Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Tenth Meeting
June 26-27, 2006
Bethesda, Maryland

Committee Members Present

Reed Tuckson, M.D., Chair
Sylvia Mann Au, M.S., CGC
Cynthia Berry, J.D.
Chira Chen
James P. Evans, M.D., Ph.D.
Kevin FitzGerald, S.J., Ph.D.
Andrea Ferriera-Gonzalez, Ph.D. (appointment pending)
Debra G.B. Leonard, M.D., Ph.D.
Julio Licinio, M.D.
Barbara Burns McGrath, R.N., Ph.D. (appointment pending)
Agnes Masny, R.N., M.P.H., M.S.N.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Steven Teutsch, M.D., M.P.H. (appointment pending)
Emily Winn-Deen, Ph.D.

***Ex Officios*/Alternates Present**

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

Executive Secretary
Sarah Carr, NIH Office of Biotechnology Activities

Monday, June 26, 2006

Welcome and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, SACGHS Chair, stated that the public was made aware of the meeting through notices in the Federal Register, as well as announcements on the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) website and through the SACGHS listserv. He welcomed new members Barbara Burns McGrath, R.N., Ph.D., Research Associate Professor at the University of Washington School of Nursing; Andrea Ferriera-Gonzalez, Ph.D., Professor of Pathology and Director of Molecular Diagnostics Laboratory at Virginia Commonwealth University; and Steven Teutsch, M.D., M.P.H., Executive Director of Outcomes Research and Management, Merck and Company, Inc. Dr. Tuckson also reported on staff departures and additions.

The Office of the Secretary of the Department of Health and Human Services (HHS) notified the Committee that the recommendations presented in the Committee's report on coverage and reimbursement of genetic tests were under consideration. The Secretary's Office acknowledged receipt of the Committee's letter on the incorporation of genetics, genomics, and family history into the electronic health infrastructure and the letter on direct-to-consumer (DTC) marketing of genetic tests.

Dr. Tuckson reported on a meeting he and Ms. Cynthia Berry had with the Center for Medicare and Medicaid Services (CMS) Administrator Mark McClellan and CMS senior leadership to discuss recommendations from SACGHS in the coverage and reimbursement report that relate to Medicare and Medicaid programs. These included the screening exclusion, billing and reimbursement of genetic counseling services, and national versus local coverage decisions. Dr. McClellan assigned followup work on these issues to his staff members. Dr. Tuckson said he was scheduled to meet with Dr. Elias Zerhouni, Director of NIH, on the following day to discuss SACGHS priority issues. Dr. Tuckson introduced Judith Yost, who presented on the status of the CMS plan to augment the Clinical Laboratory Improvement Amendments (CLIA) Program with a genetic specialty. Dr. Bin Chen, who was filling in for Dr. Joseph Boone, Associate Director for Science in the Centers for Disease Control and Prevention (CDC) Division of Laboratory Systems, joined the meeting by phone.

Oversight Session

Update on the Notice of Proposed Rulemaking on a Genetic Specialty for the CLIA Program

Judith A. Yost, M.A., M.T.
Director, Division of Laboratory Services, CMS

Ms. Yost stated that genetic tests are covered by CLIA general regulations and specialties, such as hematology, microbiology, immunology, chemistry, and blood banking. A specialty for genetic or molecular testing does not exist. Based on the recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC) to HHS on genetic testing, CMS recently incorporated a unidirectional workflow for PCR testing, quality control for PCR testing, and enhanced confidentiality requirements into the final quality control regulations.

Ms. Yost reviewed past activities related to CLIA in the area of genetic testing. An NIH and Department of Energy Task Force report in 1997 recommended enhanced oversight for genetic tests. In 1998, CLIAC presented recommendations on genetic testing oversight to HHS. In 1999, SACGT made recommendations that supported the CLIAC recommendations. In 2000, CDC published a Notice of Intent (NOI), a predecessor to a proposed rule. The NOI included the CLIAC recommendations and compared them with the existing CLIA requirements. The public comments received on the NOI varied, some stating that no changes were needed to CLIA, while others called for very prescriptive requirements for genetic testing. There were many other comments across the spectrum. In 2001, CLIAC updated and revised their recommendations based on the NOI feedback. Taking into account all of the input received, CMS developed a Notice of Proposed Rulemaking (NPRM), which was in the clearance process.

Ms. Yost explained that because the NOI comments varied widely and were difficult to address, it took several years to move from the revised CLIAC recommendations to the NPRM. In addition, some of the CLIAC recommendations were outside the scope of authority of CLIA. For example, CMS does not have authority under CLIA to require informed consent or to address clinical validity or utility. CMS was also developing a final CLIA quality control regulation and was responsible for training surveyors and providing education to the public. Once these tasks were completed, more resources were available to address the NPRM.

Ms. Yost asked for input from the Committee and the genetic testing community on several NPRM issues. These included the definition of a genetic test, handling of informed consent, clinical validity, proficiency testing, and personnel qualifications. On the latter issue, she asked for opinions on creating a balance to ensure both quality testing and an adequate labor force. She asked for input about genetic testing research labs that report results without CLIA certification.

Sources of input for the NPRM included CLIAC's recommendations, public comments on the NOI, a review of professional standards/guidelines and accrediting organizations' requirements, subject matter experts, and input from Federal agencies, particularly CDC. Components of the NPRM include the preamble, proposed standards, regulatory impact analysis on cost versus benefit, and the paperwork burden.

The regulation was on the CMS regulation schedule, with clearance pending from CDC, FDA, CMS, and NIH. Once the agencies cleared the NPRM, the Secretary would need to sign off. After the regulation was published, there would be a 60 to 90-day comment period. Ms. Yost referred the Committee to www.cms.hhs.gov/clia/ for more information.

Discussion

Dr. Tuckson asked when Ms. Yost would like feedback from the Committee on the NPRM. She asked for SACGHS input when the NPRM was in the final stages but prior to the public comment period, and after the proposed rule was published. She asked that the Committee focus on the approaches to inspecting laboratories and on educational materials for labs on meeting standards. Dr. Tuckson asked that the prior work of SACGT on this issue be made available to the Committee. He also asked SACGHS staff members to develop a document prior to the next meeting that summarized key points for consideration. The Committee would review the document and decide how to respond to Ms. Yost's request for input.

Dr. Emily Winn-Deen asked how frequent changes in technology would affect the new regulation. Ms. Yost said CMS wrote broad requirements in the regulation for this reason. Detailed information was to be provided in a guidance document that could be updated frequently.

Dr. Tuckson provided an overview of the agenda. Executive Secretary Sarah Carr reminded the Committee of their responsibilities concerning financial conflicts of interest and as Special Government Employees.

Pharmacogenomics Session

Overview of Pharmacogenomics Session and Update on Efforts of the SACGHS Pharmacogenomics Task Force
Emily Winn-Deen, Ph.D.
Chair, SACGHS Task Force on Pharmacogenomics

Dr. Winn-Deen provided an overview of the work of the Task Force on Pharmacogenomics, stating that pharmacogenomics (PGx) was identified as a priority issue by SACGHS in March 2004. Informational briefings were held in June 2005 and October 2005. An outline for a report to the Secretary was finalized in October 2005. In March 2006, a detailed review of HHS agency activities in the area of PGx was conducted. The Office of the Assistant Secretary for Planning and Evaluation (ASPE) contracted with The Lewin Group to conduct a literature review that would contribute substantially to the report's development. At the March 2006 meeting, SACGHS began the work of drafting recommendations for each topic in the report. The Task Force and SACGHS staff continued work on the recommendations through a series of conference calls. The day's session would include discussion of 13 new "strawman" recommendations and other relevant recommendations developed at the previous SACGHS meeting. In the Committee's materials, the previous recommendations were numbered (i.e., 1,2,3); while the new strawman recommendations were listed by letter (i.e., A,B,C).

Dr. Winn-Deen stated that the next steps for the Task Force would be development of a draft report based on the literature review and feedback from the Committee during the day's discussion. The Task Force planned to meet at a 1-day session in September to work intensively on the report and create a version for full Committee review in November. If consensus were reached on the report's content, it would go out for public comment and would be finalized in 2007.

Critical Path Initiative and FDA Approach to Personalized Medicine
Janet Woodcock, M.D.
Deputy Commissioner for Operations, FDA

Dr. Woodcock stated that we are living in a "golden age" of biomedical discovery, including the sequencing of the human genome and the technological and scientific advances that are following it. There are now unprecedented methods for investigating genes using new medical devices. She reported that over a period of 10 years, investment in biomedical research has doubled. Investment from industrial sources accounts for 57 percent; Federal and State Government funds and organizations such as the Gates Foundation make up the rest. Drug and biological submissions to the FDA are not increasing at a rate corresponding to the growth in R&D investments. The product development success rate has declined. This has been called a "pipeline problem" or an "industry productivity problem." The number of innovative new products coming to the market does not match the high level of investment.

The year 2004 marked a 20-year low in the introduction of novel medical therapies into worldwide markets. The costs of getting a new drug into the market have greatly increased. It is estimated that for every successful drug that reaches the market, $1.1 billion has been invested, much of it in losing propositions (about nine "losers" to every one successful product). This is disincentivizing investment in less common diseases, smaller markets, and innovative approaches.

New compounds for drugs and biologics entering Phase I development have approximately an 8 percent chance of reaching the market. This compares with a 14 percent chance 15 years ago. Dr. Woodcock stated that there is even more concern about the current Phase III failure rate of 50 percent, compared with approximately 20 percent a decade ago. Half of the drug or biological products that reach the last stages of development, where the costs are greatest, will either be ineffective, have unexpected toxicity, or will be commercially nonviable.

Many speculate about the fact that biomedical discoveries are not being effectively translated from the bench to the bedside. One explanation is that genomics and other new scientific advances are not at their full potential. It takes 10 to 15 years for some advances to be effectively applied. Some say the easy targets (e.g., bacteria) are already taken and that chronic diseases are much harder to study. Another explanation is that rapidly escalating costs and complexity decrease the willingness and ability of sponsors to bring a large number of candidates forward into the clinic. Companies typically pick only one candidate to move forward when they have a portfolio of similar candidates. Some people blame FDA for the problem. Dr. Woodcock stated that if there were no FDA requirements, drugs and biologics could go to market without testing and the translation rate would be very high. However, she said that many societal problems would result.

