DNA segment) also produced similar ranges for the different tests. It was also noted that Myriad is able to keep its pricing comparable presumably because of higher test volume; some of the higher volume is due in part to additional family members taking the test after a single family member has tested positive.

Although outside groups complained that Myriad's test was missing genomic rearrangements, Myriad responded that it had been testing for rearrangements before these complaints; and the same year as the

complaints, Myriad further improved its testing of rearrangements. Myriad has continued to enforce its patents (e.g., nine times in 2003), which can be viewed as limiting access. Dr. Evans speculated on future problems in sequencing a whole genome because genes like *BRCA* are already patented; in fact, Dr. Evans stated that 20 percent of human genes are patented.

Regarding the question of whether patents stimulated the search for the breast cancer genes, the answer is unclear—it is known that the prospect of therapeutics resulting from the research did attract industry investment that funded the search. The prospect of patenting the colon cancer genes did stimulate the search for those genes. Noting that a large proportion of gene patents are held by academic institutions, Dr. Leonard remarked that basically the drive for invention is twofold: (1) the existence of sick patients who need diagnostic or therapeutic interventions that do not currently exist and (2) the academic promotion system that requires physicians and researchers to invent and create and do research. She added that while academic institutions certainly benefit from patents that bring financial gain, it is not really the driving force for these inventions.

Case study #2: Alzheimer disease. To date, four genes have been associated with Alzheimer disease in humans, and U.S. patents have been issued relative to testing for all four of those genes. Mutations in three of these genes—presenilin-1, presenilin -2, and amyloid beta precursor protein—are highly penetrant but occur in low frequency. When mutated, these genes result in a significantly increased risk of early-onset Alzheimer disease. A particular allele of the *APOE* gene, the *APOE4* allele, increases the risk of late-onset Alzheimer disease. The *APOE4* allele is common but only partially penetrant.

Currently, *APOE* screening is not recommended for the general population but to confirm a diagnosis in individuals who have already developed dementia. Duke University holds three methods patents on *APOE* testing that are licensed exclusively to Athena Diagnostics.
Athena charges $475 for *APOE* testing but does offer reduced rates in certain situations. The lower base charge for APOE testing compared with the charge for the *BRCA* and colon cancer genes reflects the lower utility of the *APOE* information at this time. The granting of exclusivity has stopped some Canadian laboratories and the University of Pennsylvania from continuing to offer testing. The latter was charging only $125 per test.

Dr. Evans noted that it appears that the prospect of patents did not motivate the search for gene-disease associations for Alzheimer disease. The patent holder does indicate that the patent effectively restricts testing to symptomatic individuals. Patents played a role in the commercialization of the test in providing a mechanism for one entity to consolidate testing rights to the various genes. During discussion, it was pointed out that one can aggregate testing without patents too, as has been done with Lynch syndrome testing.

Case study #3: spinocerebellar ataxia (SCA). SCA is a genetically heterogeneous group of rare neurological diseases with variants in dozens of genes responsible for highly similar conditions, characterized by loss of cells in the cerebellum. This loss affects control of spatial orientation, which affects walking and balance. Of the approximately 34 genes that have been identified, tests are now available for 15 genes, but it can be difficult to determine which genes to test first. In some cases, variants in a particular gene have a higher frequency in specific populations, and testing can be prioritized. For example, a repeat expansion in the *ATXN10* gene—which causes SCA type 10—is more common in populations of Mexican and Brazilian descent than in other populations.

Athena holds the patent or exclusive license to 12 patents that identify the most commonly occurring genetic variants, constituting about 60 to 80 percent of SCA cases that appear to have a genetic underpinning. The company has been aggressive in enforcing this exclusivity. Athena also has been granted a nonexclusive license by Baylor University for the *ATXN10* gene. Dr. Leonard noted that a

consortium of laboratories used to work on SCA testing, but most of them are no longer in business due to Athena's aggressive enforcement of its exclusive rights.

SCA testing can be expensive. Testing for individual genes can range from $400 to $2,300, and the cost for all13 tests available from Athena is $7,300. It is also important to note that Athena's SCA testing panel does not test for mutations in about 20 genes that cause SCA.

Athena does offer two programs to reduce out-of-pocket costs of testing. The Patient Protection Program limits to 20 percent the out-of-pocket expenses for a patient whose insurance does not cover the test, and the Athena Access program offers free or low-cost testing to some patients. However, the latter program requires a lot of documentation, similar to what is required for participation in Medicare; this burdensome process additionally inhibits access.

Various academic institutions exclusively licensed their patents for different SCA genes to Athena, which then developed its tests and a test panel. However, the result has been a monopoly on SCA testing. While it is convenient to be able to have all SCA testing done at one site, the lack of competition raises concerns about a reduced incentive to improve testing services.

Another problem with a sole provider of the test is that any failure by that provider to obtain insurance coverage from a particular payer can harm those patients covered by that insurer. In this case, Athena has failed to obtain a coverage contract with MediCal, the state Medicaid program in California. As a result, SCA testing is not covered for MediCal participants because there is no competitor that might have obtained a contract with MediCal.

Cases study #4: hearing loss. At least 65 genes have been implicated in hearing loss in infants and toddlers, but mutations in five of these genes comprise a significant proportion of hearing loss cases. Genetic testing is available through multiple providers for *GJB2* (connexin 26), *GJB6* (connexin 30), *SLC26A4*, *MT-TS1*, and *MT-RNR1*. Of these five genes, the three that are not patented are *GJB6*, *SLC26A4*, and *MT-TS1*.

Currently test prices do not appear to correlate with patent status, possibly because Athena has not been enforcing its exclusive licenses. For example, *GJB2* testing is licensed exclusively to Athena but is offered by at least 10 other providers, and *MT-RNR1* testing is licensed exclusively to Athena but is offered by six nonprofit providers.

Dr. Ferreira-Gonzalez reported, however, on some changes in hearing loss testing based on recent experience in her own laboratory. Ten laboratories other than Athena Diagnostics had been able to offer *GJB2* testing because a company called Third Wave Technologies provided the reagents for an alternative method that detects a specific deletion mutation (35delG or 30delG). However, Third Wave has decided for economic reasons not to provide those reagents anymore. Without the reagents, Dr. Ferreira-Gonzalez's laboratory cannot perform the test, and other laboratories probably cannot offer the test either.

Dr. Evans commented that while this may be a business issue rather than a consequence of patents and licensing, it would be helpful to have Dr. Ferreira-Gonzalez circulate a summary paragraph on the development.

Local testing. Dr. Ferreira-Gonzalez also mentioned the potential value of local testing near the patient's primary care physician. Dr. Evans noted, on the other hand, that conducting testing at one site provides an opportunity for collecting a larger database. Dr. Teutsch also observed that the holder of the patent or exclusive license has an incentive for educating health care providers and the public on its tests and their usefulness. He wondered if anyone had tried to determine whether such promotion leads to

greater knowledge among clinicians than when a genetics test is being performed at multiple locations, with local laboratories informing physicians about the test's utility.

Inappropriate panel. Dr. Williams mentioned that the test supplier, Athena, also markets a test panel for Charcot-Marie-Tooth disease, even though different types of Charcot-Marie-Tooth disease can be distinguished based on clinical and electromyography findings. Consequently, after clinical examination, enough is known to identify which specific gene should be tested, and using the whole test panel is wasteful. Dr. Williams indicated that it might be worthwhile to explore this contrast between Charcot-Marie-Tooth testing and SCA testing.

Pricing data. Dr. Evans indicated that the pricing data provided today for hearing loss genetic testing are not available by amplicon and vary considerably because some tests are for certain mutations and others involve full-sequence analyses. He also indicated that the cost of hearing loss tests do not appear to correlate strongly with patents and licensing. Dr. Ferreira-Gonzalez asked about calculating the price per amplicon for the *GJB2* gene, and Dr. Chandrasekharan indicated that this can be done.

Testing complications. Dr. Williams noted that although *GJB6* is in the public domain, unlike the exclusively licensed *GJB2*, other laboratories likely will not do *GJB6* testing because it would not make sense to perform this test without first doing *GJB2* testing. Dr. Evans described a potentially related problem: suppose there is a disease that has 11 genes associated with it, and a panel is easily available to test for 10; but if the one gene that cannot be tested comprises any reasonable percentage of the cases, the panel is rendered worthless.

Dr. Evans emphasized that the enforcement of exclusive licenses could result in reduced access. How patents on hearing loss genes will affect access to gene-chip or microarray-based diagnostics depends on two circumstances: (1) whether such technology will in fact infringe existing patents on genes and (2) how aggressively patent holders (or their licensees) will choose to enforce their patent rights. Sequencing will certainly present challenges for a genetically heterogeneous disorder like hearing loss, which is covered by various patent claims.

Case study #5: hereditary hemochromatosis. A common autosomal recessive disorder with relatively low penetrance, hemochromatosis is a disorder in which individuals retain too much iron. Iron deposition over many years can lead to medical problems such as diabetes, heart failure, liver failure or cirrhosis.

Dr. Leonard mentioned that population screening for hemochromatosis was considered early on, but the idea was dropped because the gene's low penetrance meant that the test had low predictability as to who would be affected.

Hemochromatosis results most often from mutations in the *HFE* gene, which was discovered and patented by a startup company in the mid-1990s. The history of who owns the *HFE* patents and to whom the patent rights have been licensed has been complicated, and uncertainty has existed as to what extent patent rights would be enforced throughout the history of these patents. Currently, testing is available through multiple providers, but that was not always the case. Exclusive licensing and a single-provider model dominated for a time in *HFE* history.

Types of mutations. Two alterations in the *HFE* gene account for the vast majority of individuals with hemochromatosis, referred to as C282Y and H63D. Checking for these two mutations is usually sufficient; it is usually not necessary to sequence the entire gene. Methods for analyzing those mutations and a kit were patented by Mercator Genetics, which was subsequently acquired by Progenitor. Other patents in the same family were issued between 2000 and 2006 and were assigned to Bio-Rad. Patents include diagnostic methods for a panel of less prevalent mutations.

Incomplete testing. Dr. Leonard pointed out the serious potential for wrong results if a laboratory has to use a specific test kit because of licensing enforcement and the kit tests for only certain mutations (e.g., H63D) and does not take into account other mutations (e.g., S65C). Dr. Ferreira-Gonzalez stressed that Dr. Leonard is making an important point and gave another example involving acquired somatic genetic changes related to cancer where one may be forced to use specific test kits from a patent holder or licensee of the patent holder that have questionable quality.

Dr. Evans said that he would make sure that this issue is addressed in the report. He also requested that Dr. Leonard provide a memo to assist him in making this addition.

Patents as stimulus. Whether the prospect of patents encouraged the search for gene-disease association is a complex question regarding hemochromatosis. The prospect of patents and revenue from diagnostic testing probably stimulated research, particularly in the early hope for population-wide screening, which is now known not to be practical. The prospect of patents specifically led to the creation of a startup company with a business plan centered on identifying candidate genes for a number of diseases, including hemochromatosis.

Three additional groups were pursuing similar approaches for hereditary hemochromatosis gene identification. Once the association was found and published in *Nature Genetics*, many laboratories separately developed a simple test for the mutations based on that article.

The prices for targeted testing of the two major *HFE* alleles varies based on the technology and provider, with the cost ranging from $158 to $467. It is unclear how much variability in price can be attributed to the licensing issues, but the role of patents and licensing practices in test availability is more clear-cut. Patent enforcement did clearly remove preexisting competition when the patented test first appeared in the testing market.

Other genes. Dr. Williams pointed out that, as in the multiple genes with different risk levels in the Alzheimer disease case study, there are some genes rarer than *HFE* that result in syndromes of iron overload and that are more deterministic than *HF*E.

Genome sequencing. Dr. Licinio wondered if it soon will be cheaper to sequence the whole genome than to do a few of these tests and whether sequencing the genome can be done with all these existing gene patents. Dr. Williams noted that a precedent has been set in the microarray area because some microarray companies have now been asked to remove from their microarrays the Duchenne muscular dystrophy gene, which is protected by a patent.

Dr. Evans said that the 23andMe, Navigenics, and DeCODE situation is a little different because they are looking at single nucleotide polymorphisms (SNPs) but gene sequencing clearly would infringe on multiple patents. Dr. Leonard observed that as a result, a lot of royalties will have to be paid to conduct genome sequencing, making the dream of a $1,000 sequence impossible.

Case study #6: Tay-Sachs and Canavan diseases. These recessive neurological conditions are prevalent to a greater extent in the Ashkenazi Jewish population than others. Alterations in the *HexA* gene cause Tay-Sachs disease, and alterations in the *ASPA* gene give rise to Canavan disease. While DNA-based carrier screening is available for Tay-Sachs disease and Canavan disease, there is a highly effective enzyme test that was developed in the 1980s for Tay-Sachs. This biochemical test is still in use and preferred to the widely available genetic test because of the former's practicality.

HexA was patented by NIH but never licensed. The *ASPA* gene was patented by Miami

Children's Hospital, with licensing arrangements that were eventually determined by a confidential out-of-court settlement. The price of full-sequence analyses for Tay-Sachs and Canavan are similar, and the price of their targeted mutation analyses and enzyme assays are almost identical.

The developer of the Tay-Sachs DNA-based test has stated that she was not motivated by patents. The case study did not address whether the Canavan researchers were motivated by the prospect of obtaining a patent; however, the family groups that were voluntarily involved in the Canavan research were not motivated by developing and retaining a patent to any developed test. The Tay-Sachs patent neither helped nor hindered commercialization of the Tay-Sachs gene test. The impact of the Canavan patent on commercialization ultimately is unclear, in part because of the out-of-court settlement.

The original licensing scheme for the Canavan test imposed high fees and use restrictions that capped the number of tests that could be done by a licensed laboratory. The Canavan community was dismayed until an out-of-court settlement was reached that provided for more thorough and more available testing. Dr. Leonard pointed out that, in the Canavan case, people who were not medical practitioners were enforcing medically important patents in ways that no health care provider would ever do. The out-of-court settlement appears to have solved those issues.

Case study #7: cystic fibrosis (CF). CF is a recessive and currently incurable disorder that affects about 30,000 Americans. About one in 20 individuals carries a mutation in the *CFTR* gene. The delta-F508 deletion mutation is present in about 70 percent of cystic fibrosis cases. Early detection and screening arguably enable better disease management. DNA-based carrier testing and newborn screening are available and endorsed by medical professional societies. About 36 states include CF testing on their newborn screening panels.

Patents for the *CFTR* gene mutation and methods for detecting those mutations are held by three entities: the University of Michigan, the Hospital for Sick Children in Toronto, and Johns Hopkins University. All of these patents are nonexclusively licensed.

The testing price varies among 64 laboratories, not all of which offer the same type of testing. Thus, full-gene sequencing, offered by a subset of laboratories, ranges from $1,200 to $2,500, and targeted mutational analysis—for example, looking for the delta-F508 mutation (which is present in two copies in half of CF cases)—costs between $84 and $595. The price range, however, is influenced by the fact that there are a number of different test panels that one can order. One can order a panel of seven or nine fairly common mutations, up to a panel of several dozen mutations. The most exhaustive type of analysis would be full-gene sequencing.

With regard to whether the prospect of patents encouraged the search for gene-disease associations, it does not appear that gene patents were an important incentive for *CFTR* gene discovery—nor for development of special tests. Researchers and funders agreed on the need for patents as a way to make sure that nonexclusive licensing could take place. Sixty-four laboratories nationwide offer testing. Comparing prices between laboratories is difficult because the testing panels can vary regarding the number of mutations covered, and various laboratories offer different test combinations. As new techniques for genomic analysis are developed, they tend to be rapidly applied to create new tests.