FDA believes that the development process, which is the "critical path" to benefit patients, has become the most serious bottleneck for new products. The agency concluded that science is using the evaluation tools and infrastructure of the last century to develop and evaluate this century's advances. The science used to predict and evaluate product performance has not advanced at the same rate as basic science. Dr. Woodcock said this provides an opportunity to improve product development with new science, but it will require a paradigm shift in the way the research enterprise develops applied science.

FDA defines the critical path as the series of steps from candidate identification all the way to a commercial product. It involves serial evaluation of the performance of the product through preclinical testing and clinical evaluation. However, the tools available to perform the scientific tasks of evaluation and prediction are not sophisticated. FDA's Critical Path Initiative focuses on the science used for these evaluations, asking how they can be conducted more efficiently. Dr. Woodcock noted that many of the answers FDA has found relate to genetics, genomics, and personalized medicine.

Dr. Woodcock displayed an FDA schematic of the critical path for medical product development. It showed basic research leading to the discovery of targets and candidates that could potentially intervene on those targets to make drugs, vaccines, or biologics. Once these products are refined, they enter preclinical development. During Phase I, II, and III research, a marketing application must be filed and the product approved by the FDA. Dr. Woodcock said that the science used to predict safety and efficacy and enable manufacture is different than basic discovery research science or even translational research. Translational research often focuses on moving a specific product into a clinic for evaluation.

FDA is recommending that evaluative science address three key product performance dimensions: Assessment of safety, both preclinically and during clinical development; proof of efficacy; and industrialization, which Dr. Woodcock said has been neglected by all but the industrial sector. The industrialization process asks how a product can be manufactured on a commercial scale with consistently high quality. Dr. Woodcock stated that mass production of complex products is difficult and that FDA presides over a constant stream of recalls, product quality problems, and shortages (e.g., the flu vaccine). In genetics, this can lead to problems with the performance of diagnostic tests. Testing equipment that is off spec because of improper manufacturing won't provide accurate results.

The Critical Path Initiative is an attempt to bring attention and focus to the need for targeted scientific efforts to modernize the processes and methods used to evaluate the safety, efficacy, and quality of medical products as they move from product selection and design to mass manufacture. Dr. Woodcock listed its guiding principles: 1) FDA is trying to stimulate collaborative efforts among Government, academia, industry, and patient groups to focus on infrastructure and use a scientific toolkit, now in development, that that will help bring new products forward; 2) FDA is building support for the academic science bases in relevant disciplines, such as system biology and clinical pharmacology, which are currently lacking; 3) FDA is building opportunities for sharing tremendous amounts of knowledge and database content, generated mostly in the private sector; and 4) FDA plans to develop enabling standards that can be accepted internationally.

FDA published an initial report in 2004 and has had public discussions with various scientific and industry advisory committees. Multiple public-private partnership consortia were initiated using nonprofit conveners. Recently, FDA published the *Critical Path Opportunities Report and List,* which can be found on the FDA website under Critical Path. It provides extensive analysis and lists 76 distinct scientific projects that could help move products to patients in a more effective manner. FDA has identified a number of opportunities for modernization in areas such as biomarker qualification (e.g., *in vitro* diagnostics, functional imaging, and preclinical taxogenomics). Dr. Woodcock stated that the way

clinical trials are conducted must change as new biomarkers are developed and bioinformatics will be needed to support this change. Neither of these infrastructure elements is currently in place.

Dr. Woodcock defined biomarkers as quantitative measures of physiology or pathophysiology, such as liver function tests, ECGs, x-rays, or psychological tests. She explained that although biomarker discovery takes place quickly, clinical meaning develops slowly over a period of years. It is expensive and difficult work that is not attractive to funders. She said FDA is often criticized for not approving new tests, even when the data is not sufficient to do so. Dr. Woodcock stated that new biomarkers are key to personalized medicine, because diagnosis is the foundation of medicine. Very few entities have the resources to develop new biomarkers, so consortia must work together in this area. All parties—Government, insurers, academia, industry, and patients—have an important stake in this research because new biomarkers are critical to efficient and effective clinical medicine and product development.

Dr. Woodcock discussed research on several new biomarkers. She explained that individuals respond differently to drugs due to genetics. Those with a slow disposal mechanism may experience many side effects. Others are rapid metabolizers—their disposal mechanisms are hyper-efficient—and they may receive no benefit from taking an average drug dose. The Center for Devices at FDA has approved some of the first drug metabolism polymorphism tests that can be applied to important drugs, such as those that treat cancer. FDA is also interested in pharmacogenomics testing to guide dosing of the blood thinner warfarin, which can cause many side effects. About 40 to 50 percent of the variability of response to wafarin is genetically based. Tests can now determine this variability, but they are not yet commercially available. A number of parties are conducting clinical trials with the goal of improving warfarin outcomes using pharmacogenomic-directed dosing. There are many other opportunities to determine drug metabolism polymorphisms to avoid serious side effects, some of which are for approved drugs.

Pharmacogenomic markers that predict drug response or non-response allow targeting of therapy toward those who would respond and away from those who won't respond. FDA is working with NIH and the pharmaceutical industry on PGx markers that determine the genetic basis of adverse events so that those at risk can avoid harmful treatments. Another promising area of research is that of advanced imaging technologies, which can distinguish disease subgroups for therapy, rapidly evaluate response to treatment on an individual basis, and help measure responses in clinical trials.

Dr. Woodcock explained that although randomized controlled clinical trials (RCTs) marked a scientific triumph over anecdotal medicine, this model controls for the impact of variability. Today, variability is at the heart of personalized medicine. She said there are limitations to controlled trials, e.g., only one or a few questions can be answered per trial. However, there are unlimited questions about the appropriate use of medical products and their outcomes and these questions change over time. Because resources for RCTs (funding, patients, investigators, and time) are limited, this model allows for very few questions to be answered. Therefore, compromises are made when medical products are sent to market.

Dr. Woodcock stated that at the end of most drug development programs, after tremendous expenditures of time and resources, not much is known about the products tested. FDA is usually confident that a drug or biological has a measurable beneficial effect in a described population (i.e., those who were treated in the trials), but the overall treatment effect is often very small. It's not known whether a few people responded very well or whether many people responded slightly, because either can result in a statistically significant result. Many who take an approved drug will not benefit.

There are many health care consequences resulting from the current approach to medical product development. There is a cost controversy because the field can't quantify the actual value of products in the marketplace. The health care policy community has a pessimistic attitude about technology and believes it increases health care costs, lowers productivity in health care, and results in poorer outcomes for patients. Products are viewed as either "safe" or "unsafe" for the entire population; there's little appreciation of human variability.

Dr. Woodcock stated that better clinical trial designs are needed. She said diagnostics should be paired with therapeutics in development to identify responsive subgroups and prevent toxicity. A more mechanistic model is needed to explain how products work. Researchers will have to change the way they conduct trials, using adaptive designs that can answer a series of questions about who should be treated or not treated. Dr. Woodcock said this will improve the success rate and lower the costs of the development process. Products will come out of the pipeline with more information about performance. The result for patients will be treatment that is more personalized, with larger treatment effects. Ineffective therapy will be stopped more quickly and some side effects will be avoided. Products will be available earlier, leading to a higher quality of health care. Dr. Woodcock stated that the medical product development process should come to the forefront of health care policy discussions.

Q&A

Dr. Debra Leonard asked how the opportunities in the FDA's *Critical Path Opportunities Report and List* would be funded. Dr. Woodcock said the FDA does not provide direct funding for this work and that the effort will take time and rely on collaborations with other agencies, e.g., the NIH and consortia arrangements.

Dr. Francis Collins asked for more information about the not-for-profit Critical Path Institute. Dr. Woodcock said the Institute is a 501(c)3 non-profit that is developing a consortium. It is funded by the city of Tucson, Arizona, as well as non-pharmaceutical and non-industry sources and charitable organizations. The Institute received a small earmark from Congress in FDA's budget to conduct genetic cardiac safety biomarker research using the University of Utah's large genetic database. They are also participating in the warfarin project and developing a consortium on targeted therapy. Dr. Woodcock stated, however, that no one source would be central to the critical path effort. A wide range of groups around the country will work on various projects depending on their areas of interest.

Dr. Julio Licinio asked Dr. Woodcock to comment on the fact that no product is ever completely safe. She said the benefit/risk ratio associated with products can be remarkably improved through pharmacogenomics and the outcomes will be better than those currently being achieved.

Dr. Tuckson asked Dr. Woodcock to consider the appropriate role for the Committee related to the Critical Path Initiative. He also asked about the coordinated activity with the Agency for Healthcare Research and Quality (AHRQ). She stated that there is an unprecedented level of collaboration with AHRQ and with NIH's Institutes and Centers on critical path issues.

Dr. Gurvaneet Randhawa offered several comments related to the upcoming PGx discussion. He said an underlying goal of the original recommendations was to understand how the health outcomes data of clinical interventions (i.e., drugs, diagnostics, or biologics) is gathered and synthesized after regulatory approval. Dr. Randhawa said that, typically, Phase III trials focus on surrogate outcomes in highly specialized patients and do not analyze long-term outcomes in the general population. He said data is needed in the real world, which can come from many different study mechanisms, such as pragmatic clinical trials, registries, administrative databases, health plan databases, and electronic health records. He suggested that SACGHS address the limitations and advantages of each type of study design.

Dr. Randhawa said that one of the recommendations mentions the Coverage Evidence Development Initiative at CMS, which allows Medicare to cover the cost of a clinical intervention contingent on the patient's enrollment in a study to evaluate outcomes (i.e., conditional approval). He proposed that the Committee further explore conditional coverage and conditional approval. He suggested that public-private partnerships could conduct studies earlier than the drug development pathway, in Phase III or even Phase II. He asked SACGHS to make a broad recommendation addressing potential public-private partnerships in all processes, from basic research to health outcomes. He added that biomedical research needs the availability of standardized tissue and sample repositories, whether in academia or industry.

Full Committee Discussion of Pharmacogenomics Report

Dr. Winn-Deen introduced **Recommendation A**, which concerned improvements in FDA's policies and procedures to facilitate and accelerate the co-development of PGx drug and diagnostic products:

Option #A-1: FDA should continue to foster collaborative opportunities between the public and private sectors that encourage and facilitate the co-development of PGx products. Specifically, the FDA Critical Path Initiative/Office should develop a supplement to the Critical Path Opportunities List that discusses the opportunities specific to PGx. The list would serve as a mechanism to organize companies and researchers around specific projects that have a significant public health impact.

Option #A-2: FDA should continue to provide industry with guidance about best practices associated with co-development of medical and PGx products.

Dr. Leonard asked about the feasibility of co-development. Dr. Steven Gutman said it's feasible in some cases, but not others. Dr. Winn-Deen asked about the criteria FDA would use to determine whether a drug required a companion diagnostic. Dr. Woodcock said a diagnostic would be required if the drug couldn't be rescued any other way. She said a company could try to get a drug on the market without a diagnostic if the benefit/risk ratio was acceptable.

The Committee supported FDA's role in the co-development process facilitating the work of private sector manufacturers, because the agency is in a position to see patterns, not just the work of one company. They agreed to the recommendations in Options A-1 and A-2.

Recommendation B addressed how a test could potentially guide drug dosing. Drug labels usually lack sufficient information to guide physicians in dosing decisions based on PGx results. The following options were discussed:

Option #B-1: To assist health providers in determining optimal therapeutic dosage, FDA should provide adequate information as part of the label for both the drug and its companion diagnostic test. The diagnostic product labeling should clearly describe the test's analytical and clinical validity and, if appropriate, include a general warning about the need to monitor patients to ensure that the drug is producing the desired response.

Option #B-2: Given that inaccurate test results from diagnostic tests used to optimize drug dosing could lead to incorrect dosing and the possibility of adverse drug reactions or lack of patient response, FDA should establish a threshold of specificity and sensitivity for each of these tests that accounts for the unique relationship between drugs and their companion diagnostic tests.

Dr. Steven Teutsch suggested adding a Committee recommendation on translating dosing information on the drug label into the practice of medicine. He said that labels don't influence care to a great extent.

Dr. Woodcock said that Option B-1 was related to a lack of outcome data on dosing instructions and that more studies are needed to help guide clinicians. FDA doesn't have the ability to mandate such studies, but is trying to encourage them through various consortia. For the vast majority of drugs, FDA doesn't know whether PGx-directed dosing would be clinically significant and therefore can't provide guidance. When the agency has such information, they could provide it. She said that generally, dosing information that is not on polymorphisms could come from the voluntary submissions of the pharmaceutical companies.

Dr. Kevin FitzGerald asked how FDA is currently designating a drug as safe and effective and whether, with the push toward personalized medicine, that approach will shift so the standard will be raised to include dosing information. Dr. Woodcock agreed that this change would occur over time as targeted therapies are developed. She clarified that FDA will need a hypothesis-driven demonstration of significant PGx-directed dosing before they can mandate it, which could come from either a retrospective or prospective dataset, but not the dataset that generated the hypothesis.

Dr. Woodcock told the Committee that FDA issued an organized drug label format with a highlighted section that contains the most important prescribing information. It is intended for use in e-prescribing systems and has computer readable sections. FDA established a repository for this information at the National Library of Medicine. By the end of the year, all drug labels would be in the repository and when FDA approves changes in labeling, they will go into the repository immediately. FDA hopes that as e-prescribing becomes more prevalent, PGx dosing recommendations can be incorporated directly into the e-prescribing loop. Doctors would receive a signal from the system when they prescribe a drug that needs a dosing adjustment. Dr. Woodcock emphasized that traditional methods of physician education have not been effective in changing prescribing habits. Dr. Teutsch said the Government must play a leadership role with Federal agencies to move such changes into practice.

The Committee discussed Option B-2, asking whether HHS should have a role in establishing thresholds for the frequency and severity of adverse reactions that would trigger a requirement for PGx testing. Dr. Allen Rudman, FDA, stated that this is a case-by-case situation based on the therapeutic area.

Recommendation C addressed the fact that FDA does not regulate genetic tests developed in clinical laboratories, which means they can be offered to consumers without meeting the standards of safety and effectiveness required of other FDA-regulated tests. The options offered were:

Option #C-1: The Secretary should encourage FDA, CMS, and CDC to develop other mechanisms to enhance the oversight of laboratory-developed diagnostic (sometimes referred to as "home brew") genetic tests.

Option #C-2: The Secretary should clarify whether FDA has statutory authority to regulate laboratory-developed diagnostic tests and, if not, should encourage Congress to pass legislation closing this gap.

It was noted that SACGHS' predecessor, SACGT, worked extensively on the issue of oversight of genetic testing, but its recommendations were not adopted. SACGHS decided to circulate and review the pertinent documents developed by the previous committee. They agreed that it was important to clarify the gap in the oversight of laboratory-developed genetic tests during premarket review and approval. In the postmarket period, they are regulated under CLIA. The Committee also agreed to C-2, with the clarification that if it is decided that FDA does not have statutory authority to regulate laboratory-initiated tests, HHS should determine which agency ought to have this authority and should seek it from Congress.

Recommendation D concerned inconsistencies in human subjects protections regulations. The two regulations discussed were the HHS Common Rule, which governs clinical studies conducted with HHS funds; and FDA Title 21, which governs clinical trials conducted in preparation for FDA submissions. The proposed recommendation asked the Secretary to increase compatibility (i.e., harmonize) FDA and HHS regulations to minimize difficulties in study design and Institutional Review Board (IRB) approval that could complicate the development of PGx products. This was considered especially important for studies involving broad collaborations among Government, academia, and industry. The options were:

Option #D-1: The Secretary should make the harmonization of HHS and FDA regulations on the protection of human research subjects a high priority and encourage FDA and the Office for Human Rights Protections (OHRP) to work together to enhance the consistency of their human subjects research policies, regulations, and guidances.

Option #D-2: The Secretary should work with Congress to promote the passage of legislation creating a unified regulatory framework for the protection of human research subjects.

Dr. Michael Carome said that, in addition to its use by HHS, the Common Rule is promulgated by approximately 17 Federal Departments and Agencies, including DOD and Veterans Affairs, and changes would require negotiations with all of them. He questioned whether the two sets of regulations were greatly in opposition and wondered if the issue being raised was unique to PGx. Dr. Gutman said the problem is greater outside the area of PGx.

Dr. Andrea Ferreira-Gonzalez noted that although the FDA uses a more restrictive definition of human subjects, the agency recently developed a draft guidance on the use of anonymized specimens that waives the need for informed consent. She suggested asking the FDA to examine the draft guidance to assess whether it addressed the lack of harmony between the two regulations. Dr. Gutman agreed that this was a more reasonable suggestion than going to Congress and felt the Committee might be trying to fix something FDA was already working on.

The Committee agreed that SACGHS staff and the Task Force would identify the differences between the two sets of regulations, calling upon the OHRP and FDA *ex officios,* as needed. They would draft new language for Option D-1. Option D-2 was not approved.

Public Comment

John Corcoran
Examination Management Services, Incorporated (EMSI)

Mr. John Corcoran addressed two issues specific to the large population study. The first was the need to gather data on a national level across the spectrum of all data points. The second was related to the comfort and convenience of study participants. Mr. Corcoran stated that EMSI is a national organization that collects biospecimens and medical records across the country, working with more than 6,500 certified phlebotomists. Mr. Corcoran said they could offer study participants the convenience and comfort of having specimens and other data points collected in their homes or places of employment. He was present to make the Committee aware of EMSI's services.

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

Mr. David Mongillo said that ACLA represents local, regional, and national laboratories throughout the United States, whether independent or hospital-based. ACLA had several points to make concerning regulatory oversight of genetic testing. First, all clinical laboratory services are regulated under CLIA, which has requirements for appropriate training of laboratory personnel, quality control programs, and proficiency testing. CLIA requirements apply to laboratories that perform genetic tests. Further, CLIA regulations require that before introducing a new method or test that does not utilize a commercially available test kit, the laboratory must establish and document performance specifications for accuracy, precision, analytical sensitivity, and analytical specificity. Adherence to CLIA is ensured by onsite inspections every 2 years, either by a State agency or by a CMS representative. Penalties for noncompliance include the possibility of revocation of the lab's CLIA certificate.

Mr. Mongillo said ACLA wanted to emphasize that regulatory changes related to genetic testing should be made only after determining that such changes are focused on legitimate risks specifically related to genetic tests and that changes should be realistic, targeted, and effective. He said it's critically important that genetic tests continue to provide current benefits and realize the promise of great advances in diagnosis, screening, and patient monitoring. New regulations should not create undue burdens that would stifle innovation or restrict patient access to services.

Mr. Mongillo brought to the Committee's attention the question of how genetic tests will be defined for regulatory purposes. He said ACLA is concerned that an overly broad definition could sweep in many tests for which current regulatory oversight is substantial and adequate, such as for cholesterol, glucose measurements, basic blood counts, and DNA-based tests for non-heritable abnormalities. Mr. Mongillo closed by stating that ACLA pledged to work with the Committee, regulatory agencies, and health care community to address concerns without stifling innovation or affecting patient access and care.

Carol Rauch, M.D., Ph.D.
Medical Director of Microbiology and Chief of Clinical Pathology at Bay State Medical Center
College of American Pathologists

Dr. Carol Rauch spoke on behalf of the College of American Pathologists (CAP), a national medical specialty society representing more than 16,000 pathologists who practice anatomic pathology and laboratory medicine worldwide. They accredit more than 6,000 laboratories and have extensive expertise providing and directing laboratory services. Dr. Rauch said the College has been a leader in developing quality improvement programs for laboratories, including programs related to molecular pathology and cytogenetics. Pathologists have a keen interest in ensuring that gene patents do not restrict the ability of physicians to provide quality diagnostic services to patients and CAP believes that gene patents pose a serious threat to medical advancement, education, and patient care.

Dr. Rauch stated that when patents are granted, subsequent exclusive license agreements, excessive fees, and other restrictive licensing conditions prevent physicians and laboratories from providing genetic-based clinical testing services. As a consequence, patient access is limited, the quality of care is jeopardized, clinical observations as the basis for new discoveries are compromised, and training of health care providers is restricted. She said the recent trend of using patents to monopolize gene-based testing services is a radical departure from historical precedent in clinical laboratories and works against the goal of making these procedures widely accessible to the public. She said that because information about gene sequences is fundamental to understanding specific diseases, patent holders can essentially gain ownership of diseases.