Case study #8: long QT syndrome. Long QT affects about one in 3,000 newborns. The name long QT syndrome derives from the fact that the EKG of individuals with long QT syndrome, under certain circumstances and at times, shows a prolonged interval between the Q and the T waves. The EKG test, however, is often insufficient to make the diagnosis when trying to determine whether the sibling of a child who died of long QT syndrome is also affected. An affected sibling may need an implantable defibrillator. Genetic testing, therefore, is crucial. Knowing the particular mutation involved can guide

therapy, and some genes have a more malignant phenotype than others. Mutations in 12 susceptibility genes account for about 75 percent of the cases, with mutations in three genes accounting for the vast majority. The mutations affect ion channels.

The majority of these genes were discovered by a University of Utah researcher in the 1990s. The University then exclusively licensed its long QT syndrome patents to DNA Sciences for a period of several years. In 2003, DNA Sciences and all of its assets were purchased by Genaissance Pharmaceuticals. Then in 2005, Genaissance was acquired by Clinical Data, Incorporated, a subsidiary of PGx Health. There has been rapid growth in commercial testing for this disorder.

The prospect of patenting did not appear to stimulate a race for gene discovery, presumably because of the relative rarity of long QT syndrome and the anticipated small market for such genetic testing. Genaissance and then Clinical Data have made testing for long QT syndrome a substantive part of their genetic testing business plans. However, from 2001 to 2002 GeneDX and Boston University offered fee-for-service testing before patents were enforced.

The current charges for long QT syndrome genetic testing are $5,400 per index case and $900 per confirmatory test in additional family members. The cost per amplicon of $74 is at the high end of the cost range. For comparison, BRCA confirmatory testing targeted for an individual mutation costs about half as much. Most payers provide incomplete coverage of the testing. When a question was asked as to the company offering financial assistance, Ms. Aspinall pointed out that, the application process is so detailed, including requiring income tax returns, that needy patients may be too discouraged to apply.

Consumer access was adversely affected during periods when there was sole provider-enabled exclusive licensing. This limitation is a serious issue when it involves a condition that can result in sudden cardiac death. Furthermore, Clinical Data does not offer prenatal genetic testing for long QT syndrome. On the other hand, to date, there is no evidence that a virtual long QT syndrome genetic testing monopoly has had a stifling effect on the development of an improved test. The company has declined to add genes to its long QT syndrome testing panel or to sublicense rights to its panel to other companies. However, this is a common result for test developers and is probably not related to patents or licensing. In developing an assay for genetically heterogeneous disorder, developers face the difficult decision of whether particular rare genetic variants should be incorporated in the test panel.

Marc Williams pointed out that cardiologists who implant devices in long QT syndrome patients and the manufacturers who make them would benefit from the revenue from implantation; because of physicians' personal financial incentive in revenue from the implantation, physicians may order testing more broadly than is appropriate. Alan Guttmacher agreed that this was an important point in long QT testing; he observed that other genetic tests may be ordered inappropriately out of the physician's financial interest in satisfying the patient that something is being done.

Mara Aspinall, making a separate point, asked that the Committee not only consider possible future harms of gene patents but possible future benefits.

Preliminary conclusions from the case studies. Dr. Evans next reported the preliminary conclusions from the case studies. First, at times the way that patents are enforced results in barriers to access. Second, there is no clear relationship between patents/license exclusivity and the price of genetic diagnostic tests. Possibly, competition by a larger number of testing laboratories can bring prices down, but what third-party payers will allow is also a factor.

Next, there is no strong evidence of large-scale and long-term barriers to clinical access to genetic testing with the current gene patent and licensing landscape. There is also no evidence that exclusive licensing of

patents provides incentives to develop tests and make them available. Instead the drivers of test development appear to be clinical need or academic interest. Indeed, the tests for cystic fibrosis, hemochromatosis, breast cancer, colon cancer, and hearing loss were developed without patents being needed.

Purposes of patents and licensing. There are differences of opinion on several matters relating to the purposes of patents and licensing, including whether patents are a natural right or a utilitarian way to encourage discovery, whether patents in health care should differ from patents in commercial areas, and whether diagnostic testing should be treated differently from other uses of patents. Ms. Dreyfuss later corrected Dr. Evans' suggestion that patents might be natural rights; she explained that American law does not recognize a moral right in patents. Dr. Evans agreed, noting this was consistent with the Constitution's language about promoting arts and sciences.

Patent "thickets" (e.g., multiple patented genes) could interfere with multiplexed testing and full-genome analyses. Dr. Stanton responded that patent thickets have resolved themselves in other fields, with the parties forming patent pools and the technology going forward, so it is only a potential problem in gene patents that may very well be resolved in a similar fashion. Ms. Dreyfuss distinguished these situations in other fields from the situation involving gene patents. She argued that gene patent holders could go ahead and market their individual tests without cooperating, whereas in other technology fields if all the parties did not agree, there was no product at all. Ms. Dreyfuss added that gene patent holders may have reasons to cooperate, but they are not driven to it in the same way as the patent holders in these other fields. Ms. Pressman later stated that it was perhaps better to say there are information thickets; she then made the separate point that incentives are needed for people to disclose phenotype-genotype correlations, and that if these correlations could not be patented, researchers would instead choose to create restricted databases containing this information.

Dr. Stanton mentioned that Congress will reconsider a patent reform bill in March 2009. Dr. Stanton indicated that he thought the Committee's next meeting was in February and that after that meeting the Committee might be able to bring its opinion to the Senate, ahead of Congress's work in March on the patent bill.

Range of policy options. Dr. Evans stated that public input is needed on the range of policy options that the Task Force is presenting to help guide formulation of SACGHS's final recommendations on patent and licensing issues to the HHS secretary. Dr. Evans hopes for a balanced response on whether to add, remove, or modify any of the proposed policy options. The categories of potential policy options to consider and the choices (in brief) under each are as follows:

Policy option 1. Advocacy efforts by key stakeholders to ensure access.
Dr. Evans presented the following policy options:

A. Stakeholders should work together to develop a code of conduct to encourage broad access to technologies through licensing agreements for the diagnostic use of gene patents;
B. When stakeholders (e.g., academic researchers, industry, and patient organizations) work together to advance the identification of gene mutations and the development of diagnostic tests, the owner of any resulting invention should consult with those stakeholders regarding whether to seek patent protection and how any resulting patent should be licensed; and
C. Professional associations involved in technology transfer should accept and build on existing best practices and guidelines and should cooperatively reach consensus positions.

Commenting on option A above, Dr. Leonard suggested eliminating the word "quality," and Dr. Williams suggested this word be replaced with "utility." Dr. FitzGerald also suggested that HHS should bring together the stakeholders referenced in the above policy.

Dr. Au asked who would enforce option B. Dr. Evan replied that option B was merely a statement calling for all parties to get along; his answer implied that no one would enforce this provision. Dr. Williams then observed that the option was a statement and not really a recommendation; he suggested that it would be a recommendation if HHS provided a forum for such stakeholder collaboration.

Dr. Billings then expressed confusion over how these stakeholder discussions would take place if the patent application is secret until it is filed. Dr. Evans repeated the recommendation, clarifying that it calls for working together. Dr. Billings then reiterated his confusion over when the stakeholders would consult—before or after the filing of the patent application?

Dr. Evans wondered if Dr. Billings' concern would be addressed by eliminating the reference to "the owner of the resulting invention," which could be read to suggest that a patent decision had already been made, and replacing it with "those stakeholders should consult with one another." There were a few related comments after Dr. Evans' proposed rephrasing, and he reminded the Committee members that they should not be slowed down by discussing policy options that cannot be enforced and that call for actions with which few could disagree.

In a subsequent discussion on how to make this first category of policy options enforceable, the Committee members decided to add a brief preamble stating that HHS should develop a set of principles and guidance in order to facilitate the options. The discussion also led to revisions designed to make the options more action-oriented.

Policy option 2. Enhancement of transparency in patents and licensing.
Dr. Evans presented the following policy options:

A. Gene patent holders should make their patent licenses or information about these licenses publicly available;
B. NIH should amend its "Best Practices" to encourage disclosure of license information; and
C. The Secretary of HHS should seek statutory authority to enable the FDA and the Centers for Medicare & Medicaid Services (CMS) to require patented DNA-based in vitro diagnostic tests, whether offered as a test kit or a laboratory-developed test, to display on product packaging and/or company/provider websites the issued patent and published patent numbers that the company or provider owns and controls and reasonably believes covers their product or patents licensed by the company/provider in order to market the product.

With regard to options A and B, Ms. Aspinall asked what it would mean to make patent licenses publicly available. Dr. Evans explained that the information that was made public would include such things as the type of license, the license's field of use, who had the license, and the scope of the license. When Ms. Aspinall asked if the information disclosed would include financial information, Dr. Evans said it would not. She wondered why information about licenses would be useful. Dr. Evans explained that information on licenses could help one determine the degree to which licensees are adhering to guidelines on best practices. The license information also could help would-be innovators decide whether existing license terms preclude or permit their development of a particular test.

When Dr. Williams inquired about how the Secretary of HHS could enforce policies such as those in A and B, Dr. Evans indicated that the current discussion is focusing on principles and that practical issues relating to how to effect these policies will be addressed during later discussion.

With regard to policy option C, Ms. Aspinall asked if what it called for was consistent with the labeling requirements for drugs and devices, and Dr. Evans said it was. Dr. Williams wondered why option C was necessary. Dr. Evans explained that it was necessary for the same reasons that A and B are necessary.

Dr. Teutsch then prompted Dr. Gutman, FDA's *ex officio* member of SACGHS, to elaborate on current labeling requirements for genetic tests. Dr. Gutman noted that FDA labels do not capture patent license information. He also stated that it might be possible to change the labeling requirements by regulation without needing statutory changes. Ms. Aspinall voiced concern that imposing this requirement on genetic test kits but not drugs could be genetic exceptionalism, putting an unnecessary burden on start-up companies. Dr. Evans stated that this type of information could also help test developers to figure out if they are or would be in violation of anyone else's patent or licenses. He also indicated that rather than changing the policy option now the public should first have a chance to comment.

Dr. Williams pointed out that if multiplex testing is involved, the list of patent and license numbers could be very long, and Dr. Amos suggested that what is needed is a website that provided the relevant information; he added, though, that someone would have the burden of keeping the website's information up to date.

Policy option 3. Filling data gaps.
Dr. Evans presented the following policy options:

A. In order to assess the extent to which gene patent or licensing arrangements may be affecting patient access to genetic tests, HHS should develop a voluntary reporting system to encourage researchers and medical practitioners who order, use, or perform genetic tests to report such access problems;
B. Research agencies should explore using summary data from federal funding agreements to help assess the role of exclusive licensing practices in inhibiting patient access;
C. HHS should develop a uniform data collection system including database structure and standardized terminology, or enhance the existing iEdison system, and encourage HHS funding recipients to submit more data about inventions that, at the time they are patented and licensed, are reasonably anticipated to be associated with clinical genetic tests; and
D. The HHS secretary should establish an ongoing advisory board on the public health impact of gene patenting and licensing practices.

With regard to option A, Ms. Aspinall asked that it be rephrased since it presumes access problems when it could be that the patents are causing an increase in access. Dr. Teutsch asked Ms. Aspinall how the reporting system could capture positive reports about patents when most people tend to report failures rather than successes. He then suggested claims data might capture patented tests that are being done, but Ms. Aspinall responded that the Current Procedural Terminology (CPT) system prevents ones from seeing that information.

With regard to option B, Ms. Aspinall objected that the wording implied that exclusive licensing always had a negative impact; she asked for a more neutral rephrasing.

Dr. Williams then suggested citing specific agencies to the HHS secretary, and there was discussion that NIH, the Agency for Health Research and Quality (AHRQ), and others were possibilities.

With regard to option C, Dr. Evans clarified that the data would be collected by HHS and would be available for as-yet-undefined individuals or organizations, and HHS would report back to the public on what the data indicated about the effects of patents and licensing decisions on access to genetic tests.

Policy option 4. Federal efforts to promote broad licensing and patient access.
Dr. Evans presented the following policy options:

A. Federal agencies should promote wider adoption of principles that encourage limited use of exclusive licensing for genetic and genomic inventions;

B. Federal agencies should encourage wider use of the Association of University Technology Managers (AUTM) publication *In the Public Interest: Nine Points To Consider in Licensing University Technology*;
C. NIH should explore mechanisms (e.g., patent pooling) to facilitate the use of rapidly developing technologies for genetic tests that depend on multiple licenses of patents; and
D. Federal agencies should consider providing more detailed guidance on the licensing of patents protecting genetic tests; specifically, this guidance should encourage academic institutions to use terms in licensing agreements that can reduce the likelihood that any exclusivity associated with a license will lead to adverse effects on patient access. Taking steps likely to increase the number of insurers that reimburse for the test, or improving the specificity and sensitivity of the test and enhancing knowledge of its clinical validity are examples of milestones that a licensee could be required to meet to earn or maintain license rights.

With regard to option D, Ms. Aspinall asked why it was limited to academic institutions, and Dr. Evan agreed that it instead should focus on "patent holders" so that companies are included as well. Dr. Williams added that a license term requiring a licensee to increase the number of insurers reimbursing for a test is unfair because insurers do not always go by evidence in deciding whether or not to reimburse for a test. Dr. Evan suggested that public comment may address the issue raised by Dr. Williams, who agreed and asked to explore the topic again after public comment. At that time, Dr. Williams particularly would like to hear how reimbursement relates to licensing.

Policy option 5. Licensing policies governing federally funded research to facilitate access.
Dr. Evans presented the following policy options:
A. NIH should explore making compliance with its best practices publication an important consideration in grants awards;
B. The Secretary of HHS should seek clarification of the Department's authority under the Bayh-Dole Act to ensure that the goals of the statute are being fulfilled in the context of genetic diagnostic tests, in the manner reflected in the NIH *Best Practices for the Licensing of Genomic Inventions*; and
C. The Secretary of HHS should clarify the Department's authority under Bayh-Dole to require nonexclusive licensing of DNA-based inventions for diagnostic uses.

Ms. Aspinall raised a question about the sufficiency of the range of options presented so far because it does not include the other end of the spectrum in which the Secretary would require exclusive licensing. Ms. Dreyfuss observed that she views the proposed range of options as flowing from the case studies that were presented, and the case studies showed that exclusivity caused problems and did not show similar problems with nonexclusive licenses. She also commented that some universities seem to have granted exclusive licenses without thinking through the consequences. Ms. Aspinall maintained that option C went too far and that she preferred option B. Ms. Dreyfuss proposed changing option C to require a presumption of nonexclusive licensing.

Dr. FitzGerald observed that the Task Force, in crafting options, seems to have created some categories of options where all of the options could be implemented and other categories of options where one option would have to be chosen over others. Dr. Evans agreed. After the receipt of public comments, the Task Force will work on assuring internal consistency in what is proposed as final recommendations. Dr. Williams observed that several of the Task Force's proposals are for clarifications of authority as to what HHS can and cannot do. He agreed with this approach because the Committee should consider what the Department can and cannot do.

Policy option 6. Study federal implementation of intellectual properties laws.
Dr. Evans presented the following policy options:

A. A study should be commissioned on how federal agencies have managed government-owned DNA-based inventions with diagnostic uses; and
B. A study should be commissioned on how agencies have applied the Bayh-Dole Act's march-in provisions.

Policy option 7. Improving and clarifying of Patent and Trademark Office policy.
The Secretary of HHS should recommend that the Secretary of Commerce advise the Patent and Trademark Office (PTO) to undertake the following actions: (A) establish an advisory committee that would provide advice about scientific and technological developments related to genetic tests and technologies; this work may inform the PTO's examination of patent applications and other proceedings; (B) gather "nonobviousness" guidelines to assist in patent examination; and (C) develop guidelines on patentable subject matter in the wake of *In re Bilski* and its progeny.

Dr. Evans initially explained why these options direct the Secretary of HHS to make recommendations to the Secretary of Commerce. SACGHS, by charter, advises the HHS Secretary; consequently to have any influence with the U.S. PTO, which is in the Department of Commerce, the Committee must request that the HHS Secretary interact with the Commerce Secretary.

With regard to option B, Mr. LeGuyader, a PTO representative, noted that the PTO probably would not gather guidelines until after the *In re Kubin* decision was issued by the Federal Circuit Court of Appeals. The case concerned a decision by the Board of Patent Appeals and Interferences to reject, on obviousness grounds, a patent claim to a gene. With regard to policy option C, Mr. LeGuyader said that the results of some cases in process other than *Bilski* could affect development of PTO guidelines as well.

Dr. Evans noted that the *Bilski* case, which was just decided, can affect association patents. An example of an attempt to patent an association is the *Metabolite* case, in which the U.S. Supreme Court was asked to decide whether an association of high homocysteine levels with Vitamin B12 deficiency could be patented. The court did not grant certiorari (i.e., review), but Justice Stephen Breyer in a dissenting opinion said that the court should have done so because of the implications, at least in part, for medical diagnostics and for medical practice. Dr. Evans then noted that the recent *Bilski* case suggests that association patents are not going to be considered favorably, but that there are still other relevant case pending.

Policy option 8. Seeking statutory changes.
The Secretary of HHS should work with the Administration to encourage support for legislative change. In particular, the Secretary could promote some subset of the following legal changes: (A) prohibition of the patenting of an association of a particular genotype with a disease or disorder; (B) modification of the Patent Act as needed to keep patent holders and licensees from impeding patient access to a genetic diagnostic test; (C1) exemption of medical practitioners who order, use, or perform diagnostic genetic tests in clinical care from patent infringement liability; (C2) exemption of those who order, use, or perform diagnostic genetic tests during research from patent infringement liability; and (D1) requirement that patents on DNA sequences be limited to the utilities specified in the patent or (D2) prohibition of patents on DNA sequences for diagnostic purposes or (D3) prohibition of patents on DNA sequences.

With regard to these options, Mr. LeGuyader cautioned that prohibiting patenting of diagnostic types of assays potentially could have a chilling effect on the biotechnology industry because these patents are a large part of companies' patent portfolios, whether or not these patents are enforced.

Dr. Evans acknowledged that the recommendations in policy option 8 are controversial. Dr. Williams noted that they will likely elicit polarized public comments, which will likely put the Committee in the position of having to decide between the opposing perspectives. Dr. Williams expressed the view that

public comment would not help the Committee members decide whether to recommend any of the statutory changes. He also stated that the options were all negative and not balanced.

Dr. FitzGerald observed that when the Committee has been unable to reach consensus in the past, it has recommended that the Secretary create a group to look into the unresolved issues. Dr. FitzGerald suggested this course of action might be appropriate here as well. Dr. Evans objected to this idea because it simply punted the issues to another group.

Dr. Keckler commented that the most severe options in this category did not flow from the case studies. Ms. Dreyfuss responded that the first recommendation—the prohibition of association patents—does flow from the case studies. Dr. Evans added that some of the options reflect recent legislative proposals, and the Task Force felt it would be remiss if they were not included. Dr. Telfair agreed, but also suggested that the section needed a preamble.

In replying to Dr. Williams' earlier remark that the public's reaction to the options could be predicted, Dr. Leonard cautioned that one cannot presuppose how members of the public will react. Dr. Ferreira-Gonzalez expressed that adding a preamble was a good idea and that this range of options should be offered for public comment.

Ms. Aspinall suggested that to make the options truly broad an option was needed calling for maintaining the current patent system and ensuring that exclusive licenses are easily granted and can be used on a regular basis. Dr. Evans stated that this seemed reasonable. Ms. Aspinall added that another option would be to reinforce the system as the best way to get innovative tests.

Dr. Evans responded that there are few people who would advocate that there be nothing but exclusive licenses. Ms. Aspinall replied that Dr. Evans' point raised the issue presented earlier by Dr. Williams: namely, after the public comment period, do the Committee members make their decisions based on the popular vote by the public or do the Committee members make their decisions on the options based on their own thinking even if it goes against the majority of the public comments.

Dr. Teutsch suggested that the Committee's role is not to count votes based on public comments. While compelling public comments should be considered, any decisions should be based instead on the Committee's collective judgment. He added that he hoped members of the Committee do not feel that they are there representing the company or academic institution for which they work. The Committee's aim for the moment, Dr. Teutsch explained, was to decide on a range of options that is reasonable and upon which public comment should be sought.

Members then reached a consensus to include the status quo as one of the options for public consideration.

Dr. Amos, referencing Mr. LeGuyader's earlier remark about an option having a chilling effect on the biotechnology industry, expressed that the options had economic implications that have not been considered. He then seconded Dr. FitzGerald's earlier idea that another group look at these issues. He believed this was appropriate because no one at the table had expertise in economics. Dr. Evans responded that after the public comment period the Committee can decide whether it has sufficient expertise to issue recommendations.

Dr. Williams suggested that since the case studies do not address association patents, the preamble needs to explain why that issue is included among the options. Dr. Telfair indicated that the preamble also should ask the public for very specific comments and recommendations.

Ms. Aspinall voiced concern that options C1 and C2 undercut the patent system entirely. Dr. Evans replied that these options are natural extensions of the 1996 Ganske-Frist amendment. Ms. Dreyfuss then explained how each of the options has a basis in court decisions.

Ms. Aspinall agreed that these ideas are logical extensions. She added that as long as these options are only up for discussion and not set forth as SACGHS recommendations, she can accept them for now. Dr. Evans agreed that there would be a preamble explaining that these options were not recommendations.

When Dr. FitzGerald asked if the DNA sequences being referred to are human or include other organisms, Dr. Evans said that the sense of the Task Force is that the topic is human health. He asked other SACGHS members if that interpretation should also include human pathogens (e.g., SARS), and Ms. Dreyfuss commented that she would include them. Mr. LeGuyader then commented that he sees options D2 and D3 as having a chilling effect on industry, but that pathogen DNA should be included if this was in fact the option that would be put forward. He did not think that the DNA for microbes used in industrial protein production should be included, however.

During further discussion, Dr. Evans proposed the term "medically relevant" DNAs and RNAs instead of DNA and RNA sequences "related to human health." When Ms. Dreyfuss and Dr. FitzGerald objected to this rephrasing, Dr. Evans recalled that the Task Forced had proposed that any prohibition of patents on DNA sequences be limited to those sequences used "for diagnostic purposes," and this would prevent the proposed change from sweeping too broadly. Ms. Aspinall said that she would prefer that option D3 still be included because its total prohibition on DNA sequences does not discriminate against a particular industry. Ms. Aspinall later asked whether this option was meant to extend to proteins as well, and Dr. Evans explained that it included DNA and RNA and patents on proteins was beyond the scope of the study and the purview of the Committee.

Further discussion. Dr. Evans and Ms. Aspinall first reviewed the prior decision to add a preamble and an option calling for maintaining the status quo. Dr. Evans then asked whether there should be an option encouraging exclusive licensing but no Committee member spoke in favor of it, so it was determined that it would not be added.

Dr. Teutsch then explained that the next steps would be for the Task Force to use today's discussion as a basis for revisions to the report, and the Task Force, but not the Committee, would then review the report one final time before sending it out for public comment from February to April. Dr. Evans added that the Task Force will present its analysis of responses at the June 2009 SACGHS meeting, work further on the document over the summer, and bring the final recommendations to SACGHS at its October meeting.

When Dr. Leonard asked whether the request for public comment would include an invitation for new suggestions as well, Dr. Evans said that it would, and Dr. Teutsch referred everyone to page V under tab 3 in the briefing book for the request for public comment statement that had already been drafted.

Several members then predicted that the public would respond with numerous comments. Ms. Aspinall wondered whether any other organizations should be added to the dissemination list to broaden the distribution; Dr. Evans responded by inviting all committee members and the public to send any additional names to include on the list.

Dr. Teutsch thanked the Task Force for all its work.

Public Comment Sessions

December 1, 2009, comments

American College of Medical Genetics (ACMG). Dr. Michael Watson, ACMG Executive Director, stated that ACMG is the only organization with a policy opposing patents and licenses for genetic material and currently focuses on unfair patent/licensing issues. He noted that there is little evidence that patents have led to products and limited evidence that they improve services. Typically, patent enforcement begins to take place when diagnostic tests have become well enough developed for population-based screening to begin. Because of the high costs of litigation, not much litigation occurs.

ACMG also believes that patents should not be imposed in cases of multiplex technologies. However, just recently a patent holder ordered a gene to be taken off an array. This action seriously interfers with the practice of medicine. Fortunately, a settlement was reached allowing the gene to stay in the array in this one situation.

Another example highlights manufacturers' limitations in developing a molecular test that would evaluate variants in multiple genes associated with hearing loss. One of these genes is also associated with Jervell and Lange-Nielsen syndrome, a form of long QT syndrome. A patent holder is refusing to allow this gene to be included in the hearing loss panel because it imposes on the long QT patents. One solution would be to separate diagnostic tests via legal amendments to patent/licensing law while keeping protections of gene patents for the development of therapeutics. Dr. Watson also referred to a case currently in circuit court that should be followed: Mayo Labs vs. Prometheus Labs; this is similar to the prior Metabolife Labs v. Lab Corp. case.

Association for Molecular Pathology (AMP). Dr. Debra Leonard, AMP member, reviewed AMP's recently rewritten position on gene patents and the exclusive licensing of genetic discoveries. AMP is concerned that patent holders are monopolizing genetic testing and restricting what can be done. Medical care needs to take precedent. Genes are products of nature that should not be patentable. Furthermore, litigation costs have a chilling effect inhibiting the development of tests to benefit patients. Government standards are needed that require licenses to be nonexclusive.

Consequently, AMP recommends (1) discontinuing the patenting of genes via either judicial review or an act of Congress; (2) academic and research institutions holding existing patents should not grant exclusive licenses; (3) promoting access by establishing financial terms for test licenses that are reasonable and prohibiting sole source tests. Stakeholders should work together to create innovative models that increase patient access to health care and achieve greater benefits.

Agendia BV. Guido Brink, Director, Regulatory Affairs and Reimbursement, noted that genetic tests were defined in the draft SACGHS report on patents and licensing practices as tests performed using molecular biology methods to test DNA or RNA. He explained that Agendia does not assess mutations but provides testing for gene expression profiles, which he thought met the report's definition of genetic test. He noted, however, that mutation assays were the only genetic tests highlighted in the case studies, expression profiles were not included. Mr. Brink recommended that the Committee consider the types of tests evaluated in the report and perhaps redefine "genetic test." Dr. Teutsch expressed appreciation for this suggestion.

Clinical Data, Inc. Dr. Carol R. Reed, Executive Vice President and Chief Medical Officer of Clinical Data, Inc., first pointed out that PGx Health, which offers the Familion test for long QT syndrome is a subsidiary of Clinical Data, Inc. She cited this test as a good example of the use of exclusive licensing to develop a profitable commercial product. She further explained that this commercial test relieved research laboratories of having to sequence the genes commonly associated with long QT syndrome and freed their resources to identify rarer causative genes.

Dr. Reed also discussed patient access to genetic testing. She believed that patient access is more directly affected payer reimbursement policies than patents or licensing practices. The company has invested significantly in staff to deal with managed care. For example, the company has obtained Medicaid coverage in 38 States, with coverage pending in the remaining 12 States, and is an approved Medicare provider. Without patent protection, the company would not have exerted this effort.

Dr. Reed's third major point was that Clinical Data understands the importance of expertise in the interpretation of mutational analysis tests. She explained the importance of being able to draw a direct relationship between a discovered mutation and the structural relationship to the protein and to have a normal database against which to compare frequencies of mutations and other variants identified during testing. Dr. Reed warned that whole-genome scans may be dangerous because variants will be identified without the appropriate background against which to analyze and interpret the results, which could place patients at risk for inappropriate interventions.

Lastly, she suggested to Dr. Stanton that he consider including the cost of interpretation of genetic tests and the resources needed for that effort in his cost modeling.

December 2, 2009 comments

Facing Our Risk of Cancer Empowered (FORCE). Dr. Sue Friedman, Founder and Executive Director, explained that FORCE is an organization devoted to improving the lives of individuals and families affected by hereditary breast and ovarian cancer, and that the goal of her testimony was to alert SACGHS to a growing issue regarding more frequent genetic testing that is affecting the community that FORCE serves.

Consumers assume that these genetic tests have clinical utility and have been validated, and they tend to get most of their information from the companies offering the tests because of the lack of knowledge about genetic testing in the health care community and a gap in oversight. Doctors also tend to get information directly from the companies, which would not be allowed to do this direct-to-doctor marketing if they were pharmaceutical companies and under FDA oversight.

The FORCE help line receives calls daily that show that dollars are being wasted, the wrong tests are being ordered, the wrong individuals within a family are being tested, and the individuals and families are being given wrong information about what the results mean. Such problems do not occur when people are referred to genetics experts. There are standard-of-care guidelines for hereditary breast and ovarian cancer. For example, the National Cancer Comprehensive Network (NCCN) panel (on which Dr. Friedman participated) developed standard-of-care guidelines for genetic testing that include obtaining a three-generation pedigree and having access to genetic experts.

Dr. Friedman referred to patient cases of inappropriate and harmful experiences and spoke of one example in which a woman was allowed in her obstetrician/gynecologist's office to fill out her own form requesting a genetic test, ordered the wrong test, proceeded with a lumpectomy, and only afterwards found out that her decision was based on the wrong test. If she or her doctor had called on the expertise of a genetics expert, this unfortunate event could have been avoided. There have also been situations in which people are told that their test results were normal when they have a mutation or are informed via telephone while they were driving that they carry a BRCA mutation. In addition, FORCE receives frequent reports of full-sequencing BRCA testing being ordered when a $300 or $350 mutation panel would have been more appropriate.

Dr. Friedman also shared her experiences hearing sales representatives promote specific genetic tests to health care professionals and say that they do not need to refer patients to genetics experts. At a professional society meeting, she saw a nurse raise a continuing education guideline booklet produced by a genetic testing laboratory and say that all the information needed to start doing genetic testing in their offices was provided in the booklet.

Dr. Friedman then proposed to SACGHS that there be at least one government agency that has oversight and jurisdiction over genetic tests, including tests performed in laboratories certified through the Clinical Laboratory Improvement Act (CLIA). This agency would also have oversight on how these tests are marketed to consumers and physicians. She also noted that physicians and patients need to be educated that when there is no medical emergency, there is time to wait until they are able to consult with a genetics expert.

Dr. Friedman also stated that consumers are being denied standard of care, that laboratories (which may not have qualified personnel to provide genetic counseling) need to be held accountable for their marketing materials directed to consumers and physicians, and that there needs to be an agency to track adverse events.

Discussion. Dr. Teutsch thanked Dr. Friedman and said that she had addressed issues that had not been covered sufficiently in the SACGHS oversight report. Dr. Evans commented that FORCE has been a huge help to patients and can be even more helpful if it compiles its reports of problems systematically. He also agreed with the need for identifying better ways for patients to have access to genetic information.

Dr. Friedman cited a positive example of providing access to information. At the time Myriad was conducting a direct-to-consumer marketing campaign in New York, the State developed posters that went in primary care and obstetrician/gynecologist offices that explained the standard of care with regard to genetics. She also stated that to the extent that funding permits, FORCE will continue to assist patients.

Personalized Medicine Coalition (PMC). Dr. Amy Miller, PMC Public Policy Director, explained that this organization represents stakeholder groups within the framework of personalized medicine and that part of PMC's charge is to educate consumers and doctors on personalized medicine, including consumer genomics, a topic that has received a lot of attention. Based partly on some federal conversations in 2008, PMC has taken three different tacks to address consumer genomics.