Dr. Rauch said College members have received cease and desist notification letters from patent holders or exclusive licensees indicating that continuing their patient testing would be patent infringement. Examples of diseases for which testing has been halted due to patent enforcement include breast cancer, Alzheimer's disease, Canavan disease, and Charcot Marie Tooth disease.

The study by the National Academy of Sciences (NAS) Committee on Intellectual Property Rights in Genomic and Proteomic Research and Innovation recommended that policymakers take steps to prevent the increasingly complex web of intellectual property protections from impeding potential breakthroughs in genomics and proteomics research and public access to those findings. However, the College believes the study's recommendations fall short, as there are no specific protections for physicians and other providers of clinical laboratory services against gene patent infringement enforcement.

CAP called upon SACGHS to carefully review the information in the NAS report on the clinical impact of gene patents, consider further investigation of this impact, and develop recommendations for the Secretary of HHS to address the growing negative impact of gene patents on clinical testing.

Michele Schoonmaker, Ph.D.
Association for Molecular Pathology (AMP) Professional Relations Committee

Dr. Michele Schoonmaker stated that AMP is an international medical professional association representing over 1,400 physicians, doctoral scientists, and medical technologists that perform genetic testing, as well as other testing based on knowledge derived from molecular biology, genetics, and genomics. The Executive Council and the Professional Relations Committee of AMP reviewed the SACGHS document on undertaking a large U.S. population cohort project and supported the concept for the study. They planned to provide detailed written comments, but wanted to comment publicly on two facets of the report: clinical validations of research findings and patient safety.

Dr. Schoonmaker stated that as molecular pathology laboratory professionals, AMP's members would serve as the interface between the public and scientists if the study were to go forward. Consequently, policy decisions that touch on the Health Insurance Portability and Accountability Act (HIPAA) and CLIA are of great concern. She said that while the draft report states that an investigator has no therapeutic relationship with the subject, AMP members do have a relationship with their patients, with all the attendant clinical, legal, and ethical responsibilities. They direct CLIA-certified laboratories that would be appropriate locations for clinical validations of research results prior to reporting to subjects. AMP members were prepared to engage in substantive discussions to define the clinically relevant information that should be returned to individual subjects. AMP felt that the draft report focused heavily on the scientific aspects of the project and recommended that the processes and policies relevant to clinical implications and patient safety be addressed. Dr. Schoonmaker said AMP is committed to the success of the project and in translating its results for the public health. She invited the Committee to contact Dr. Wayne Grody, Chair of the AMP Professional Relations Committee, for information.

Judith Lewis, Ph.D., RNC
International Society of Nurses in Genetics (ISONG)

Dr. Lewis spoke on behalf of ISONG, an international nursing specialty organization dedicated to fostering the scientific and professional growth of nurses in human genetics. ISONG submitted comments on the large population cohort project, which they supported. They stated that it was essential to engage the general public and the nursing community before moving forward with the study and they offered several recommendations for strengthening and clarifying the document.

The first suggestion was to broaden "health care providers" to providers and patient care personnel, including nurses, social workers, psychologists, and other health care professionals. They recommended rewording the following statement to make it stronger: "The public's willingness to participate in a large population project will be assessed before embarking on such an expensive endeavor." Dr. Lewis said that measures to assess the public's interest should include focus groups with representative community-based agencies, including lay health care workers. Also, since nurses are present throughout the health care system, it's essential to seek input from nurses and nursing organizations on all aspects of the enrollment of various subpopulations. ISONG asked that nurses be included in ongoing consultation with the international community and the private sector to explore opportunities for collaboration and that nurses and nurse researchers be identified as important members of a multi-disciplinary team approach to the project. They asked that nurses be included in an independent committee for the project's duration.

Full Committee Discussion of Pharmacogenomics Report, Continued

Recommendation E stated that: "HHS should promote public access to data on pharmaceutical products that have failed to demonstrate effectiveness in studies involving a general population cohort but might be successful in specially tailored clinical trials using PGx technology and targeting specific subpopulations. With the cooperation of the pharmaceutical industry, HHS should establish a publicly accessible database cataloging these data. The database's intent will be to rescue failed pharmaceutical products by encouraging diagnostic device manufacturers to collaborate on research, leading to the development of companion medical products. Submission of data should be voluntary, and provisions should be made to limit the extent of disclosure of confidential and/or proprietary information."

Dr. Winn-Deen suggested that this recommendation would not apply to typical pharmaceutical company research. HHS has no authority in this area, and the datasets from private trials belong to the drug companies. She said this recommendation might apply to cooperative group studies conducted using NIH

funds in which samples were taken. However, most cooperative group studies are conducted on drugs that have already obtained FDA approval. Dr. Teutsch stated that diagnostic companies might wish to get in touch with drug study sponsors to develop collaborative relationships to do further work. He suggested tying the recommendation into this process. Dr. Collins stated that neither pharmaceutical companies nor NIH researchers need further stimulus from HHS to obtain drug approval. Ms. Agnes Masny agreed, but suggested that the recommendation move to Option A-1 and become an example of an opportunity for co-development. The Committee agreed to delete the recommendation.

Dr. Winn-Deen led a discussion on whether **Recommendation F** was needed, which would state that further efforts are needed to optimize the use of PGx methods to support the approval of new indications for existing drugs. The Committee felt that this recommendation was only applicable in the post-marketing phase, which was addressed in Recommendation 5-A. They decided to add language to 5-A on the application of PGx to existing drugs.

Recommendation 3, developed at the previous meeting, stated that FDA should work to identify a genetically diverse set of patients for clinical trials that goes beyond self-identified racial and ethnic categories. FDA should also develop guidance to encourage the inclusion of diverse populations in premarket and postmarket trials. In addition, the field should work toward understanding the actual genetic basis for responses to drugs and should not use race as a surrogate marker.

Recommendation G concerned Phase IV clinical trials for PGx. The Committee discussed whether FDA's system for postmarket surveillance for adverse drug reactions should be improved:

Option #G-1: FDA should mandate phase IV clinical trials for pharmaceutical products developed in conjunction with diagnostic tests. Furthermore, HHS should ensure that FDA has appropriate resources to monitor compliance of required studies.

Option #G-2: The structure of the current FDA Adverse Event Reporting System (AERS) is difficult to search and use. FDA should modify the AERS system to enhance its usability and utility. For example, FDA should continue with ongoing efforts to develop a standardized set of terminology (e.g., "myocardial infarction" instead of "heart attack"). The new standardized terminology should facilitate data searches and analyses and identification of potentially problematic adverse event patterns. To ensure that data submitted to the new AERS are accurate and represent actual adverse drug events, only health providers should be permitted to submit reports. FDA may consider developing a separate adverse events reporting system to allow the general public to submit problems arising from use of medical products.

Dr. Rudman said FDA was looking into conducting the Phase IV process in a systematic manner, rather than on a case-by-case basis. He felt that Phase IV clinical trials should not be mandated because they may not be necessary if safety and effectiveness have already been demonstrated. Dr. Rudman recommended seeking the advice of Dr. Paul Seligman in the Office of Drug Safety for an opinion on Option G-2. Dr. Gutman agreed that in Option G-2, emphasis on drugs was appropriate, because diagnostics and device issues were already being examined. He described FDA's efforts to convert to an electronic medical device reporting system. He also said that a new system was being piloted to explore active surveillance rather than passive surveillance.

Dr. Collins described the importance of an AERS reporting system and the ability for FDA to link back to individuals experiencing adverse reactions. By obtaining biospecimens, it might be possible to determine why certain reactions occurred. He said that FDA and NIH had been in discussion on this topic. He stated that genome association studies make it possible to determine causality based only on

several hundred cases. The current AERS system does not have the necessary searchability to conduct this kind of followup for common adverse reactions. Dr. Teutsch felt Recommendation G was not specific to pharmacogenomics. He agreed with Dr. Collins that the AERS system works well for rare events, but is inadequate for finding common problems, such as myocardial infarctions, which are not likely to be reported in the current system.

Dr. Winn-Deen explained that Recommendation G's link to PGx was the potential for research to be conducted that could find a biomarker for an adverse reaction, possibly leading to development of a companion diagnostic. Dr. Rudman added that another important PGx issue is the ability to determine efficacy. Dr. Randhawa suggested broadening the recommendation to include safety and efficacy and extending its reach to other relevant HHS agencies. The Committee agreed that more work by the Task Force was needed on this recommendation.

Recommendation H stated that oversight is needed to address potential public health concerns about PGx tests offered directly to consumers without the involvement of a health provider:

Option #H-1: Due to the complexities of interpreting gene-based test results, FDA should require the labels of PGx tests offered directly to consumers to include information sufficient to enable consumers on their own to make informed decisions about use of the product, accurately interpret the results, and make informed health decisions based on the test results. FDA should take steps to prohibit direct-to-consumer (DTC) marketing of any PGx tests that could not be appropriately and safely used by a consumer without the involvement of a health provider.

Option #H-2: FDA should require as a condition for pre-market approval that companies offering PGx tests directly to consumers without the involvement of a health provider should make available telephone-mediated genetic counseling.

Option #H-3: HHS should support measures for CLIA-waived tests that are approved for sale over the counter to be allowed to be directly marketed to the consumer, as these tests must already meet the requirements for having detailed directions for use and interpretation of the results. All other tests (low, moderate, and high complexity) should involve a consultation with a health professional.

Option #H-4: Due to the complexities of interpreting gene-based test results, the Secretary should encourage Congress to pass legislation prohibiting the marketing of PGx tests offered directly to consumers without the involvement of a health provider.

Dr. FitzGerald felt Option H-1 wasn't viable. He pointed out that the Committee already discussed the difficulties of labeling, and he felt consumers should not have to deal directly with these problems. He asked what criteria would be in place for those conducting genetic counseling by telephone and felt that Option H-2 was also not viable. Dr. Leonard said that since physicians are not integrating PGx into clinical practice, the Committee should not advocate for taking away the right of consumers to have access to PGx information. She suggested encouraging the FDA-FTC collaboration effort to examine the marketing, use, and safety of PGx tests.

Some members of the Committee expressed the opinion that the general public may not be ready to make decisions about the risks and benefits of PGx products (Option H-3). Others felt that the Committee was not in a position to prevent people from taking DTC tests. A number of Committee members thought that it would be better to focus on educational materials in the report, rather than DTC marketing.

The Committee decided to discuss **Recommendation I,** below, at a later time:

Option #I-1: Studies should be conducted to examine the effect that future PGx products will have on the FDA and the Federal Trade Commission's ability to monitor direct-to-consumer marketing of PGx tests. Specifically, the ability of the two organizations to act on misleading claims should be assessed.

Option #I-2: The Secretary should encourage Congress to provide FDA and the Federal Trade Commission with sufficient resources to monitor direct-to-consumer marketing of PGx tests and act on any misleading claims.

Recommendation J stated that: "HHS should convene a group of experts (comprised of academia, industry, and other private sector organizations) to develop criteria for prioritizing all PGx research needs according to feasibility, public health need, and impact on public health. The group should also assess both current and potential PGx projects and rank them according to their relative priority. The group's ranking should be used by HHS agencies for decisionmaking regarding support and resources."

The Committee was not clear whether such a group of experts was already in place and did not want to discuss the recommendation until more information was obtained. Additional input from Dr. Rochelle Long about current NIH activities was suggested.

Recommendation K addressed whether additional research is needed on genome-wide biochemical pathways, stating: "Drug metabolism is a complex process that typically involves multiple biochemical pathways. Understanding genome-wide pathway interactions will be key to the success of PGx. PGx research efforts at NIH should focus on improving our knowledge of the protein-protein interactions occurring between biochemical pathways. The knowledge gained should be applied to PGx products developed in the future."

Dr. Collins stated that the word "metabolism" should be removed from the recommendation because the issue is broader and includes variations in the target and all other things involved in the pathway. He said this recommendation is a central goal of the Pharmacogenomics Research Network (PGRN). The collaboration is associated with the database Pharm-GKB, which attempts to collect information about pathways and examine how variations in particular genes and proteins might play a role in differential drug responsiveness. This issue was already a very high priority. The Committee decided that additional input might be needed from Dr. Long.

Recommendation L stated that HHS should provide more assistance by fostering PGx technologies for neglected diseases in both underdeveloped and developed countries, as follows: "NIH, in collaboration with FDA, should support research that encourages the development of PGx products for diseases not actively being addressed by research and development in the private sector. Additionally, the Secretary should urge Congress to provide the private sector with additional economic incentives, such as extension of patent protection and tax incentives, to encourage research and development of PGx products for these neglected diseases." The discussion also took into account **Recommendation 4**, which asked for an amendment to the Orphan Drug Act so that an FDA designation of orphan drug status would trigger orphan status for the companion diagnostic.

Dr. Joseph Telfair commented that organizations such as the American Public Health Association (APHA) are already addressing these issues through their formal policies. He said the Committee needed more information from APHA. Dr. Leonard said she was not comfortable with recommending that NIH direct more attention to neglected diseases than to the leading killers of Americans, such as cardiovascular disease. Ms. Suzanne Goodwin was tasked with contacting speakers who could present more data on this subject to the Task Force. Dr. Tuckson pointed out that the Committee would need to prioritize its efforts and could not address every health care problem.

Dr. Winn-Deen asked the Committee to consider issues relating to the measurement of health outcomes, described in **Recommendation 5**. Dr. Randhawa pointed out that the recommendation emphasized prospective randomized studies to determine whether promising PGx findings translate into improved patient care. He said it's not clear that this is the best study design for translational research. Dr. Winn-Deen said that The Lewin Group would be asked to look at different categories of outcomes research and add this information to the literature review.

Dr. Barbara McGrath reminded the Committee of Dr. Woodcock's point that there must be a paradigm shift away from randomized controlled trials. She wondered if NIH and FDA were ready to accept this change. Dr. Tuckson suggested that perhaps a more important question was whether CMS and other purchasers of health care would accept a paradigm shift. Dr. Teutsch expressed the opinion that it is important to develop a methodology for good alternatives to RCTs that are credible and have dealt with issues of validity.

Recommendation 6 concerned increased usefulness and searchability of existing databases. Dr. Sherrie Hans encouraged the Committee to take into account all Federal databases, including the Department of Veterans Affairs' (VA) electronic medical records on almost 7 million veterans. She stated that collaboration between VA and HHS could provide opportunities for health outcomes research. Dr. Telfair stated that he would refer staff members to information on databases in the HHS system.

Dr. Winn-Deen displayed a slide on **Recommendation 7**, which addressed the evidence base for the economic value of PGx. She asked that any comments be sent to SACGHS staff members.

The Committee discussed **Recommendation M,** which stated that: "HHS should take steps to ensure that staff with relevant policy and programmatic responsibilities are sufficiently knowledgeable about PGx issues to meet the coming challenges expected from the integration of PGx technology into routine clinical practice. PGx knowledge among HHS staff can be enhanced through training programs, educational modules such as formal coursework, seminars, workshops, case studies and practice models, and attendance at PGx conferences. Efforts should also be made to recruit individuals with expertise in genetics and PGx for research, medical product review, and clinical outcomes analysis."

Several Committee members felt strongly that the recommendation was pejorative and implied that HHS staff members do not take the initiative to educate themselves about new areas of importance. Others suggested that the wording be changed to lay the groundwork for continuing education in PGx. The Committee did not believe that a recommendation directed solely at educating HHS staff was necessary.

The Committee did not address **Recommendation 8** on the public's acceptance of PGx technologies because it had been discussed sufficiently. Dr. Winn-Deen moved on to **Recommendation N,** which stated that: "HHS should convene a group of experts to explore liability issues associated with PGx products and to devise strategies and recommendations to address the societal and legal challenges associated with the clinical use of PGx technologies."

Dr. Winn-Deen stated that, as with any other medical procedure, there is liability potential associated with PGx technologies. She asked whether there are liability issues for physicians who don't order a test that is recommended for use in conjunction with prescribing a drug. If the patient refuses a test and experiences an adverse event, is there liability? She asked whether "standard of care" begins when FDA approves a test and a drug, when insurance companies pay for it, or when there is a consensus among providers that a test be used in a certain way? Dr. Leonard asked about liability when genetic variability information is on a drug label without dosing recommendations. She said there is not enough information on the label for clinicians to use the drug effectively. Dr. Evans commented that the Secretary is not responsible for setting the standard of care and he suggested focusing on practical advice. Dr. Tuckson asked the Committee to consider which of the recommendations would support the involvement of medical societies in writing guidelines and standards of care.

Dr. Winn-Reed noted that the Committee had already discussed **Recommendations 9 – 13**. They related to PGx best practices, distribution of PGx information, interpretation of test results, Medicare coverage of PGx tests, and inclusion of PGx data in electronic health records, respectively. She invited those who had not done so to provide comments to SACGHS staff. She asked Committee members and *ex officios* to provide feedback to The Lewin Group on the literature review.

Dr. Tuckson thanked Dr. Winn-Deen for chairing the PGx Session and stated that she would be transitioning off as Chair of the Task Force but would continue work as an *ad hoc* member.

Large Population Studies Session

Update on SACGHS Draft Report on Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment, and Disease
Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Tuckson stated that the Committee's inquiry in this area was shaped by a request from the NIH Director, Dr. Elias Zerhouni. The Director asked that SACGHS identify key policy issues associated with undertaking a large U.S. population cohort project on genes, environment, and disease; and provide advice on the scientific, public, and ethical processes and approaches that might be used by HHS policymakers to make optimal decisions about such an effort. A draft report and recommendations were prepared and reviewed at the previous meeting and decisions were made about conducting a broad public outreach to solicit comments. The report was released for public comment on May 22, with a deadline for responding by July 31. Comments were sought through the SACGHS website, a "Dear Colleague" letter to over 1,000 individuals and organizations, selected media through the NIH Office of Communications, and announcements in the *Federal Register* and the *NIH Guide for Grants and Contracts Notice*. The report and request for comments were also disseminated through a number of Government, academic, media, industry, and consumer listservs.

Environmental Components of Gene-Environment Studies
David Schwartz, M.D.
Director, National Institute of Environmental Health Sciences

Dr. Schwartz addressed four issues: 1) the need and importance of precisely measuring environmental exposures when considering susceptibility for a variety of diseases; 2) how the Exposure Biology Program within the Genes and Environment Initiative (GEI) is taking important steps to develop precise measures of exposure; 3) how the Exposure Biology Program could work with the Committee on the

issue of population-based studies; and 4) policy issues relevant to genetics and environmental concerns about the etiology of disease. He stated that a focus on environmental exposures when considering genetic risk factors would accelerate basic discoveries about the etiology of disease. He referred to Walt Willett's article in *Science* (2002), which stated that between 70 to 90 percent of the origin of major diseases in the United States is found in behavior and exposure. Less than 5 percent of these complex diseases (e.g., colon cancer, stroke, heart disease, and diabetes) are caused by single gene mutations. In addition, a meta-analysis of twin studies indicates that 20 to 50 percent of the etiology of asthma, diabetes, prostate cancer, breast cancer, and Alzheimer's disease is factors that are environmental, rather than genetic.

Dr. Schwartz stated that studies of generalized forms of asthma have demonstrated a genetic etiology. The loci that have been associated with the development of asthma throughout the genome indicate that almost every chromosome has a location associated with the risk of developing asthma. Multiple exposures account for the disease's etiology, which is a very complex biological process. There are many phenotypes of asthma, from the development of airflow obstruction, to wheezing, to the requirements for medication. A study of environmental exposures could create a narrow pathophysiologic phenotype that would facilitate understanding the genes and biology that underlie the disease processes. This approach has been successful in leading to an understanding of specific aspects of the human biology of disease pathogenesis, individual susceptibility, the impact on prognosis and treatment, and the distribution of disease in populations.

With the support of Secretary Leavitt, Dr. Zerhouni, and NIH Institute Directors, Dr. Collins and Dr. Schwartz developed the GEI. It examines genetic and environmental variation as a way of understanding the etiology of complex human diseases. The Initiative is combining whole genome association studies with more precise measures of exposure as a way of looking at the risk factors for complex human diseases. The GEI has an Exposure Biology Program that is developing personalized biological measures of exposure to allow researchers to look at genetic variation and environmental exposures in combination to assess the risks of developing disease.