One approach is PMC's effort to bring the leading consumer genomics companies together to develop standards of operation in their field. The companies that have joined PMC in this effort are 23andMe, DECODE, and Navigenics. They have now agreed on a number of scientific standards of practice that they will present at a conference sponsored the Centers for Disease Control and Prevention (CDC) and NIH on consumer genomics later this month. They will be transparent where they have not agreed on standards. They will send out a brief document on this effort before the CDC-NIH conference and will have their scientific teams available to answer questions from the field.

The second tack is educational and involves preparation of a consumer guide for genetic testing. The aim is to develop a balanced document that addresses some of the scientific issues and some of the concerns about these products and how they can be used.

The third approach integrates with the second as PMC will convene a roundtable at which consumers and health care providers who work with these particular consumer groups can talk about standards in this field and what consumers want from these products. PMC wants to know what consumers find useful and risky about genetic tests.

PMC, which has presented to SACGHS several times in the past, plans to continue to keep SACGHS informed about its work. Dr. Teutsch thanked Dr. Miller and expressed appreciation for her work towards achieving good standards.

Standards Development Initiatives to Enhance Oversight and Advance Innovation of Genetic Technologies

Dr. Teutsch introduced this session by noting that in SACGHS's 2008 oversight report (*U.S. System of Oversight of Genetic Tests: A Response to the Charge of the Secretary of Health and Human Services*, available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf), control and reference materials that are used in performance assessment programs play a critical role in assuring the quality and analytic validity of genetic test results. The SACGHS report identified a number of significant gaps in the oversight of clinical laboratory quality and called for (1) stronger CLIA requirements related to proficiency testing and (2) more support for the development of reference materials and methods for assay, analyte, and platform validation; quality control; performance assessment; and standardization.

The National Institute of Standards and Technology (NIST) and CDC are the federal agencies most involved in addressing these quality control and reference material needs. Currently, reference materials are available for only six of the more than 1,300 clinically available genetic tests. There are many challenges to the development of these materials, including the cost and time involved in producing them. Dr. Teutsch thanked Dr. Amos, the ex officio member from NIST, for suggesting that SACGHS schedule this session on initiatives that are underway to improve standards and assessments.

Clinical Diagnostics Standards Development at the National Institute of Standards and Technology

Dr. Willie May, Director of NIST's Chemical Science and Technology Laboratory, outlined his talk as covering the following topics: organization and basic mission, new initiatives involving bioscience and health (of which genetic testing is currently a very small part), and connection to the international measurement standards community.

Organization and mission. More than 100 years ago, NIST(then called the National Bureau of Standards) was founded and charged with providing the measurement standards infrastructure to support manufacturing, commerce, and the makers of scientific apparatus, to work with other government agencies, and to support the academic sector. This charge is still quite relevant and the focus on standards is still important as NIST shifts to respond to major societal problems. The current wording of NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve quality of life.

Extramurally, NIST administers the Malcolm Baldridge Quality Award and is involved in the Hollins Manufacturing Extension Partnership and the Technology Innovation Program. Intramurally, NIST's 10 laboratories, including the one that Dr. May directs, are responsible for maintaining the expertise and facilities for providing a measurement standards infrastructure.

Biosciences initiatives. NIST's work in the biosciences addresses measurement standards-related challenges and aims to provide confidence in results from measurements of complex biosystems, with resulting economic and societal benefits. The biosciences have been a focus of the current administration; a couple members of the Committee on Advanced Technology, a NIST oversight committee, have urged a bioscience focus as well.

In the 1920s, a collaboration began between NIST and the American Dental Association that has led to many innovations, such as polymer composite dental fillings and the air turbine drill. Also in the 1920s, NIST started a program in radiation physics; while it focused initially on X-ray calibration, it now includes standards for mammography and radionucleides for radiopharmaceuticals.

NIST's first program involving small molecules was with oncodiagnostics in the 1970s; NIH provided some support to provide primary references for electrolytes and metabolites. Then in the 1980s, NIST added serum-based standards. Biomarkers for proteins, peptides, and DNA were added around 2000.

NIST spends a little more than 10 percent of its appropriated funds on bioscience-related activities, with about $38 million focused on biosciences. Only about $10 million has been appropriated for that effort; other monies come from reprogramming by individual laboratory directors. A strategic plan is under development to support growth and to improve coordination among the programs of individual laboratories.

International Measurement Standards Community. NIST's projects in health care include participation in an international agreement (initiated in 1999 and now signed by more than 200 national measurement institutes) to conduct formal international comparisons for quality control and vetting of techniques. Dr. May showed examples of international comparisons measuring creatinine, cortisol, and progesterone in serum.

Also around 1999, in response to a European Union directive that said that the traceability of values assigned to calibrators or reference materials must be assured through available reference materials of a higher order, U.S. manufacturers of in vitro diagnostic devices (IVDs) asked for help so they could still sell their products in the European Union. NIST convened a stakeholders meeting that resulted in establishing a global consortium of IVD manufacturers, professional societies, national metrology institutes, and regulatory bodies.

This organization was named the Joint Committee on Traceability in Laboratory Medicine, and it produced a database of higher order reference measurement procedures, certified reference materials, and laboratories that provide reference measurement services to the clinical chemistry community. Dr. May showed examples of close comparisons of measurements by different countries using the reference procedures and materials of this Joint Committee.

Future bioscience plans at NIST include looking at tools to visualize disease signatures and focusing on quantitative medical imaging and protein measurement science. Standards for genetic diseases are not yet included, but if today's discussions determine that NIST's current general capabilities cannot support that effort, Dr. May stated that there may be an opportunity to amend the plans.

Question-and-answer session. Ms. Aspinall inquired how NIST goes about developing standards. Dr. May explained that often a scientific organization will describe a need. NIST staff frequently attends professional meetings to interact with stakeholders and ask about their highest priorities. If NIST can allot resources within a reasonable time period, it may choose some of those priorities to address.

When asked how NIST disseminates information, Dr. May said that NIST posts the information on its website and also puts it into its Standard Reference Materials catalog but needs to do a better job communicating about the existence of both these resources.

Dr. Licinio wondered if NIST could arrange for comparisons of results when the same tests are conducted by different genetic companies. Dr. May said it might be possible although usually CAP (College of

American Pathologists) and other accrediting bodies do this comparison. NIST would look carefully at both materials and methodologies.

NIST does do rechecks of its reference materials on a regular basis, the time scales vary.

Case Studies in Standards Development

Nucleic Acid Tests

Dr. John Butler of the Biochemical Science Division in NIST's Chemical Science and Technology Laboratory indicated that he would cover past, present, and future topics. In the past his division has had extensive experience with developing forensic DNA reference materials and genotyping assays and technologies. Currently, the new Applied Genetics Group (AGG), which is led by Dr. Butler and one of six NIST groups involved in genetic testing, is consolidating forensic DNA with clinical genetics and agricultural biotechnology efforts and working with genetic genealogy. Future plans include genetic testing standards. One aspect is the possibility of collaborating with the CDC's Genetic Testing Reference Materials (GeT-RM) coordination program.

NIST first became involved with standards for forensic DNA after Congress in 1994 granted the Federal Bureau of Investigation (FBI) authority to establish a national DNA index system (i.e., a national database for DNA testing) and NIST had a representative on the related DNA advisory board. The quality assurance standards that NIST consequently developed are used now around the world.

The American Society of Crime Laboratory Directors Laboratory Accreditation Board accredits and audits laboratories performing DNA testing. Each individual forensic DNA analyst must perform two proficiency tests (per test type) per year and participate in continuing education to keep up with new technologies. Validation of analytical procedures is conducted at the instrument or method level using the NIST reference materials. At the protocol level, standard operating procedures are used to make sure that the instruments are used consistently from analyst to analyst. The checks and balances continue with internal size standards that are run with individual samples and confirmation of the interpretation of results by a second analyst. In addition, defense attorneys and defense experts for court cases can examine the data as part of discovery requests.

The tests that are used have changed over the years. Beginning in the 1980s, restriction fragment length polymorphism analysis was used for initial DNA "fingerprinting," then polymerase chain reaction (PCR) techniques were introduced in the mid-1990s, followed by mitochondrial DNA sequencing in the late 1990s, and, most recently, Y chromosome testing. When technologies are dropped, the reference materials are phased out.

Dr. Butler showed a slide with 12 different samples characterized for 22 autosomal, short tandem repeat (STR) markers that are used in forensic testing around the world. Recently, NIST has added 26 new STR markers. However, as these markers are expensive to make and certify, NIST encourages laboratories to make traceable materials instead of just using purchased reference materials.

After reviewing the steps in forensic DNA testing, Dr. Butler mentioned that in 1997 the FBI defined 13 core STR loci for forensic analysis. There is also a gender identification (sex-typing) marker, amylogenin, that is present on X and Y chromosomes. There is some overlap with Europe, which does use NIST standard materials. More than 6.5 million profiles are in the U.S. database. A laboratory cannot put its results into the database unless it has run an analysis with a NIST standard reference material (SRM) to affirm the accuracy of the results.

NIST SRMs are also used in paternity testing, which is overseen by the American Association of Blood Banks.

Forensic DNA testing and paternity testing rely on information about STRs, and Dr. Butler referred to a NIST website (http://www.cstl.nist.gov/biotech/strbase/) for more information on STRs. Different genetic tests may use different DNA primers, and because of binding site mutations, may produce different results. NIST does a lot of work to calibrate and sequence the regions and define why a particular new assay or kit does not work properly. NIST also develops new assays, new software, and training materials. Funding comes from the National Institute of Justice as well as from internal NIST funds.

Dr. Butler then briefly mentioned available DNA reference materials, work involving RNA, efforts to help with nomenclature to assist the genetic genealogy community to insure consistent results across laboratories, and efforts to provide standard DNA fragments for characterizing Huntington disease. Dr. Butler noted that he welcomes input on what types of materials to certify, such as a sequence, a specific genotype, and the quantity of DNA that is present.

Proteomic Tests

Dr. David Bunk of the Analytical Chemistry Division of NIST's Chemical Science and Technology Laboratory indicated that helping to standardize and improve the measurement quality of proteomic clinical research is a new effort for NIST. Currently, proteomics is mostly used for medical research and medical diagnostic research although it will probably reach clinical diagnostic laboratories soon. Either way, the measurements still need to be standardized.

Proteomics is defined as the identification and quantification of all proteins of a sample—whether of the human proteome or specific tissue proteomes. While top-down proteomics does measure intact proteins, the vast majority of proteomic research is done using an approach called bottom-up proteomics, in which proteins are degraded into peptides, and these peptides are measured. Thus, a lot of the work is done with peptide-based reference materials.

The current goal of clinical proteomics is to identify and quantify a human protein or proteins in which a change in structure or concentration can be used to diagnose disease. Proteomics is still in the discovery and verification phases. When it reaches clinical proteomics, large-scale, large cohort studies will be needed.

NIST has become involved in trying to achieve better measurement quality in proteomics. The Human Proteomics Organization has published a number of studies looking at inter-laboratory comparisons of proteomic investigations. Unfortunately, there has been little comparability in from laboratory to laboratory.

NIST is partnering with the National Cancer Institute (NCI), which decided about three years ago to develop a program to evaluate proteomic technologies. NIST is advising NCI on inter-laboratory study designs and developing the materials that are being used in inter-laboratory studies. In turn, NIST staff is learning about proteomics.

NIST's goal is to develop reference materials, standard operating procedures, and validation tools for proteomics for the entire biomarker pipeline (discovery to verification to clinical use). Horizontal standards will support measurement quality at individual steps, and vertical standards are designed to apply through all pipeline steps.

NIST currently has two reference materials in production. The horizontal standard is a mixture of synthetic peptides, so it is not application-specific. It is designed to improve quality in mass spectrometry instrumentation. For a vertical standard, a yeast proteome is the reference material, designed to validate the procedures throughout the pipeline.

NIST also wants to develop higher-order measurement tools for assessing performance of affinity reagents in proteomic arrays and multiplex arrays and to develop and validate novel affinity capture reagents. The aim, of course, is to help improve the outcomes of clinical proteomic research.

Metabolomic Tests

Dr. Karen Phinney of the Analytical Chemistry Division of NIST's Chemical Science and Technology Laboratory introduced metabolomics and outlined some goals and issues.

Introduction. Dr. Phinney said that metabolomics represents the endpoint of genomics and proteomics, examining samples of, for example, serum, plasma, or urine from the viewpoint that these samples reflect the exact metabolic processes going on at that period of time. This approach is a way to evaluate phenotype—to see how factors such as diet, stress, exercise, disease, and health affect metabolism.

Goals. In the past, individual metabolites have been followed while diagnosing and treating various diseases, but metabolomics is unique, looking at panels or signatures of different analytes and their levels under different circumstances in the case of health or disease. Using these patterns or signatures to segment people into different groups (e.g., healthy and diseased), ideally one can come up with disease diagnoses and also identify appropriate interventions. The patterns of metabolites might also offer information about the genome. The drug industry is interested in metabolomics as a potential mechanism to identify toxicity. For example, if particular markers that indicate liver toxicity have been identified and measured, it might be possible to predict ahead of time whether a particular pharmaceutical will have adverse effects.

Thus the overall goals include identifying new diagnostic tools, therapeutic targets (i.e., metabolic pathways), and drug toxicities and studying gene functions.

Issues. Measuring thousands of metabolites simultaneously will require large and complex data sets. Consequently, besides dealing with sampling, instrument variations, and platform variations, software will be needed to handle these large data sets. Software will also be needed to help identify a small number of significant metabolites among thousands. Validation is also needed in a clinical setting to prove whether these metabolites are significant.

Two years ago NIH asked NIST to help NIH-funded metabolic researchers to evaluate their technologies. NIST expects to have ready in 2009 a reference material that is based on pooled plasma. To be indicative of a mix of male and female, different age groups and ethnicities, and healthy individuals, NIST has pooled samples from male and female African Americans, Asians, Caucasians and expects to be able to prepare a similar sample again when needed some years from now. NIST has measured about 40 metabolites in the plasma pool for which it already has standard procedures and is working collaboratively with others to identify additional metabolites.

Furthermore, recognizing that metabolomics is an evolving field, NIST researchers anticipate developing additional standards (e.g., for heart disease or male vs. female) and addressing the bioinformatics needed for large data sets and for comparisons among different instrument platforms or laboratories. Thus, additional needs include control samples for specific populations, tests for aligning complex data sets,

validation of statistical models for pattern recognition, and reporting standards (the metabolic standards initiative).

Standards and Measurement Challenges Facing Stakeholders

Regulatory Challenges: FDA and the Quest for Standards

Dr. Steven Gutman, Director of the FDA Office for In Vitro Diagnostic Device Evaluation and Safety, spoke about the long history of FDA's interest in standards and lack of implementation.

History. Although FDA developed standardized, traceable methods for measuring glucose and hemoglobin in the 1980s, these were not routinely accepted by the public. In addition, while the original 510(k) regulations for "me-too" devices called for standards, none were developed. Eventually, regulations called instead for special controls, and me-too devices most show that they are "substantially equivalent" to the original device. Novel, high-risk devices must be shown to be de novo, safe, and effective. Neither of these regulatory programs calls for or requires identification of standards, traceability, or performance against standards, which Dr. Gutman considered a weakness in the FDA regulatory toolbox.

Various FDA staff members have continued to promote standards, and FDA became a founding member of the Clinical and Laboratory Standards Institute (CLSI) as well as an active member of the International Standardization Organization (ISO) Technical Committee 212, an active member of the Institute for Biodiagnostics (IBD) subgroup of the Global Harmonization Task Force, and an early proponent of the CDC's standardization program.

Dr. Gutman's office frequently references standards when writing guidance, when developing special controls, and in decision summaries (see http://www.fda.gov/cdrh/oivd/index.html).
OVID tracks standards produced by NIST, CDC, the World Health Organization, and other legitimate sources (including CSLI and ISO) and uses a formal recognition process to list selected standards on its website. Device sponsors can accelerate their negotiations with FDA by showing that they conform to relevant standards.

There are incentives for producing better standard products. One is the European IVD directive (mentioned earlier by Dr. May), and another is accelerating FDA negotiations. The standards for reporting diagnostic accuracy (STARD) initiative and other efforts to provide clinical standardization will be successful only if there is a strong underpinning of analytical standardization.

Dr. Gutman commented that looking at proficiency testing surveys will show many laboratory and company differences. For new assays, there is neither proficiency testing nor quality-control material. While NIST is making a start, there are huge numbers of new assays, with some protected by intellectual property rights that might cause difficulties in creating cross-laboratory standards. There is some optimism about possible change, however, because of an increasing trend towards evidence-based medicine even in the laboratory.

Clinical Challenges: Standardizing the Evaluation of Diagnostics

Dr. Jeff Cossman, Chief Scientific Officer at the Critical Path Institute (C-Path), explained that C-Path is a nongovernmental and nonprofit agency that serves as a neutral party to assist communications among FDA, industry, patient advocacy groups, and researchers. It also has a number of consortia interested in the safety of laboratory tests, efficacy of targeted therapies and companion diagnostics, dosing based on genotype (e.g., warfarin), and major diseases (e.g., Alzheimer disease and Parkinson disease). C-Path

aims to help improve the methods that are used to develop drugs and diagnostics, by verifying the quality and accuracy of biomarkers, sharing information across consortia, and reaching consensus on best-of-class methods that FDA accepts. Using this approach, FDA would better understand new biomarkers and, in a sense, preaccept them as part of the application for review.

Needs and bottlenecks. Dr. Cossman observed that a common theme among the consortia is the need for reliable diagnostics. Bottlenecks in the FDA regulatory review process, however, can slow the introduction of new products to the market. Lack of a standardized process contributes to the bottlenecks. Manufacturers submit data in different formats, use different methods to analyze data, and use different types of clinical samples. Another bottleneck is the acceptability of diagnostic tests by payers; they want evidence that the tests are valuable and perform as claimed.

Solution. Dr. Cossman explained that C-Path and consortia members see a potential role for creating an entity—called the United States Diagnostics Standards (USDS)—whose sole focus would be to evaluate diagnostic tests before they are submitted to FDA. This approach is used in other industries such as semiconductors (e.g., Sematech) and pharmaceuticals (e.g., U.S. Pharmacopeia). An underwriter's laboratory is not a new idea, but new to the diagnostics industry.

USDS would provide two levels of evaluation of a diagnostic: (1) analytical evaluation, which would measure performance characteristics (e.g., finding the correct level of a particular analyte), and (2) clinical evaluation where clinical data are available (e.g., association of a biomarker with a clinical condition, prediction of treatment response). USDS could also determine whether or not a new diagnostic is equivalent to a predicate. In addition, this entity could evaluate laboratory-developed tests (LDTs), which are frequently used in genetic testing, but usually are not submitted to FDA for review. Intellectual property or special methods would be kept confidential. Reference standards will be maintained on a case-by-case basis.

Manufacturers would own the evaluation data, as they pay for the USDS analysis. The USDS report could be used voluntarily by manufacturers in their submissions for FDA approval. If the USDS analysis showed that test performance is not acceptable or the test is not useful, manufacturers can use that information as they see fit.

What value is added by USDS review? This approach would improve reporting to FDA and hopefully expedite the review process for manufacturers. It would also provide a format to compare competing products and provide evidence of test performance to providers, consumers, payers, and investors. USDS would not be another regulatory hurdle. C-Path is also examining ways of being synergistic with and complementary to other agencies such as NIST, CDC, CLSI, and the College of American Pathologists (CAP). For example, NIST could develop standards for testing platforms.

Plans are underway, with economic development seed money, to establish USDS in Arizona. Dr. Maryellen de Mars, Director for Clinical Biomarkers, and Dr. Ralph Martel, Chief Operating Officer, C-Path, will be assisting with the startup. USDS is looking for its first demonstration case, possibly in genetics or cancer.

Question-and-answer session. Dr. Williams asked Dr. Cossman to comment on the possible evolution of a voluntary program to a regulatory requirement for the kind of testing that USDS will do. He mentioned two examples of voluntary programs evolving into requirements—the National Committee for Quality Assurance and the Joint Commission—and noted that it could happen de facto if payers started requiring use of USDS. Dr. Cossman said that he could not predict the future at this early point, but he certainly does not want USDS to become a second FDA.

When Dr. Ferreira-Gonzalez asked how Dr. Cossman expected to avoid the situation that Dr. Williams described, he said that if a pattern emerges where payers require USDS data, then the situation could become unavoidable. He does not know now how to solve this problem but does not want it to happen and invites proposals for solutions. Currently, one large insurance company has told him that it does not have the capacity to judge whether testing such as USDS offers would be needed.

Future Directions in Clinical Diagnostics Standards Development

Dr. Michael Amos, an ex officio member of SACGHS and a biosciences advisor in NIST's Chemical Science and Technology Laboratory, first cautioned that the ideas he will offer are not official NIST programs or policies and then said that he will talk today about some of the harsh realities that will drive health care change in the future, some lessons learned and what he thinks will happen, the fact that laboratory medicine will drive a lot of this change, some measurement challenges and the role measurement technologies and standards will play, and a potential plan to enable the change.

Health and health care. Dr. Amos provided the following statistics: 83 percent of health care costs are for chronic diseases; which constituted nearly $1.7 trillion of the $2 trillion spent in 2005; 43 percent of that amount is spent on hospitalizations. If current trends were to continue, our grandchildren would be spending more on health care than they earn.

Furthermore, millions suffer from diseases for which little is known about the genetic bases. Growing numbers of children are being diagnosed and treated for chronic diseases, including children under age 5 who are taking drugs for type 2 diabetes. Meanwhile type 1 diabetes is growing at a rate of about 5 percent per year.

Medical research. Medical research is not particularly innovative or productive. In addition, manufacturer-reported adverse events are growing. Only a modest number of diagnostics have been approved by FDA since 1995.

Change. Dr. Amos stated that these trends in health care and medical research are not sustainable: a new development paradigm is really needed. Consequently, medicine will need to change its focus to keeping people well and learning more about the transitional state between wellness and disease. Being able to keep people out of the hospital will depend on laboratory medicine, with genomics, proteomics, and metabolomics dominating. Complex disease signatures, comprised of hundreds or thousands of data points, will be the biomarkers of the future. Patterns of biomarkers (probably based on parameters in blood) will be person specific so individuals will become their own controls in clinical trials.

Dr. Leroy Hood, Co-Founder of the Institute of Systems Biology, believes that diagnostics will deal with organ-specific blood protein fingerprints. This systems medicine approach will integrate measurements and computer analyses to evaluate health status.

Drug companies will develop their markets around interventional therapeutics and treatments like cholesterol and statins. They will be using the same model but basing it on the complex disease signatures. This approach will necessitate a change in drug companies basing their market numbers and projections on the number of people they can treat, which is calculated by projecting the number of people to come down with a disease based on historical data.

The metrics of morbidity and mortality show that people suffer and die of chronic diseases, and this trend is not changing even as we sore towards a projection of $4 trillion in health care costs by the year 2015. Instead, the health care markets could be based on the number of people with preventable diseases. The metric would be the number of people positive for a valid predictive biomarker, and the outcome would

be that more people would die of trauma and in their sleep from old age rather than spending 70 percent of health care dollars in the last two years of life on terminal care. For diabetes alone, the potential savings are at least $50 billion.

With visualization of disease signatures will come a need for new types of standards, applying many of the approaches and procedures discussed earlier today. Development will be needed in such facets as protein measurement science and clinical analyses. Dr. Amos concluded by suggesting that it would be wonderful to have a targeted goal, such as the identification of a certain number of disease signatures by the year 2020.

Questions-and-Answers Session (with all speakers on standards)

CDC perspective. When Dr. Teutsch inquired about any additional comments from the CDC perspective, Dr. Lisa Kalman, GeT-RM Program Coordinator at CDC, stated that having reference material is really key to assuring the quality of testing not only for the day-to-day quality control, but also for proficiency testing. She noted that proficiency testing was an important aspect of the recent SACGHS oversight report.

CDC has counted only six different diseases for which there are higher-order reference materials from NIST or FDA or another reliable source. In contrast, on the Gene Test website, there are more than 1,300 genetic tests currently available. The CDC, through the GeT-RM program, is trying to address this gap by organizing a volunteer effort in the genetic community.

CDC is beginning to characterize publicly available cell lines and DNA from the Coriell repository. This effort will provide a larger supply of materials with identified genotypes that laboratories can use for quality control and proficiency testing needs. Currently, the projects that CDC is working on are mostly driven by requests from CAP for proficiency testing materials.

In one large project for pharmacogenetic materials, CDC will work with more than 100 DNA samples for five pharmacogenetic loci as well as obtain other data from other laboratories on other loci. In addition, CDC will try to do a project for array comparative genomic hybridization (CGH). CDC also had a project for Duchenne muscular dystrophy (which CAP requested), but all laboratories are discontinuing their testing because of the patent issue.

CDC and NIST. Dr. Ferreira-Gonzalez voiced appreciation for the fact that Dr. Kalman through collaboration with professional organizations or end users of different laboratories has identified current needs with respect to both proficiency testing and reference materials. She then asked about the level of cooperation between the GeT-RM program and the NIST genomic program. Dr. Kalman said that she talks to NIST on a regular basis both through her program's yearly advisory committee meeting, which some NIST staff attend, and by direct contacts in the area of molecular oncology.

Dr. Williams inquired, given Dr. Amos's vision for the future, about the NIST vision regarding where to invest its limited funds for biomedical standards. After indicating that he agrees with Dr. Amos's vision for the future, Dr. May said that in the short term, the focus of NIST's new activities will be on medical imaging and protein measurement science. For the next two to five years the emphasis will be on improving capabilities to support medical imaging and developing more core competencies in protein measurement science. Creating these capacities will contribute to being able to address the disease signature issue as well as the issue of follow-on biologics.

In the longer term, NIST will continue its work in genetics , but expansion will be in the two areas cited above. Certainly, the Biochemical Science Division of the Chemical Science and Technology Laboratory

will have a greater emphasis on genetic testing and DNA-based diagnostics and has reorganized to better address these areas.

Dr. Williams then commented that it does not appear that NIST is planning any work on proficiency testing, an area identified in the SACGHS oversight report. Dr. May then suggested that a memo to the NIST acting director about this need would be appropriate. Dr. Amos said that while genomics will be an integral part of disease signatures, at the present time his colleagues have decided not to do genome-wide association studies and are looking at next-generation sequencing instead.

SACGHS role. Ms. Aspinall commented that it appears timely for SACGHS to take action to support its priorities, perhaps by writing a letter to NIST.

Priorities. Dr. Teutsch agreed that letter-writing would be appropriate. In addition, when SACGHS reviews its priorities tomorrow, he hopes members will continue to work on ways to get recommended actions underway from the oversight report as well as other prior SACGHS reports.

More about NIST. Dr. May noted that NIST will soon get a new director, who will probably honor the identified priorities of bioscience and health. He also invited SACGHS to meet sometime on the NIST campus.

December 2, 2009

SACGHS Priority Setting

After welcoming new participants, Dr. Teutsch reviewed the steps leading to today's goal of finalizing future study topics, deciding how SACGHS will address them, and agreeing on a strategic plan for moving forward. Recognizing in February that the Committee was nearing completion of the study agenda it had set up in 2004, SACGHS members decided to use a similar approach to look ahead, identifying some of the emerging issues and unresolved issues that continue to need the Committee's attention.

Brainstorming in February was followed by some preliminary decisionmaking about priority topics in July. At this meeting, Dr. Paul Wise, Chair, and other members of the Task Force on Priority Setting reviewed the issues the Committee identified in July, laid out some policy questions and action steps, and started to identify timelines. SACGHS hopes to have a chance to meet with the incoming HHS Secretary and his/her staff to talk about how the Committee's priority-setting decisions dovetail with their priorities—to begin to work together.

Review of Priority Setting Process and Proposed Priority Issues

Dr. Wise, Chair of the SACGHS Task Force on Priority Setting, reviewed how the February 2008 brainstorming session generated 73 potential priority issues, which the Committee reexamined in light of discussions with ex officio members about the concerns of their departments and agencies as well as public commentary and interviews with individuals selected for their expertise.

In July, Committee members ranked the priority issues using a Likert scale, and based on these rankings areas emerged that were the most important and relevant. Then SACGHS members looked for affinities among the different issues. This effort resulted in seven clusters areas, and issue briefs were developed for each area.

The issue briefs covered the following seven topics: coverage and reimbursement for genetic services; ensuring the clinical utility of genetic information; genetics education and training, with attention to workforce diversity; informed consent, privacy, and discrimination issues in genomic data sharing; implications of consumer-initiated use of genomic services; public health applications of genomics research, with attention to health disparities; and genetics and the future of the health care system.

Discussion of Proposed Priority Issue Areas

Dr. Wise briefed meeting attendees on the organization for the rest of this session. First, each priority topic was described by the lead Committee member for that topic. The order of presentations did not reflect any type of ranking by importance. Second, after all seven presentations, SACGHS members discussed policy questions and proposed action steps for each priority topic, and then worked to develop an overarching and flexible action plan without any formal vote-taking. Factors that were considered during the discussion included whether the central elements are reflected in the issue briefs and whether the Committee can reach consensus as to which of the seven areas deserve immediate attention.

Cluster 1: Coverage and Reimbursement for Genetic Services
Marc Williams, M.D.

Dr. Williams said that in general the coverage and reimbursment priority topic focused on unresolved issues from SACGHS's February 2006 report [available at http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf] and examining strategies to remove obstacles to implementation of the report's recommendations. However, the issue brief also identified other concerns such as addressing underserved populations that do not fully benefit from genetic services and examining the best approaches to avoid inappropriate application of reimbursement audits (such as medically unlikely edits) to procedure-specific current procedural terminology (CPT) codes that are appropriately used multiple times for molecular diagnostic testing.

The original report had nine recommendations, and SACGHS is anticipating a letter from the HHS Secretary's representatives later this month regarding some of the follow-up issues that the Committee has previously discussed.

True costs. One policy question to focus on at this time is approaches to revised payment rates to reflect the true costs of genetic tests. Currently, the Medicare fee schedule undervalues many of these tests compared to their true costs.

Genetic counselors. Another ongoing issue is billing related to certified genetic counselors, particularly their access to CPT evaluation and management (E & M) codes. Genetic counselors certainly play an important role in the traditional genetic testing field and ought to be paid accordingly.

Medically unlikely edits (MUEs). A newer issue concerns the application of reimbursement audits—specifically MUEs—to procedure-specific CPT codes. In the course of processing DNA, certain CPT codes are appropriately used in multiples. Applying MUEs would remove the multiple codes, and only one CPT code of a given type would be reimbursed. However, this approach is probably not reflective of the actual work that occurs in the laboratory.

Family history. The SACGHS coverage and reimbursement report recommended that in certain cases a personal history of disease can include having a family history of the disease, which would make it possible for beneficiaries with a family history of a disease to meet the "reasonable and necessary" standard for Medicare coverage. The Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) allows Medicare to cover preventive services recommended by the U.S. Preventive Services

Task Force (USPSTF). SACGHS could explore how USPSTF defines cases in which family history of a disease could be considered to be personal history, which would allow coverage for some subsequent interventions. Another related issue is how to reimburse clinicians fairly for the collection and use of family history information. The August 2009 NIH-sponsored State-of-the-Science-Conference on Family History will probably provide the best assessment of where the current evidence is relating to the science of family history.

Another issue was raised in conjunction with the May 2008 SACGHS pharmacogenomics report [available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_report.pdf]. Dr. Williams pointed out that CMS recently listed pharmacogenomic testing as a potential national coverage decision (NCD) topic. If CMS were to make a NCD, it is unclear whether it would be for all PGx tests or certain tests or categories of tests. It would also be important to clarify that PGx testing is considered diagnostic testing and not a screening test. Additionally, implementation of a pharmacogenomic NCD must be associated with recognition and resolution of laboratory reimbursement issues.