As an example, Dr. Schwartz said the Hepatitis B virus places individuals at risk of developing hepatocellular carcinoma. It had been recently discovered that exposure to aflatoxin through aspergillus flavus, a spore that contaminates food, also places individuals at risk of developing Hepatitis and hepatocellular carcinoma. This was discovered by identifying biomarkers of exposure to both the Hepatitis virus and aflatoxin. Examination of dietary history had not revealed the relationship. Dr. Schwartz said this demonstrates the importance of biomarkers for understanding the contribution of dietary factors to the risk of disease. It took researchers 25 to 30 years to make this association and develop preventive strategies. He expected that the Genes and Environment Initiative will compress such timelines to 5 years.

Currently, researchers are able to measure the human environmental exposures of polyaromatic hydrocarbons (PAHs), particulates in the air, dietary factors, and physical activity. Their association with the risk of developing various diseases is measured through questionnaires and by monitoring substances in blood, urine, air samples, DNA adducts, and protein adducts. However, this approach makes it difficult to understand the mechanisms that underlie the associations or to predict disease pathogenesis and progression. These exposure data are limited in that they rely heavily on questionnaire information and environmental assessments. They lack sensitivity and specificity, are qualitative and not quantitative, and lack precision. They do not address the contributions of diet or lifestyle. This limits researchers' ability to make definitive conclusions about relationships between exposure and genes to the development of human disease.

Dr. Schwartz said the Genes and Environment Initiative will help researchers develop mechanistic linkages that are better predictors of disease risk. Two efforts are taking place in the Exposure Biology Program. One is the development of new technology, which will take approximately 4 years. The second effort is adapting existing technologies to various exposures that are important to the risk of developing disease. Researchers expect to develop assessments of exposure that are personalized and that will indicate whether someone is biologically responding to specific exposures. Dr. Schwartz stated that these exposure assessments would provide tools useful to the large population study, as well as case control and cohort studies examining diet, nutrition, physical activity, and environmental exposures.

Dr. Schwartz closed by stating that the policy considerations that relate to environmental assessment address privacy and confidentiality of data, public involvement in the studies, consensus policies for data access and sharing, public and private dissemination of data, and determining the level of public participation beforehand.

Social and Behavioral Components of Environment in Gene-Environment Studies
John K. Hewitt, Ph.D.
Institute for Behavioral Genetics at the University of Colorado

Dr. Hewitt discussed the types of issues addressed by behavioral geneticists, who compare genetic influences and environmental influences. He spoke to the Committee about shared environmental variation and non-shared environmental variation in families. Shared environmental variation makes family members more similar to each other. Non-shared environmental variation makes individuals in the same household different from one another.

Twin studies for common disorders find a large contribution from genes for most traits, such as body mass index (BMI), IQ, or heart rate. Studies of common phenotypes indicate that a large amount of environmental variation differentiates members of the same household. Individuals who share a family environment and are genetically identical across the entire genome (monozygotic or MZ twins) are quite similar, but not identical. Individuals who share a family environment, with only half of their genes similar, are often very different. Dr. Hewitt stated that environmental differences within the same families might be as important as environmental differences across different families.

Using the example of BMI, he said there are substantial genetic influences throughout adulthood, with some genetic influences in middle age that are independent of genetic influences in younger adults. Individuals who are leaner for environmental reasons early in adult life are unlikely to sustain their leanness. Environmental influences must be chronic to be influential over long periods. Dr. Hewitt said that the influence of the environment and of genes may change during development.

He described the environments measured by social scientists. As an example, he said the national longitudinal study of adolescent health (AddHealth), led by social scientists at the National Institute of Child Health and Human Development (NICHD), has focused on characteristics of the school, the family, romantic relationships, the neighborhood and community, peers, and the work environment. In the school environment, they measured such factors as the percentage of students who smoke in school, school cohesion, demographic composition, and socioeconomic status. In the family, they measured such factors as parents' health, child maltreatment, household structure, shared activities, and closeness. In the neighborhood, they measured crime, violence, religious participation, and poverty.

Dr. Hewitt stated that epidemiological studies that measure environments and correlate them with outcomes are always at risk of drawing invalid inferences if the environments are correlated with

differential genotypes. Behavior genetics analyses indicate that the genotype of the individual plays a role in selecting from the available environments and developing a gene-environment correlation. This is of interest when looking at diet, nutrition, and activity levels. He said there is an interaction at play; the individual chooses from a range of options. Any large-scale population cohort study that measures genes and environment must make sure the design and analytic strategy are open to that interpretation.

Dr. Hewitt suggested to the Committee that the large population study be enhanced by adding a deliberate, systematic sampling of genetically identical pairs of twins whose environments could be assessed in great detail. The use of identical twins would avoid the confounding of the gene-environment correlations that are typically found in large-scale, region-to-region studies.

Q&A

In response to a question on assessing shared environment in a study of 1 million people, Dr. Hewitt replied that questionnaires and interviews can assess the important variables of parental psychological disorders, parental substance use and abuse, parental style, and maltreatment of children. Another significant class of variables relates to school, neighborhood, and community characteristics, which, to some extent, can be obtained through databases from census tracts.

Dr. Schwartz added that the Genes and Environment Initiative plans to develop the biological markers of response to various forms of stress in the environment. They hope to identify the biological fingerprint that places an individual at excess risk of developing a disease based on a specific genetic susceptibility.

Dr. Telfair asked both speakers for their opinions on the areas that should be prioritized in the large population study, given the resource limitations. Dr. Hewitt said it depends on the outcomes they are most interested in. He noted that BMI is related to a wide range of common diseases and he recommended studying diet and physical activity. Dr. Schwartz noted two components: the opportunity to identify and alter environmental exposures that are relevant to the risk of developing disease and identifying disease at a much earlier stage.

Dr. FitzGerald asked the speakers if national databases in other countries show proof of principle precedent for their suggestions. Dr. Schwartz replied that there is proof of principle that specific exposures and specific gene changes are associated with the risk of developing disease or the likelihood of preventing disease from occurring, although not in relation to large population studies. Dr. Hewitt stated that there are large-scale national studies of twins in Norway, Sweden, and Denmark, but they are different from the proposed large-scale study in the U.S.

Dr. Randhawa asked about the utility of determining that some individuals have a high-risk genotype for BMI, since it is already recommended that people eat a healthy diet and exercise. Dr. Hewitt said the intent for genetics would be to develop pharmacological interventions that might help control behaviors that lead to obesity. Environmentally, no one has devised an intervention that makes a clear difference in obesity. Dr. Schwartz replied that the results of studying BMI would allow public health officials to effectively target populations for more intensive interventions.

Dr. Licinio asked the speakers if they agreed with the number of proposed study subjects, i.e., 1 million individuals. Dr. Hewitt said yes, although he was making the case for enhancing the large-scale study with a more focused study using MZ twins. Dr. Schwartz agreed with the large scale of the study.

Dr. Tuckson thanked the speakers and adjourned the meeting for the day.

Tuesday, June 27, 2006

Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Tuckson stated that the first session would address the impact of patents and access issues on genetic technologies, a priority identified in March 2004. The Committee postponed exploration of the issue because of the ongoing National Academy of Sciences (NAS) investigation by the Committee on Intellectual Property Rights in Genomic and Proteomic Research and Innovation. At the previous SACGHS meeting, Dr. David Korn presented the findings of the NAS committee. After a careful review of the NAS report by a SACGHS task force, the Committee concluded that while the NAS report explored the research issues related to gene patents and licensing thoroughly, the clinical practice and economic issues warranted further examination. Before deciding whether to move forward on the issue, the Committee sought additional background information and invited several experts to present at the meeting. Dr. Tuckson turned the floor over to Dr. Debra Leonard, Chair of the SACGHS Task Force on Patents and Access to lead the session.

Patents and Access Session

Patenting and Licensing Fundamentals and the Nature of the Access Problem
Debra Leonard, M.D., Ph.D.
Chair, SACGHS Task Force on Patents and Access

Dr. Leonard reiterated that the NAS recommendations did not fully address clinical practice and economic issues and added that the recommendation relating to diagnostic testing (urging the establishment of procedures to enable results from patented tests to be independently verified) was, in SACGHS' assessment, of questionable feasibility. She described the three presentations to follow and asked the Committee to use the information presented as background for considering whether SACGHS should make recommendations to the Secretary.

Dr. Leonard presented basic information on gene patents and patent enforcement. Patents grant the right to exclude others from making, using, or selling inventions for a limited period of time. An "invention" is anything made by man that is new, non-obvious, and useful. Patent protection is granted by the U.S. Constitution to promote the progress of science and useful arts. Inventors must publish or make available to the public the nature of their inventions. Patent holders have the options of completely restricting use by anyone (including themselves), creating a monopoly situation in which the patent holder is the only user, or providing an exclusive license to a single user. Other options include pure competition, in which there is broad licensing and use of the patented information, and holding for the public good, which allows anyone to use the information.

The types of DNA currently being patented include the chemical composition of DNA, RNA, messenger RNA, cDNA sequences, probes or markers, transgenic organisms, vectors that can be used for cloning or gene therapy, cell lines, and microbial strains. DNA methods being patented include genetic diagnostic methods, methods of using probes or test kits, and therapeutic processes.

Gene patents are a rapidly growing subset of broader DNA patents. Such patents claim the observation of an individual's genetic makeup at a disease-associated locus when the observation is being made for the diagnosis of a specific disease. It permits true monopolization of a medical service, and in many cases, is almost a monopolization of a disease. Dr. Leonard said gene patents are held for BRCA-1 and 2 for breast cancer, HNPCC for colon cancer, Alzheimer's disease, compulsive disorders, hypertension genes, Gaucher's disease, and Canavan disease.

Dr. Leonard described her experiences with patent enforcement as an M.D. and a molecular biologist. The focus of her medical practice is on the translation of genetic and genomic science into diagnostic tests for patient care. She clarified that she is not a researcher and described how gene patents have limited her medical practice. She was previously able to test for Alzheimer's disease, but in 1997, was required to send this testing to Athena Diagnostics, which patented a test and became the single provider of this service. She said the patenting companies are not limited in what they can charge for testing. Athena Diagnostics also exclusively licensed the patent for testing of spinocerebellar ataxia type 1, which can cause movement disorders. SmithKline Beecham Laboratory obtained exclusive rights to three patents for hemochromatosis testing. They charged an up-front fee of $25,000, plus a per-test fee, which prevented Dr. Leonard's lab from continuing to perform testing. Another patent stopped them from testing for Canavan disease and from conducting a broader screening panel for Jewish women those tests for a number of diseases. Myriad Genetics is now the patent holder for the BRCA1 mutation and is the exclusive provider of full BRCA1 sequence testing. This patent also monopolizes BRCA2 testing, because labs need to be able to test for both. Currently, the only place to have full gene sequencing done for BRCA1 and BRCA2 in the United States is Myriad Genetics. Dr. Leonard said that patents also affect disease testing for leukemias and lymphomas, and noted the potential for patent enforcement for spinal muscular atrophy, myotonic dystrophy, EGFR, Gleevek, BCRAbl mutations, and many other genes that predict disease risk.