Access. Another important set of concerns are whether reimbursement issues impact access to genetic services and how access can be improved for underserved populations.

Action steps. The proposed action steps included the following: continuing to monitor the recommendations from the 2006 coverage and reimbursement report, continuing to engage with CMS officials in discussions related to these recommendations; engaging with the laboratory community to assess generating support for the application of the inherent reasonableness authority to the clinical laboratory fee schedule; through allowances in MIPPA, evaluating opportunities for Medicare coverage of clinical preventive services based on USPSTF recommendations with which the Medicare Evidence Development and Coverage Advisory Committee concurs; and encouraging collection of demographic data to obtain a better sense of access to and utilization of genetic services in underserved populations.

Discussion. Dr. Ferreira-Gonzalez mentioned that a number of laboratory associations in the community and in industry are looking at reviewing the coding for genetic testing. She suggested that SACGHS might want to interact with these professional organizations on an ongoing basis to stay up to date on these efforts.

Cluster 2: Ensuring the Clinical Utility of Genetic Information
Dr. Teutsch

Dr. Teutsch noted that SACGHS has looked at clinical utility several ways in the past few years.

Studies, standards, and a dedicated organization. One challenge in establishing the clinical utility of tests is the paucity of clinical studies that look at clinical utility. For the existing studies, there is no clear set of accepted evidentiary standards against which to judge them. Nor are there currently any organizations dedicated to performing utility assessments, although a number of them are involved to varying degrees.

Data handling. Another challenge is the huge amount of information that will come from whole-genome sequencing and the need for some entity (or entities) to perform utility assessments to ensure that application of the information will benefit patients.

Entities. Several existing groups have begun clinical utility assessments of genetic information. The CDC's Evaluation of Genomic Applications in Practice and Prevention **(**EGAPP) group has been working to define standards and has performed a few assessments. Various commercial and noncommercial entities also perform technology assessments. Hayes, Inc. provides information largely to the payer community, and BlueCross BlueShield's Technology Evaluation Center makes its evaluations public.

Evidence-based practice centers and some other organizations assess genetic tests as part of larger efforts to assess technologies. The Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health is definitely concerned with these issues and with how to get effective technologies translated into the health care system.

SACGHS recommendations. The SAGCHS reports on pharmacogenomics, coverage and reimbursement, and oversight of genetic testing have all touched on this issue to varying degrees. SACGHS has recommended that the Secretary create a public-private partnership to define the types of underlying studies that are needed for assessments and the standards by which they should be judged. This entity would also perform utility assessments and disseminate clinical guidelines based on those assessments.

Dr. Teutsch explained that the issue of clinical utility raised several policy questions. One is what would be the most effective group for defining evidentiary standards and conducting reviews. Another question is how might the Government better inform those involved in research and development about the evidentiary needs for clinical utility determinations in general and in the case of specific technologies and specific conditions. Another policy issue is further defining the structure and scope of the entity that would perform utility assessments.

Dr. Teutsch then presented the possible projects or actions the Committee could take up in exploring this priority topic. One possible action step would be to provide a forum for discussion to help define the evidentiary needs and standards for evaluating clinical utility. Another action step would be for the Committee to recommend that any governmental organization or group tasked with assessing clinical utility apply different clinical utility assessment methods for different clinical users of genetic tests.

Another possible project would involve developing brief reports on how clinical utility assessments, which tend to be scientific, can incorporate contextual issues, such as cost, cost effectiveness, ethics, feasibility, acceptability, to better inform the users—particularly patients, regulators, payers, health care providers, and performance measurement specialists—about ways to use that information in their decisionmaking. The Committee could also look at how to better inform those involved in research and development about the evidentiary standards so that the research community would have better direction on the types of clinical studies to conduct.

A final possible step would be for the Committee to define in greater detail the type of group described earlier, that is, a group that would establish evidentiary standards for clinical utility assessments, create methods for utility assessment, and perform those utility assessments on a more systematic basis than current approaches.

Cluster 3: Genetics Education and Training
Barbara Burns McGrath, R.N., Ph.D.

Dr. McGrath observed that the need for basic genetic education and ongoing training was an early high priority for this Committee and was again identified during the 2008 priority-setting activity.

Goals. The Genetics Education and Training Task Force that was formed in November 2007 has focused on the needs of three entities: (1) health care professionals with and without expertise in genetics, (2) public health providers, and (3) consumers and patients. Three workgroups were formed and are collecting data to identify gaps in genetics education and training of health professionals and consumers.

Government roles. The Task Force wishes to explore how HHS can (1) help with genetics education and training, (2) help increase the diversity of the genetics health care workforce (this effort would fit with the

Healthy 2010 goal of addressing health disparities), and (3) play a role in accreditation, licensure, and certification of genetics professionals.

Policy initiatives and programs. The Task Force has been taking an inventory of genetics education initiatives and programs in the private and public sectors and assessing which ones have been implemented or are still in the planning stages. The Task Force also plans to look at the types of genetic information reaching consumers and patients. This effort will entail looking at a range of materials such as promotional materials from commercial companies and the works of health communicators including clinical educators, lay health educators, academic researchers, and those in industry.

Action steps. Proposed short-term actions included (1) having a brief meeting with FDA to determine how it regulates promotional materials for medical devices and (2) talking with representatives from industry about establishing voluntary standards for the educational aspects of promotional materials.

The major proposed long-term action is the development of an in-depth report. Subsequent to the data gathering activities of the three work groups, a draft report would be developed. By the current timetable, the draft report would be released for public comments in 2009, and a final report would be submitted to the HHS Secretary in 2010.

The Task Force also plans to assess whether the report's findings and recommendations would apply to additional constituencies such as health care administrators, payers, policy makers, and laboratory staff.

Discussion. Dr. Kirchner asked about potential interactions between the educational responsibilities and recommendations of the Genetics Education and Training Task Force and those of the Clinical Utility Task Force. For example, it is important to notify people about tests that have not been validated and perhaps should not be used. Dr. McGrath agreed, saying that clinical utility information needs to be shared with providers and practitioners as well as with consumers and patients.

Dr. Williams reported that a task of the EGAPP working group and the associated stakeholders group of EGAPP is to disseminate information related to their evaluations. Dr. Wise noted that the upcoming discussion after all the issue brief presentations will include looking for commonalities and creating linkages.

Cluster 4: Informed Consent, Privacy, and Discrimination Issues That Relate to Genomic Data Sharing

Kevin FitzGerald, S.J., Ph.D., Ph.D.

Concept and challenges. Informed consent is a process by which people are supposed to receive all the relevant information they need to make an informed decision about testing, procedures, or interventions. For genetic and genomic services, the informed consent process is challenged by rapidly evolving technologies and the complex nature of information obtained through these technologies. Another challenge is maintaining the privacy and confidentiality of genetic information.

New concepts. It may no longer be possible to keep data completely unidentifiable, which may require conceptualizing informed consent in a new way. Both research and clinical practice are likely to be affected. New levels of vigilance and attention will likely be required. These concerns may have been raised first by the National Bioethics Advisory Committee in 1999. Others would argue that these issues are not new and may just be extensions of prior concerns from the 1970s and 1980s when the Belmont Report examined the effects of research on human subjects.

Thought questions. Dr. FitzGerald posed the following questions: How do we to take these challenges to the public? How do we engage the public? How do we cross generational divides? How can informed consent be provided for a whole population? How can the consent process be improved and what strategies should be used? Is it effective to use teach-backs techniques (in which taught individuals teach back to the health care provider) to assist in educating and engaging people?

Roles. Dr. FitzGerald also asked about the roles of SACGHS and of HHS in light of the August 2009 report on the ability to identify individual sequence data from complex DNA mixtures (Homer et al, PLoS Genet., 2008, 4(8): e1000167). The research demonstrated a method of identifying specific individuals within a study based on summary-level statistics and indicated that further research is needed to determine how to best share data while fully masking identity of individual participants

Legislation. Regarding legislation, one question is how existing laws, such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Genetic Information Nondiscrimination Act of 2007 (GINA) affect the informed consent process. Another question is what legislation is being proposed that could impact informed consent.

Action steps. Proposed action steps for SACGHS include the following: (1) monitoring GINA and proposed legislation for their impact on informed consent; (2) soliciting public input on concerns pertaining to privacy and confidentiality of data collected and stored in large-scale genomics studies; and (3) developing recommended elements of disclosure for use in the informed consent process for research involving sharing of genome datasets.

Discussion. Dr. Fox proposed adding the Department of Veterans Affairs to the list of agencies with which SACGHS would cooperate, and Dr. FitzGerald concurred.

Cluster 5: Implications of Consumer-Initiated Use of Genomic Services
Sylvia Au, M.S.

Ms. Au stressed that because of the rapid growth of direct-to-consumer (DTC) genetic testing and marketing, a comprehensive consumer protection strategy is likely needed.

Concerns. DTC genetic testing generates the following concerns: (1) the relative value of the information provided (which relates also to cluster 2, clinical utility), (2) the level of consumer understanding (related to cluster 3, training and education), (3) the provider community's ability to understand and translate information for patients (again related to the education cluster), and (4) the potential risk of misuse of information by consumers or third parties (related to cluster 4, consent, privacy, and discrimination of genomic data sharing).

Prior activities. Relevant past SACGHS activities include (1) letters that the Committee wrote to the HHS secretary in 2002, 2004, and 2006, expressing concerns about the advertising claims made by companies offering DTC genetic services, and (2) an information-gathering session at the July 2008 SACGHS meeting to explore what was going on in the current landscape of DTC genomic services.

Policy questions. Noting that this cluster a large number of policy concerns, Ms. Au highlighted the following issues: (1) whether DTC genomic tests will be regulated similarly to other complex laboratory tests; (2) whether the recommendations in SACGHS's oversight report will be sufficient regarding DTC genomic services; (3) the best formulas to predict risk of disease based on SNP analysis; (4) criteria to determine whether an association between a particular genetic marker and a phenotype is strong enough for that marker to be included in the genetic testing and reported out; (5) whether there should be standards for formatting raw data from the whole-genome scans; (6) how the clinical validity and utility

of SNP-analyses will be assessed and communicated to consumers; (7) when sufficient data are produced to change previously recommended risk calculations; (8) whether requirements for public education and informed consent are needed before DTC testing; (9) the appropriate roles and responsibilities of healthcare providers, consumers, and public health programs in this nontraditional approach to genetic testing; (10) whether personal genome services fill specific health care or public health needs; (11) whether providers and consumers are adequately prepared for the information provided by these services; (12) the benefits and potential drawbacks of DTC personal genomic services; (13) how the health care system and providers will be affected by the availability of these personal genome services; (14) what is known about consumer interest in personal genome services and consumer understanding of these services; (15) criteria that should be considered in determining the value of the personal genome service; (16) criteria for determining whether previously tested individuals should be contacted to inform them of revised risk assessments; (17) criteria that the companies should follow in marketing DTC services; (18) privacy concerns; (19) cautions and benefits consumers should consider when sharing their genomic information with others, such as their family members, social networks, clinicians, and employers; (20) whether GINA applies to this type of personal genome service, and whether these companies are actually covered by GINA; and (21) whether personal genome services exacerbate health disparities.

Ms. Au noted that most personal genome services are paid out of pocket and currently are not covered by insurance.

Action steps. Possible action steps include (1) monitoring the outcome of all the federal and nonfederal workshops related to genetic testing' (2) as a short-term action, develop a checklist that patients could consider when they are trying to determine whether or not they want to purchase DTC genomic services (the Personalized Medicine Coalition has developed a basic checklist that could be accepted or adapted); (3) preparing a brief report on selected key issues; and/or (4) preparing an in-depth report.

Discussion. Dr. Williams recalled that a public commenter at a prior meetings voiced concern that some companies may sell to others information provided by the consumer at the time of genetic testing. When he suggested including this concern, Dr. Fomous commented that it could be added in to an existing, more general question in cluster 5.

Cluster 6: Public Health Applications of Genomics Research
Joseph Telfair, Dr.P.H., M.P.H., M.S.W.

Dr. Telfair began by explaining that public health genomics is a multidisciplinary field concerned about effectiveness and responsible translation of genomic-based knowledge and technology, with a focus on population health. The field focuses on (1) policy and actions that promote health and prevent and control disease and (2) the interplay of genes, behaviors, and physical and social environment factors.

One goal of public health genomics is to ensure that the benefits of genetics and genomics are realized across many diverse populations and groups. Accomplishing this goal requires assessment, policy development, and assurance plus the knowledge base that comes from research.

Policy questions. Dr. Telfair posed the following questions:

- What are the characteristics of the diverse systems of health care?
- How does management and delivery influence the provision of genetic tests?
- How do clinical or preventive services work?
- What are the leading opportunities and responsibilities for public health systems to contribute to the development and implementation of the new genomic knowledge and technologies to improve health, to prevent disease, and to address health disparities?

- What are the opportunities, challenges, and benefits of incorporating genomics into existing and future public health investigations and surveillance systems to advance knowledge?
- What are the opportunities and responsibilities for incorporating evidence-based genomics and knowledge and technologies into public health programs to improve health and prevent disease?
- What is the best way to collaborate within the public health infrastructure, working within and across health care delivery systems, employers, businesses, communities, academia, media, and others, particularly consumers?
- What steps can be taken to address ethical, legal, and social issues in public health genomics research and practice?
- How does informed consent for DNA testing in public health differ from informed consent for other public health services and in clinical practice?
- Under what circumstances is new consent for archived specimens needed for public health investigation?
- What are the immediate and long-term benefits and risks of population-based disease registries are?
- How can concerns about potential stigmatization of the population groups that result from research on testing programs be addressed?
- What policies should be in place to share large amounts of data collected through gene, environment, and disease association studies?
- What are the emerging concerns as new technologies are developed?
- Will advances in technologies and knowledge shift current conceptions of injury in toxic tort suits or the preexisting condition exclusion in GINA?
- What tools are needed to understand how genes interact with physical and social environmental to perturb biological pathways and cause injury or disease?
- How can federal investment in genomics encourage translation into population health benefits?
- Is it cost effective to tailor interventions based on genetic information?
- What steps must be taken to assure a competent public health workforce with a sufficient knowledge base and skills to ensure appropriate use of genetic information to promote health and prevent disease and to educate the general public to be informed consumers of genomic applications?
- How can public health agencies prepare the workforce and their constituencies to ensure that information about gene-environment interaction is used appropriately?

Action steps. Dr. Telfair suggested several possible action steps for public health genomics. As a short-term action, SACGHS could organize sessions at its meetings to highlight the field of public health and policy questions associated with advances in understanding gene-environment interactions and the potential for genetic and genomic testing to exacerbate and lessen health disparities. SACGHS could also be used as a forum to promote collaboration within and between HHS agencies for efforts such as (a) preventing the stigmatization of individuals, families, or populations at risk for or with genetic conditions and (b) implementing an assessment process that will provide guidance for how and when genetic tests can be used to promote health and prevent disease

Other actions steps include performing a systems review of relevant agencies to assess mechanisms that are in place or could be in place to disseminate information about the distribution of genotypes in different populations and to assure effectiveness, accessibility, and quality of public health services. SACGHS could also develop brief reports on selected public health topics such as (a) the impact of genetic and genomic testing on health disparities, (b) how characteristics of different health care systems influence provision of genetic tests and subsequent clinical provision of preventive services, (c) building a competent public health workforce to ensure appropriate use of genetic information to promote health and prevent disease, or (d) whether it is cost effective to tailor interventions based on genetic information.

Cluster 7: Genetics and the Future of the Health Care System
Mara Aspinall, M.B.A.

Ms. Aspinall presented two key questions regarding the future of the health care system and genetics: (1) Is personalized health care achievable, and if so, with what costs and benefits? and (2) What infrastructure changes are needed to foster or adopt personalized medicine or personalized health care? As background to this topic, Ms. Aspinall observed that our current health care system is characterized by high costs and poor outcomes.

Ms. Aspinall then elaborated on the first issue she presented: the possible costs and benefits of personalized medicine. She explained that while genomic medicine stands to benefit public health, some genomic technologies may increase costs; others, though, may decrease costs. Another cost of this approach to health care is that since the science is in its infancy, considerable research will be needed to translate molecular discoveries into effective health care tools. Finally, for genomic medicine to benefit all people, a greater understanding of the genetics and epigenetics of subpopulations will be needed.

Ms. Aspinall then discussed the kinds of infrastructure changes that will be required to facilitate personalized health care. She observed that a more cost-effective approach to health care delivery will be needed, along with an increase in the number of genetic counselors and clinical laboratorians. There will also be a need for the integration of health information technology into health care. In addition, monitoring systems will be required to determine the effectiveness of personalized health care. Finally, government may need to create greater incentives for businesses to pursue innovations for personalized medicine.

This priority topic raises a number of policy issues that Ms. Aspinall presented. First, how should Government agencies invest resources in genomic medicine? Second, should the Government promote the adoption of a new approach to health care delivery? Third, should financial incentives be offered to attract more students to clinical laboratory careers? Fourth, what other steps can HHS take to promote the development and integration of health care information technology? Fifth, what systems are needed to improve genetic health technologies, to ensure their delivery to the appropriate patients, and to monitor their public health benefit? Sixth, what steps can Government take to provide incentives for businesses to pursue genetic diagnostics and targeted therapeutics? Seventh, how can the Government best use it resources to learn about differences in genetic and epigenetic variations among U.S. subpopulations?

Ms. Aspinall next presented some possible actions that the Committee could take in pursuing answers to these policy questions. A short-term action would be organizing a panel of chief medical officers from health plans to discuss the future of health care. The Committee could also work with other HHS agencies to avoid duplicating work completed by other agencies on the future health care system. Another possible action step would involve preparing brief reports on some of policy questions raised by this priority topic.

Two areas that may warrant in-depth work are structural models for health care delivery and ensuring that the genetics of subpopulations is not overlooked as genomic medicine moves forward.

Discussion. Dr. Evans indicated that any future work by the Committee on a need for more laboratorians should also include the need for more clinicians who focus on genomic aspects of health care. Ms. Aspinall said she appreciated this addition. She also agreed with Ms. Dreyfuss's suggestion that the Committee should be focusing less on incentives for businesses to pursue the development of diagnostics and therapeutics than on promoting the development of diagnostics and therapeutics. Ms. Dreyfuss explained that the emphasis on incentives was not valuable since incentives can sometimes harm, rather than promote, development. Dr. Teutsch suggested that the Committee's work on electronic health

records focus more on the need for clinical decision support tools than on data storage issues. Ms. Aspinall also supported this recommended change.

Dr. Williams added a more general point, noting that all of the priority topics recognize the need for robust information technology systems. So in moving forward on these priority topics, the Committee will need to continue its collaboration with other groups working in this area, particularly whatever group takes up the work of the American Health Information Community.

Determination of Priority Issue Areas and Action Plan

Dr. Wise invited SACGHS members to consider together whether the action steps outlined for each cluster reflect the insights and wishes of the Committee and whether the linkages that cut across clusters offer any new ways to present them to the public and the new administration. He then referred to the summary grid of the major points made in each of the cluster presentations. Dr. Teutsch noted that the goal for this session is a sense of organization and priorities, including short- and long-term actions.

Cluster 1: Coverage and Reimbursement. Dr. Williams proposed adding another action step to the coverage and reimbursement priority topic—looking at coding systems, which is a cross-cutting issue. Besides affecting reimbursement, it involves data collection, thereby affecting clinical utility. Some other members agreed, with Dr. Ferreira-Gonzalez pointing out that this step could be a short-term project involving interactions with professional groups that are already looking at coding systems.

Obstacles. When Dr. Wise inquired about the primary obstacles to moving forward on coding and what has to be done to make headway, Dr. Williams said that some of the barriers relate to a lack of clarity relating to some interpretations of the statute and regulations, and that SACGHS's letters have asked for clarifications—which may be provided in the expected letter from the HHS Secretary later this month. SACGHS will need to revisit these issues with the new administration if this clarification is not provided.

Dr. Wise identified as a second barrier the fact that different stakeholders handle different parts of the system: The American Medical Association controls CPT but not International Classification of Diseases (ICD) codes. Perhaps the HHS Secretary, with SACGHS as the facilitator, could convene the interested parties to revise this truly arcane system.

Dr. Evans observed that the existing system favors procedure-based reimbursement, which does not fit with genetic services (or some others such as psychiatry and primary care). Dr. Williams noted that not only are genetic counselors poorly reimbursed clinically; genetic testing is under-reimbursed as well.

When asked for ideas on how to move some of these issues forward, Dr. Roche mentioned a CMS publication that describes how CMS addresses payment and reimbursement issues related to new technologies. He offered to continue to interact with SACGHS staff on new issues for which an old coverage and reimbursement system was not designed to address. He cited a recent editorial in *New England Journal of Medicine* entitled "Payment Now, Benefits May Follow" that critiqued how CMS pays for a particular type of medical imaging (see http://content.nejm.org/cgi/content/short/359/22/2309). Dr. Roche cautioned that any changes at CMS can have huge effects.

Dr. Teutsch then commented that health reform will necessarily have to include financial reform too. Dr. Evans added that it is time for the promoters of genetic services to find ways to demonstrate their value, and Dr. Ferreira-Gonzalez said that it is a cross-cutting issue. Ms. Aspinall mentioned that a major recommendation developed by a recent Summit on Personalized Health Care in Utah was the need to reform the reimbursement system; she added that if reimbursement changes, utilization can change too only with sufficient resources.

Another recommendation from the Utah meeting was that the public and professionals need to have confidence in emerging products. Ms. Aspinall said that obtaining evidence of clinical utility may ensure that confidence, but Dr. Ferreira-Gonzalez voiced concern about the amount of time needed to acquire the necessary data.

The public. Dr. Licinio cautioned that while SACGHS's recommendations are directed to the health care field, what is missing is a way to find out what the public really wants. He recommended using a broad survey or community engagement process, which would be part of the cluster 5 activities. Dr. McGrath agreed strongly with his suggestion.

Cluster relationships. Dr. Teutsch observed that cluster 1 deals with various tactical issues that are relevant to the current system and how to optimize it in the short term. Other clusters will deal more with broader and longer-term subjects. Dr. Kirchner wondered how to identify a threshold as to when it is justifiable to spend public money on reimbursement. Cluster 2 concerning clinical utility is relevant to this question, which may require a plan addressing appropriate minimum or necessary amounts or evidence.

Dr. Williams agreed with Dr. Kirchner, noting that the current reimbursement system is disconnected from the system of evidence and quality and is based on work units and an evaluation system that tends to favor procedures over nonprocedural activities.

Dr. Kirchner also suggested that cluster 1 should consider payment for the additional research needed to strengthen the level of evidence. There is a CMS precedent for this approach. Dr. Williams noted that, in turn, once evidence is developed in opposition to a procedure, it can be quite difficult to get physicians to change their ways and drop it. He cited the sad and expensive situation of how a single liability case caused payers to cover bone marrow transplantation in breast cancer situations, costing the United States possibly $500 billion, along with some morbidity and mortality, for a procedure that turned out to be useless in the vast majority of cases.

Cluster 2: Clinical Utility. Dr. Williams proposed that the clinical utility Task Force highlight the funding disparity across the translational research arena, a topic that SACGHS heard about at a previous meeting. He recommended that the Committee push for a redistribution of funds to move more money from basic research into translational research.

Dr. Guttmacher wanted to know from what areas of basic research Dr. Williams proposed to take money. Dr. Williams explained that there is too much money being spent on genome research and some of it should be spent on looking at the clinical value of genomic information. Dr. Guttmacher responded that this type of clinical research cannot be done until there is a greater understanding of genetics, which would be gained through basic research.

Dr. Ferreira-Gonzalez suggested that SACGHS focus on trying to identify and/or recommend sources of funding for the necessary clinical utility research.

Obstacles. Dr. Teutsch cautioned that because of personalized medicine's focus on tailoring of treatments to individuals or at least subgroups, clinical utility studies in this area will have to be done with smaller numbers of patients, not by large clinical trials. The research is going to be more complicated than the kinds of studies that have been done in traditional clinical epidemiology.

Dr. Williams, echoing one of the possible action steps for this priority topic, added that research efficiency could be improved if the individuals conducting the earlier stages of research were given a view of the evidence that would be needed to move things into the clinical arena.

Cluster 3: Genetics Education and Training. Dr. McGrath first noted that today's discussion makes the cluster's first action item – talking to FDA about devices and educational standards – even more relevant. The Genetics Education and Training Task Force's activities involve gathering and synthesizing data about existing and future programs in the public and private sectors. Dr. McGrath also noted that medical education is organized in traditional silos such as internal medicine, pediatrics, obstetrics and gynecology. She proposed finding ways to change the silos to fit a systems approach to medicine.

Ms. Dreyfuss remarked that she was struck by comments that patents were important for education. She noted that relying on patentees to educate consumers about their patented product is not a good recipe. Ms. Dreyfuss endorsed SACGHS addressing this topic. Ms. Aspinall cautioned that not all patent-holders produce inadequate educational materials but recognized that even high-quality materials can be perceived as biased. A regular educational process would ensure not having to depend on individuals involved in commerce.

Identifying this cluster as one of the most important, Ms. Aspinall commented that the first short-term action related to FDA is not consistent with the rest of the in-depth report or the policy questions and should be considered in one of the other clusters—perhaps cluster 6 (public health), as there are certainly current issues concerning FDA requirements and laboratory tests. There are a number of associations and groups working on these concerns.

Dr. Teutsch said that this topic was probably not addressed sufficiently in the SACGHS oversight report and that a lot of promotional materials have escaped the FDA labeling system. Mr. Daynard noted that the Federal Trade Commission (FTC) challenges advertising for just two reasons: (1) the claim is blatantly false, and (2) the claim lacks substantiation. He then asked some questions: Should the evidentiary standard here be a randomized clinical trial, which takes a lot of time and money, or would case control association studies suffice? Is the FTC the right agency to say what these evidentiary standards should be? The topic of evidentiary standards needs to be addressed.

Dr. Telfair pointed out that education is not only multidisciplinary but also a multidirectional process that has to be comprehensive, particularly when involving the general public, specific consumers, and professionals of all types. Consequently, there needs to be a way to both monitor and evaluate the specific outcomes of this multidirectional education process. Dr. Telfair proposed adding this issue within the cluster's action steps.

Dr. Williams proposed making explicit the now-implicit concept that complex information requires informatics tools and education in informatics. Dr. McGrath then posed a related question—should there be a recommendation for better coordination across the many groups using the electronic health record? Dr. Williams observed that there have been coordination efforts, including by the National Coalition for Health Professional Education in Genetics, and there is now a proposal to establish a national electronic clinical decision support repository, much like Guidelines.Gov. It is likely that SACGHS will want to be in contact with these efforts.

Dr. Kirchner proposed including the establishment of a web-based information area that would list the evidence that is accumulated for associations between genetic markers and disease. This evidence could be indexed (1) by genetic findings and specific genetic markers and (2) by specific disorders. Professional editors maintaining such a website would assess the reliability of published data before including these associations.

Dr. McGrath responded that there are some existing data-gathering sites that need to be pulled together. She agreed with Dr. Kirchner that this would be of great utility to everybody in health care and also to the public.

Dr. Frohboese, from the Office for Civil Rights, asked whether the report on priorities will include cultural competence and workforce diversity as key issues, as she has not seen them highlighted in the background materials. Dr. McGrath clarified that these issues (identified as critical in a 2004 resolution of the Committee) will be a major bullet in the report in progress.

Cluster 4: Informed Consent and Genomic Data Sharing. Dr. FitzGerald cited the pursuit of personalized health care, application of technologies, accessibility of information in large databases, and interoperable health care records as creating the need to look at informed consent and protection of confidentiality and privacy. Whether SACGHS needs to have a role is a question that invites a discussion of pros and cons.

One specific issue is what to do with the information from newborn screening. It would be logistically efficient to put this information into some kind of national database as soon as possible and use it for longitudinal study. Additionally, the Department of Defense and the Department of Veterans Affairs have large databases of medical records. The Department of Commerce and the Department of Justice also have issues that are relevant to this cluster (e.g., civil rights).

Dr. Evans recommended that everybody read the short article by Patrick Taylor about some of the nuances of consent as well as privacy issues. Dr. FitzGerald then referred to a quotation from the committee preceding SACGHS, "The major distinction between consent to research and consent to treatment is that, in the first, there should be no presumed benefit and, in the second, there is no reason to proceed without a presumption of benefit."

Dr. Williams proposed as a short-term action having an educational sessions focused on different stakeholders' approaches to privacy. Two particular groups to include are the Marshfield Personalized Healthcare Coalition especially regarding their approach to consenting individuals and reconsenting and recontacting) and the Vanderbilt program for residual blood specimens and use for research. Representatives of DTC genetic testing entities should also be included, and it would also be useful to hear from experts who have written on differences in how the consenting process is approached.

Dr. FitzGerald inquired about the scheduling of a Health Research and Services Administration (HRSA) meeting in February. The meeting agenda includes a session on informed consent, which might help SACGHS to identify any duplicative efforts. As Ms. Au will be attending the HRSA meeting, she was asked to monitor it and then inform other Committee members on whether SACGHS should schedule an educational session on informed consent.

Dr. Carome, of the Office for Human Research Protections (OHRP), said that one higher-order issue related to the question “when does research involving genetic data and associated clinical information rise to the level of being research on human subjects?” Human subjects research involves obtaining individually identifiable private information.

If research involving stored specimens, stored DNA, and stored clinical information is done in a way in which it is coded or all identifiers are deleted and not replaced with a code, then in the view of OHRP no informed consent is needed. However, a question implied by one of the policy questions in this cluster is: With evolving genetics and information technologies, are data or specimens that we have considered not

identifiable now identifiable? This issue may need to be explicitly acknowledged in the policy discussion.

Cluster 5: DTC Genetic Testing. Ms. Au suggested that among the broad range of policy questions related to consumer-initiated services some could be easier to answer and many could be referred to other clusters because of overlap. Her question for the Committee then is whether SACGHS wants action at the level of monitoring and commenting or would prefer a proactive, detailed report.

Level of action. Dr. Evans said that he views monitoring as too passive, and Dr. Telfair agreed but stated that evaluating outcomes is not. To do evaluation well requires being better informed, which starts with a review of current activities and assessing what outcomes need to be assessed. Dr. Teutsch then asked whether the assessment of the landscape that the Committee did in July would be sufficient or whether more is needed.

Dr. Telfair commented that a systems review actually takes into account work that has been done and then uses information that is missing as well. The key is to develop accessible, targeted outcomes that would work. Ms. Au cautioned that this could be a moving target because, for example, of the huge updates in activities related to DTC genetic testing that have occurred in the six months since the July information-gathering session. Dr. Evans stated that it would be essential to accomplish any assessment rapidly; otherwise, the Committee should just monitor.

Dr. Kirchner pointed to a strong interaction between the cluster's goals and the educational component. Dr. FitzGerald wondered about referring to and building on how consumer-initiated services were addressed in the oversight report. Dr. McGrath said that an alternative approach would be to make this a stand-alone topic for SACGHS as it has become a more urgent issue than when SACGHS first began to discuss DTC genetic testing. She added that she is not aware of any other government agencies looking at this topic.