Dr. Leonard said that a "sole provider" of a medical service eliminates competition for pricing, reduces innovation and testing methods, dictates medical practice, constrains clinical observation, slows the discovery process, limits the education of medical students and residents, and is not in the best interest of the public health. She contrasted current medical genetics—a focus on diseases caused by mutations in a single inheritable gene—with the future of genetic medicine, which will based on understanding the role of genetic variations in common diseases that are affected by many genes. She stated that gene patents will limit this future because one provider will set national practice standards. In addition, there will be no competition for test cost, quality, or method; and advances in scientific knowledge gained through broad clinical practice and observation will be limited, as will medical education, medical practice, and the broad availability of genetic testing.

Dr. Leonard reported on the recent Supreme Court decision on LabCorp versus Metabolite Laboratories, which concerned a patent on the correlation between homocysteine and vitamin deficiencies. The case was dismissed as "improvidently granted" and sent back to the lower courts. Dr. Leonard read from a dissenting opinion, which stated, "... that correlation is an unpatentable natural phenomenon..." and, "To fail to [decide this case] threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment and may force doctors to spend unnecessary time and energy to enter into license agreements, may divert resources from the medical task of health care to the legal task of searching patent files, and may raise the cost of health care while inhibiting its effective delivery."

Dr. Leonard presented philosophical questions for the Committee's consideration: Should gene patents be granted? Are gene patents inventions or are they claiming a product of nature? Do gene patents inhibit

or promote the progress of science? Are patent incentives needed for discovery or clinical implementation of patented genetic information? Should exclusive licensing of fundamental medical knowledge be allowed to continue? Is sole ownership of a disease in the best interest of the public health? She stated that changes could be made through the courts, legislature, or the Executive Branch by revising the practices of the U.S. Patent and Trademark Office (USPTO). One specific legislative change could be to exempt medical personnel who perform genetic tests from patent infringement actions. This would extend a 1996 law that protects physicians from patent infringement lawsuits when they are using medical process patents. Pathologists and laboratorians were specifically excluded from this protection when the law was drafted. Mandating broad licensing at reasonable royalty rates to prevent exclusive licensing for genetic tests is another potential change that would address current problems.

Data and Analysis of the Impact of DNA-Based Patents on Access to Genetic Technologies and Services

Mildred Cho, Ph.D.
Associate Director, Stanford University Center for Biomedical Ethics

Dr. Mildred Cho summarized the results of studies conducted at the University of Pennsylvania in 2000 and 2001 on the impact of patenting activity on the practice of clinical genetic testing and on research and development. She and her collaborators looked at cost and access to testing services and the ability to conduct research and development to improve clinical genetic testing services, and assessed whether intellectual property protections provide incentives for the development of new genetic tests.

The two studies surveyed medical laboratories that provide clinical genetic tests in the U.S. Study 1 examined the impact of patents on the labs' abilities to provide clinical genetic testing services. Study 2 examined the labs' provision of genetic tests for a specific disorder, i.e., hereditary hemochromatosis.

The results of Study 1 indicated that 65 percent of the labs surveyed had been contacted by a patent or license holder and 25 percent were prevented from continuing at least one test service. For-profit testing companies were more likely to report being prevented from testing than university laboratories. A total of 11 tests were affected, including BRCA1/BRCA2, ApoE, Canavan disease, SCA, FraX, and Myotonic dystrophy. Of the patents involved, 10 were held by universities, 7 resulted from research funded by the Government, and 4 were held by not-for-profit companies. Of the labs that were contacted by a patent holder, more than half decided not to perform or develop the test.

The researchers sought opinions from laboratory directors about the effect of patents on their work. They were asked about the patient's ability to access testing; whether the costs had gone up or down; whether patents affected the quality of testing; and whether there was an impact on their ability to develop new tests, share information with other laboratories, and conduct research. The responses were overwhelmingly negative, with respondents citing lower access, higher costs, and lower quality.

Study 2 examined the effect of patents by Mercator Genetics, which developed a method of positional cloning and discovered an association between HFE mutations and hemochromatosis. Three patents were issued to Mercator in early 1998 for genetic testing of two of the more common variants. Mercator went out of business and merged with Progenitor. Progenitor licensed the patents for clinical testing exclusively to SmithKline Beecham Clinical Laboratories (SBCL) for an up-front payment, and payment guarantees were continued until a kit became available for use by clinical labs. In the summer of 1998, SBCL began enforcing patent rights. Sublicenses cost $25,000 for academic labs and 5 to 10 times more than that for commercial labs, plus royalties of up to $20.00 per test. In the fall of 1999, SBCL was sold to Quest Diagnostics. The patents were not actively enforced for several years.

In April 1999, Bio-Rad Laboratories acquired the patent portfolio from Progenitor, subject to the exclusive clinical-testing license held by SBCL. In 2001, Bio-Rad began offering a test kit for the mutations C282Y and H63D. The company offered to license labs to perform testing without its kits, but at a cost that made the kits more attractive. At the time of Study 2, 54 of the 58 labs that were performing HFE testing received a letter from SBCL. More than one quarter of labs had not developed and were not performing the HFE test because of patent enforcement. Over half of the labs that were performing the HFE test (60 percent) had introduced it before the first patent was issued in 1998 and after the key findings were published in 1996 about the association between the mutations and the disease. The mean time from publication to adoption of the test was very rapid (14 months).

According to Dr. Cho, the studies demonstrated that patents and licenses have had a significant effect on the provision of clinical genetic testing services. She said lab directors think that cost, quality, access, and research have all been adversely affected. Labs don't appear to require patents as an incentive to rapidly move findings into clinical practice. However, patents may provide incentives to conduct the research necessary to identify genes associated with disease.

A third study examined licensing by surveying a subset of institutions in the patent database that held patents in a particular class relevant to DNA tests: class 435/6, for molecular biology inventions that involve nucleic acids. The subset was the approximately 100 institutions that were assigned three or more patents. The researchers interviewed patent holders by telephone about their licensing practices at 27 not-for-profit institutions and 19 for-profit institutions. Dr. Cho said the results indicated that a very small proportion of not-for-profit institutions filed patents. However, for-profit institutions file almost all of the possible inventions that could be patented. Behavior concerning licensing is very different. Non-profits tend to license exclusively, while for-profit institutions tend not to provide exclusive licenses.

The results of Study 3 indicated very little agreement among license holders about what constituted a "research tool" versus a "target," reflecting the difficulty of creating a clear distinction between clinical practice and research in the area of DNA diagnostics.

Dr. Cho and her collaborators concluded that most DNA-based interventions may not be controlled by patents and exclusive licenses, especially in the non-profit sector. However, clinically important patents on diagnostics may be more likely to be subject to patents. Dr. Cho noted that there are few other studies of the impact of patents and licenses on clinical practice. She closed by stating that one recent study found that nearly 20 percent of human genes are claimed as U.S. intellectual property.

The Role and Economic Impact of Gene Patents in Drug and Diagnosis Development
Mark McCamish, M.D., Ph.D.
Chief Medical Officer, Perlegen Sciences

Dr. Mark McCamish explained that Perlegen is a private company that conducts extensive research on polygenic contributions to disease and he emphasized the need for patent protection to support research in this area. He stated that because of the variability in drug response, a "one size fits all" approach to drug treatment is not working. He said the blockbuster model of drug development is dying and that many failed drugs actually work better than approved drugs for treatments of certain subsets of people. He expressed the view that linking a drug to a genetic test that subclassifies a specific patient population and gaining the intellectual property rights can expand the protection of that drug for many years, allowing industry to support further development of the targeted treatment.

Dr. McCamish said Perlegen is focused on improving patient care through better selection of therapies, changing the health care paradigm, and capturing sustainable market value through exclusivity. Their approach is to identify variability in drug response, use tests to exclude non-responders, and discover the genetic contribution. He said the impact will be an increase in appropriate product use.

Dr. McCamish explained that a pharmacogenomic diagnostic is generally a probability assessment, not an exact diagnostic. Therefore, more than one option for care is necessary. He said PGx can be used to test across a broad spectrum of genes to help determine whether a patient has a probability of responding to a drug. Using PGx, a probability assessment can be done without having to treat the patient for weeks to see if they respond. This approach enhances patient care and can be beneficial for drug sales. He said the questions that arise are, Who will order this test? Who will pay for it? Who will interpret it? He suggested that genetic counselors could help individuals understand the probability assessment and advocate for reimbursement.

Dr. McCamish emphasized that PGx tests must have clinical utility, not just scientific relevance. He gave an example from the journal *Nature* to demonstrate that the application of PGx knowledge is almost as difficult as discovering the technology. In China, a 93 percent positive predictive value and 100 percent negative predictive value was shown for one allele associated with carbamazepine-induced Stevens Johnson Syndrome. This is a very severe dermatologic adverse event in response to the drug. However, as there are only eight cases of Stevens Johnson Syndrome per 1 million patient years, this discovery is not very useful. The cost of screening would be high and would benefit very few people.

Dr. McCamish stated that there are 3.2 billion base pairs in a genome and the variances between individuals is less than 1 percent. Researchers primarily focus on common single nucleotide polymorphisms, of which there are 6 to 10 billion. Ultimately, researchers want to develop a test for 10 to 50 of these polymorphisms, because that will provide the predictive power to determine whether a patient is at risk of having a disease or is likely to respond to a drug. He said this process is difficult, but the technology is improving, allowing them to accomplish more over time.