Dr Wise wondered why other SACGHS members are viewing this topic as important. He suggested that to be a high priority, the issue would need to be framed in a way that engages a broader challenge to the health care system and to public awareness about the importance, the relevance, and the implications of genetic insights.

Learning from the past. Dr. Williams advised in his response to look at analogous movements of consumer-driven care, such as complementary and alternative medicine and nutriceuticals. The huge amount of interest in complementary and alternative medicine ultimately led to the formation of an NIH Center specifically devoted to looking at the science and evidence behind complementary and alternative medicine. Similarly, SACGHS could take a look at DTC testing issues from the perspective of science, including evidentiary standards. Furthermore, looking at the amount of consumer spending on nutriceuticals, which do not always help and, in some examples, have caused harm, can also inspire a wish for SACGHS to take action to help consumers.

Dr. FitzGerald generalized the debate to looking at health care as a consumer good, driven by market forces and consumer desire, vs. a societal obligation delivered by a certified professional community.

Dr. McGrath referred back to how the HIV and AIDS activism of the 1980s highlighted which populations and subgroups needs were not being met by the science. Similarly, SACGHS might shine a light on the groups that genetic services and the genetic technologies are not particularly helping, which is another way to look at the issue of disparities. Dr. Teutsch noted that it is best to address emergent technologies early is to help shape them in the development stage.

Health disparities. Dr. Frohboese wondered how doing a report on how DTC marketing may be impacting health disparities would get at the issue, and Ms. Au responded that she anticipates that a Task Force would be formed to detail the approach. Dr. Wise mentioned that SACGHS has talked in the past about differential access and differential provision of genetic services. However, altering public discourse could be an aim as well.

Suggested priorities. To help when SACGHS reaches the point of spelling out its priorities for actions within all the clusters, Ms. Aspinall proposed giving a lower priority to an in-depth report and a higher priority to a brief report. Dr. Billings added that it could be worthwhile to consider whether there are gaps or areas not covered by other clusters that should still be part of the purview of the Committee. One area might be the treatment of people with Mendelian genetic disorders. Another area is the relationship between the work of this Committee and its topics and the NIH research portfolio (including specifically the interface between the National Human Genome Research Institute and the Committee).

Cluster 6: Public Health Genomics. Dr. Telfair stated that on behalf of the public health community he recommends balance and assessment; too often programs are too far underway before any assessment is started. Referring next to the list of short-term actions, he said that a systems review means looking (1) at commonalities between program areas and issues of interest to SACGHS and (2) at the assurance of effectiveness, accessibility, and quality of services.

Dr. Telfair also urged proceeding in a systematic way. For example, after reviewing what agencies are doing, the Committee would need to look next at how to work together in areas of mutual interest and concern. He also proposed considering the social, ecological, and environmental fit by looking at the interaction of genes, environment, and health applications.

Cluster 7: Genetics and the Future of the Health Care System. With regard to the proposed action of gathering chief medical officers from health plans, Dr. Williams suggested including chief medical officers not only from payers but also from integrated health systems, hospitals, and academic medical centers. In addition, innovative administrative leaders should be included. Ms. Aspinall agreed with this broader perspective, saying that was her intent.

Ms. Au mentioned the funded work of Debra Doyle, Washington State Department of Health, in which Ms. Doyle brought together leaders of health care plans and third-party payers to discuss what they were doing currently about genetic reimbursement and what they thought the future would be. Ms. Aspinall added that someone had suggested during the break that the Committee should hear from key health care providers from medical associations and someone from the hospital systems.

Dr. Williams indicated that some exciting research, including work with small molecules and with RNA, is bringing medicine closer to having some treatments for traditionally untreatable genetic disorders. Consequently, he agrees with Dr. Billings about keeping the Mendelian diseases on the futures agenda—probably in a monitoring slot.

Cluster linkages. When Dr. Telfair asked if planning will include workforce development as well as education of the workforce, Ms. Aspinall said this is addressed in one of the policy questions. One aspect is that personalized health care could lead to more nonphysician care, in turn leading to a different type of educational program. This cluster would note that but the education cluster would address it more thoroughly. Dr. Telfair added that the previously cited desire for integration among the clusters might be appropriately applied here.

Dr. Wise observed that health care reform cannot realistically move forward without engaging in a purposeful way the explosion in genetic insight and capability, and that this look at the future is an

intensely anticipatory project for the Committee to take on—looking at big-picture issues. He also called attention to Dr. Telfair's point that genetics in the service of reforming the health care delivery system could embrace clinical utility and added its links to reimbursement policy shifts and workforce as well. Both Dr. Wise and Ms. Aspinall recognized the potential of integrating additional SACGHS issues with health care reform. This approach may be a particularly useful concept to share with the new administration.

Further discussion of priorities

Dr. Teutsch recalled that monitoring will continue on previous committee recommendations in reports on genetic discrimination (where indeed there has been substantive progress), oversight of genetic testing, and pharmacogenomics as well as on policy issues related to previous large population studies. Dr. Wise then stressed that committee members will not be voting on priorities but getting a sense of the group as to how to prioritize the cluster issues and what should be the next steps.

Dr. Williams suggested retaining the seven clusters and their leadership while choosing topics from within them to focus on as a Committee. Some topics would derive elements from more than one cluster (e.g., the education report). Dr. Evans proposed identifying specific niches in which can be done quickly, and Dr. Kirchner identified decisionmaking about whether to have an informed consent educational project after a March meeting review of the report from the upcoming HRSA meeting. Similarly, reviewing the report from University of Washington for the March meeting could help identify the types of people to invite to discuss the future of health care with the Committee, possibly in July. By March, the relevant interests of the new administration might be better known too.

Ms. Aspinall wondered how quickly the Committee would be able to meet with the new administration and possibly present the priority topics at that time. Dr. Wise suggested that this fits well with the next SAGHS agenda item, which is putting together a brief report of activities and plans with a cover letter that would precisely introduce not only the Committee to the new administration but its strategic contributions to the issues of the day.

Dr. Wise added that it might be possible to frame the seven clusters with four strategic contributions: (1) genetics in the service of reforming the health care delivery system, which includes coverage and reimbursement, clinical utility, ensuring that there is a capable workforce, and genetics and the future of the health care system; (2) genetics will be crucial to improving public health and population-based prevention; (3) individual engagement with genetics and protections and the public's growing awareness and engagement with genetics, which includes DTC marketing and protections and informed consent; and (4) ensure that the new genetic technologies will enhance equity in health outcomes; which includes ensuring reduction of disparities in health as the health of all is improved.

In the cover letter to the new HHS secretary, the Committee would first speak of needing to make sure that genetics is a central part of health care reform and indicate that SACGHS recommends specific priorities, as addressed by the four strategic components and seven priority clusters.

Ms. Aspinall expressed appreciation for Dr. Wise's framework and proposed getting the letter out rapidly to reach the Secretary and his/her staff before SACGHS's March meeting. Dr. Evans suggested that instead of indicating that health care reform can bring genetics into the fore, emphasis should be on how the advent of genetics in medicine is going to drive medical care. Dr. Teutsch acknowledged the usefulness of Dr. Wise's framework and asked Committee members to focus now on which priority issues to tackle within the resources available. This effort probably means identifying the more important short-term topics as well as some larger reports to undertake over the next few years.

Dr. Ferreira-Gonzalez cited the critical shortage of laboratory personnel, which is affecting everyone. One aspect of this issue is that there are not enough schools; another is lack of incentives for entrants and for retention in the field. Dr. McGrath commented that the Genetics Education and Training Task Force could include laboratorians but had not made them an initial priority. Ms. Aspinall stated that, as part of anticipating future issues, availability of the personnel is long-term issue in cluster 7. Dr. FitzGerald suggested that if a near-term crisis would derail long-term planning, attention should be given to this topic now.

Other Committee members, however, mentioned that the current crisis is a shortage of all types of laboratorians, that SACGHS had previously made a decision not to include this topic in the education and training cluster, and that developing a brief report could, with all SACGHS's other activities, take two or three years. One possibility would be something shorter than a full report to help with the solution rather than evaluating the problem.

Ms. Aspinall suggested that the specific aspect to address, which could be included in the education cluster, is having SACGHS take a stance on seed funding for community colleges to take on programs in laboratory medicine. That approach has been incredibly effective in the education field. The appropriate funding sources tend to increase in the context of a recession and retraining.

When Dr. Williams questioned if reimbursement issues could affect retention in laboratories, Dr. Ferreira-Gonzalez said that it could be involved – as well as the inability to compete with higher salaries in other fields such as informatics. Dr. Williams also inquired whether any of the several Banbury conferences on education and genetics ever addressed the laboratory personnel issue, but Dr. Ferreira-Gonzalez thought the topic would have been broader than what the conferences would address.

Dr. Wise mentioned reports from some other groups on the topic, including HRSA and the Bureau of Health Professions. Also some professional groups have been working and advocating on this issue. What then would be the role of this Committee? Dr. Ferreira-Gonzalez responded that the Committee could look at what at other groups have been doing or what has been reported and see if there are areas that need further discussion. Dr. FitzGerald observed that the topic could fit in with the cluster on genetics and the future of the health care system. He asked if we have a $1,000 genome in the near future, what would that do to the demand for clinical laboratorians? More genetic counselors and clinical geneticists could be needed too.

Dr. FitzGerald returned to the topic of monitoring to add the DTC testing issue to help the Committee decide how it wants to frame its own actions in this area. Dr. Evans proposed picking out as short-term priorities (1) the letter to incoming HHS Secretary emphasizing the importance of genetics and the changes it will bring about and that it has to be factored into plans for health care reform and (2) some kind of DTC checklist of questions consumers could consider before purchasing services.

When Dr. Evans also advocated continuing action on reimbursement issues as a high priority—necessary for the practical functioning of the field—Dr. Williams said that he understands this continuing action had already been decided.

Dr. Teutsch summarized actions for the Committee's future agendas. Under coverage and reimbursement services (cluster 1), the actions are monitoring and interacting with CMS on implementation of prior SACGHS recommendations. The salient recommendations for clinical utility (cluster 2) have already been made as part of the oversight and pharmacogenomics reports. The discussion of genetic education (cluster 3) leads to considering the laboratorian component; other efforts are already underway. Informed consent (cluster 4) will become important as whole-genome testing becomes more available, but SACGHS needs to learn from the upcoming HRSA meeting before identifying whether there is a specific

area for the Committee to address. There has also been strong interest in a short-term assessment of the DTC genetic testing (cluster 5). While a lot of ideas were cited about public health applications (cluster 6), doing something with a systems review appears to be the priority. The biggest topic, in Dr. Teutsch's view, is genetics and the future of the health care system (cluster 7), with an immediate plan to assemble a panel of stakeholders in the payer community for the next meeting, while recognizing that this topic will be an ongoing major effort.

When Dr. Billings asked whether the regulations and recommendations associated with GINA are part of the discrimination cluster, Dr. Teutsch replied that it is included in the topics to be monitored (relating to previously issued reports). Dr. Billings then asked about being more aggressive as the incoming administration will have some impact on the regulations and enforcement of the legislation. Ms. Leibig, of the Equal Employment Opportunity Commission (EEOC), said that in terms of Title II of GINA, the EEOC is moving along as quickly as possible. Draft regulations will be developed, and there will be a 60-day comment period. Title I regulations will be issued independently. Ms. Carr suggested that it might be possible to have a fuller report on the GINA rulemaking at the March meeting. Dr. Billings said that he would still like SACGHS to educate the leaders about any key components of the law from the Committee's point of view.

Regarding cluster 7, Ms. Aspinall commented that after hearing the discussion she would expect the Committee to focus on three priorities: workforce, health information technology, and monitoring and evaluating clinical effectiveness of genetic technologies. She said that a bigger issue is the choice between two different approaches for organizing the seven clusters of priorities—whether to organize by the framework proposed by Dr. Wise and send that report to the HHS Secretary or whether to prioritize among the seven clusters, then either start working on them or send them to the new Secretary showing that prioritization.

Dr. Teutsch indicated that his emphasis right now is on the Committee clarifying its own thinking and action priorities and that the seven clusters will definitely be presented to the HHS Secretary in some format. Dr. Wise then thanked the Task Force members and the OBA staff for their help and cooperation.

Review of Draft Progress Report

Priorities framework. Dr. Teutsch presented a slide showing the framework that Dr. Wise had suggested, including the proposed wording. The first part related to the Committee's energies that will be devoted to improving the health care system and the role of genetics in this effort.

The second part of the framework focused on genetics and public health and population-based prevention. Dr. Teutsch will work with Drs. Kolor and Telfair to identify one or two specific items that the Committee can address. Dr. Evans advocated focusing on using genomic data to stratify populations for risk in the context of screening, or a similar topic. Dr. Teutsch noted that this would fit with the population aspects, but that category also needs to deal with some of the environment-gene interactions and the risks that accrue to communities and subpopulations.

The third part of the framework addressed privacy and protections issues as well as DTC genetic testing. The fourth part highlighted the cross-cutting issue on equity (which includes fairness, disparities, and access).

Draft progress report. Dr. Teutsch indicated that the priority framework just discussed will be incorporated into a letter to the incoming HHS Secretary. The framework of the letter includes (1) a general briefing on the Committee's prior activities, (2) priority issues that the Committee proposes to address based on prior reports and readiness for quick action, and (3) future directions for the Committee.

The issues that are identified in the cover letter will be further developed in a brief report entitled *The Integration of Genetic Technologies into Health Care and Public Health: A Progress Report and Future Directions for SACGHS*.

When Dr. Teutsch asked Dr. Wise, who helped to draft the progress report, to comment, Dr. Wise stated that the approach was to have the cover letter make the broad, general case for both the existence of this Committee and where we think the central issues are going and then provide additional background and more detailed discussions, still relatively brief, in the appended document.

Dr. Frohboese commented that the letter is well drafted and will be helpful to the new HHS Secretary as well as instrumental in making sure that this Committee's views are before the Secretary at the earliest possible moment. When she asked about the framing of the strategic contributions, Dr. Wise indicated that they will probably be presented via bullets in that paragraph that covers the topic broadly.

Dr. Teutsch then asked Dr. Frohboese for advice on how best to facilitate delivery of the letter during the transition period between administrations. Dr. Frohboese explained that during the transition planning process, each HHS operating division and staff division meets with members of President-Elect Obama's transition team. However, she advised waiting until the new HHS Secretary is in place, then working through the Office of the Secretary to identify who the point person is going to be in the Secretary's office to handle these issues and establishing that contact.

Ms. Au suggested highlighting the opportunities for immediate action in the appended report. Ms. Aspinall wondered if these opportunities for immediate action should be highlighted in the cover letter instead. During further discussion, it was decided to keep the cover letter broad and the specifics in the appended document. Ms. Au then suggested that the opportunities for immediate action become a separate, independent attachment, with summaries.

Dr. Keckler recommended identifying the point person as soon as possible and making sure that person, as well as the HHS Secretary, receives the cover letter and attached progress report.

Concluding Remarks

Dr. Teutsch reminded everyone of the draft statement that Dr. Telfair and Ms. Au have prepared on competency in the area of genetics to send on the Committee's behalf to the Council on Linkages Between Academia and Public Health Practice, which is revising its competencies for the public health workforce. Committee members may provide suggestions now or send them to Dr. Fomous in advance of the Council's December 15 due date.

Dr. Teutsch next reviewed the meeting's agenda topics and the progress made on them, including the draft patents report and accompanying policy options that will be released for public comment; the update on metrics standards that are being developed at NIST, FDA, and CDC; the constructive discussion of priorities and action steps; and the draft progress report for the incoming administration.

Dr. Teutsch then thanked everyone present for their productive participation and announced that the Committee's next scheduled meeting on March 12 and 13, 2009, will again be at the Humphrey Building.

ADJOURNMENT

The meeting was adjourned at 1:48 p.m.

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

Steven Teutsch, M.D., Ph.D.
SACGHS Chair

Sarah Carr
SACGHS Executive Secretary