He gave an example of looking for a risk stratifier for myocardial infarction (MI) and said that subjects with comorbidity, such as hypertension, diabetes, or hyperlipidemia, are at greater risk. These individuals take many classes of medications for these diseases and optimal control in each disease area is associated with fewer MI events. However, multiple surveys reveal that these diseases are not being adequately controlled. He said the subset of this population that is at greatest risk should be optimized with treatment and medication adjustment. Dr. McCamish said that research on PGx approaches for this situation would be very costly because the study would need to involve hundreds of patients who have had MIs and hundreds of controls. The two groups would be compared statistically to see whether there was an association between SNPs of interest and a specific event or disease. The difficulty would be that a single study association provides no value, because there are many false positives. The findings would have to be replicated or validated in some way to find the SNPs that are truly predictive and could provide the basis for diagnostic tests. Finding some of these characterized phenotypes would cost millions of dollars, a substantial investment.

Dr. McCamish said the value of such a genetic test would be extremely limited because a one-time test is very expensive. This expense could preclude general use to guide treatment, particularly with generic drugs, and therefore the reimbursement issue is key. He asked who would perform the test, reimburse for it, and how it would be marketed once approved. These issues would create significant barriers for physicians. Dr. McCamish said that without exclusivity and patent protection, such an approach would not be pursued. Expensive research will not be funded without some basic protections.

Dr. McCamish gave an example of a drug-diagnostic development approach to decrease an adverse event. The goal would be to reduce a class effect adverse event by 50 percent and simultaneously introduce a new drug in that class. In his example, the adverse event would not be immediately life threatening, but could lead to hospitalization. Other drugs would be available for treatment of the disease. Providing information to the physician about the increased risk of this adverse event would allow other options to be explored. This would require simultaneous development of a diagnostic with the drug and also require identification of an acceptable diagnostic prior to entering the pivotal trial. He said that the difficulty of producing these data and a lack of patent protection would prevent researchers from pursuing this approach.

He described a simple trial approach for obtaining approval for both the drug and the diagnostic. The researchers would create intellectual property or a patent portfolio to protect use. Most drugs would be stratified based on treatment with a placebo or the drug itself. The researchers would try to provide clinical utility for the diagnostic test at the end of the trial. They would stratify patients into groups at high risk and low risk for adverse events. In each strata, they would randomize to drug treatment or placebo treatment. At the end, they would conduct a primary efficacy analysis, comparing the placebo against the treatment within the low-risk group. They would perform the same type of analysis for the high-risk group. The safety analysis would look at all patients. The diagnostic clinical utility analysis would compare the percent of adverse events in the high-risk and low-risk groups among subjects given the treatment. The need for replication might require an additional Phase III trial. These steps would be taken to generate the intellectual property and a label that would restrict use of the drug to a subpopulation with a low risk of adverse events.

Dr. McCamish stated that a patent on the association of a PGx diagnostic is critical, but not sufficient. One gene is not sufficient to detect a high probability of disease. He stated that the clinical utility must be adequate to convince FDA to restrict use of the drug. Dr. McCamish said that, in this case, the intellectual property would not protect use of the drug without use of the diagnostic. Reimbursement would not be likely if the test is only informative, which is a problem companies now face. Clinicians are reluctant to adopt a technology that is merely informative. He said the threat of litigation might be an incentive for clinicians to adopt a test. Dr. McCamish said a label that recommends or requires use of a test could speed its incorporation into clinical practice.

A genetic diagnostic test targeting efficacy could also be useful if other treatment options are available. Subjects could be assigned beneficial treatments sooner. Those who would not benefit from the drug would be treated with other therapies.

Dr. McCamish stated that the recommendations in the NAS document were excellent, but he offered additional suggestions. Concerning NAS Recommendation 7, he suggested that the industry scientists who are developing new technologies should be added to the USPTO. He believed the report should endorse the utility standard that patent applicants show "specific benefit in currently available form." Concerning Recommendations 10 through 12 on the validity, features, properties, and inherent characteristics of the invention or the diagnostic, he said they are already under the authority of FDA if the diagnostic is approved. If they are not approved, they may not be widely used.

In closing, Dr. McCamish suggested several ways to lower barriers to routine clinical use of appropriate PGx diagnostics. He said FDA support and the Critical Path Initiative are very important, including finalization of the co-development guidance. In addition, he stated that patent protections of the discovery of validated genetic and proteomic associations are critical to protect investments in research. He advocated for education for USPTO on emerging science and said continued NIH support is needed

for basic and clinical science. Dr. McCamish said support for access to anonymized samples for exploratory research is necessary and he recommended that a group be commissioned to focus on reimbursement decisions.

Roundtable Discussion

Dr. Licinio noted that technology is changing rapidly and said the idea of conducting genetic tests one-by-one for each disease is becoming obsolete. He felt that patents would create a roadblock to more efficient technology development. Dr. McCamish agreed that multiplexing of tests will increasingly take place and said it will be important to find the balance for research, moving new treatments out, and expanding treatments to the largest number of patients. In response to a question, Dr. Leonard stated that a company developing an *in vitro* diagnostic test kit and selling it to laboratories would be preferable to a single provider of a laboratory service. Dr. Leonard made the point that patent protections are necessary, but said licensing and enforcement needs to be changed.

Dr. Collins stated that during the human genome project, a decision was made to release data every 24 hours without filing any intellectual property claims. This strategy expanded to other types of genomic data, such as the data generated through the HAPMAP project. Traditionally, such discoveries have led to patent applications and Dr. Collins said the Patent Office is not likely to change its perspective that a discovery of a gene variant that is connected to a disease risk phenotype is patentable. He suggested that the solution come from those who are doing the science. He said the *NIH Guidelines on Research Tools* states that the goal of public benefit ought to guide those who are receiving NIH funds. More recently, NIH issued *Best Practices for Licensing of Genomic Tools*, which guides NIH grantee institutions on licensing patents on genomic tools. It discourages exclusive licensing to prevent monopoly situations that keep prices high and limit access and the potential for better quality.

Dr. Collins said the HAPMAP approach is allowing researchers to discover gene variants that are associated with common diseases. No single gene variant for those diseases will be definitive, but many gene variants will be found that together contribute to disease risk. Once this information is assembled, clinicians will have the ability to predict individual risk for common diseases and drug responses. He said the field has an opportunity to prepare for that time. He said it would be a "colossal mess" if, in order for a provider of laboratory services to put together a multiplex testing panel, they had to conduct years of legal work and pay royalties on each individual discovery that is separately owned.

Dr. Collins made the point that many pharmaceutical companies would prefer that the discovery of gene variants associated with common disease be considered pre-competitive and placed in the public domain. They are confident that they will capitalize on their ability to find a small molecule that goes after a target and do not think the target itself should be owned by anyone. He noted that the Genetic Association Information Network (GAIN) project, a public-private partnership between NIH and the private sector reflects this approach. Pfizer, Perlegen, Abbott, and Affymetrix are contributing the genotype services. Seven studies of common diseases were to begin in the fall of 2006, and the first data was expected in early 2007. The intellectual property policy states that all of the data from this effort will be placed in a public database so that it can be shared with other investigators. This will prevent third parties from trying to claim ownership. The GEI will also strive for immediate public disclosure of data to discourage constraints on its use.

Ms. Berry asked how useful it would be to make a distinction between discovery of a gene and a genetic variant versus development of a test to locate or identify it. Dr. Leonard said that distinction would solve the problem. She said that if a gene-disease association is considered a natural phenomenon, then

researchers are merely identifying its existence, as with gravity, and it would be in the public domain. She said that although some test kits are patented, she and her colleagues have the ability to use basic information to detect disease associations if no test kit is available.

Dr. FitzGerald asked how gene patent issues are handled in Europe. Dr. Leonard said the Task Force might want to find out more about the European patent system.

Dr. Winn-Deen asked Dr. Leonard's opinion about a sole source for a kit. Dr. Leonard described two situations in which technical problems with the only kit available for testing caused problems.

Dr. Collins asked Dr. Joseph Hackett if it matters to FDA whether a test is conducted by a single laboratory source or non-exclusively licensed and available from multiple sources. Dr. Hackett said it would not matter.

Dr. Licinio asked about testing for susceptibility to disease. He said some genes have a 5 to 10 percent or a 2 to 3 percent effect in terms of causing a disease, which is also affected by environmental factors. He asked how testing is dealt with in these situations, particularly when the effects are only seen in a certain population. Dr. Cho said it depends on how the patent claims are framed, which does not necessarily reflect the way scientists think about how effective the tests are or whether they are diagnostic. She said the predictive or diagnostic value is irrelevant to the way patent law works. She also said laboratories are moving toward multiplex testing and that there has not been extensive enforcement on the massive numbers of multiplex tests kits that have come out.

Dr. Hans asked if Dr. Leonard's suggestion to exempt medical personnel who perform genetic tests from patent infringement actions would have an impact on Perlegen's business model. Dr. McCamish said he couldn't speak for diagnostic manufacturers, but exempting medical practitioners and labs from patent enforcement would be problematic in terms of developing diagnostics of clinical utility, particularly in the polygenic area. Dr. Leonard asked why it is a problem for labs to conduct diagnostics if a company makes money from their drugs. He replied that diagnostic companies that invest heavily in the diagnostic itself may not continue to invest if their money can't be recouped.

Dr. Cho stated that the research to find many associations has been Government-funded and there has been little private investment. She said in certain cases, such as the HFE example, Mercator lost their investment and the patents didn't save them. She agreed with Dr. Collins that as the field moves toward multiplex testing, the greater the number of associations in the public domain, the fewer the number of investments needed.

Dr. Tuckson asked Dr. Leonard to clarify the work she does and how it compares with patented diagnostic kits. She explained that as an M.D. with a Ph.D. in molecular biology, she uses molecular biology methods in the clinical setting, meeting all regulatory and quality standards. If a paper is published that reveals that there is a mutation at a certain point in a gene, she can design primers or use the primers that were published to amplify the region, cut it with a restriction enzyme, run it on a gel, and determine whether the variant is there. She can then offer this process as a clinical diagnostic test. She said discovery of the genetic variant disease-association is the remarkable part. Once that is known, she can use "prior art" to test for that genetic variant in any patient for the purpose of diagnosing the disease. The question is whether the discovery of the genetic variant disease-association is like discovering gravity, i.e., should it be patentable? She believes such information should be in the public domain.

Dr. Tuckson asked Dr. Hackett at what point a diagnostic test conducted by Dr. Leonard would be regulated by FDA. Dr. Hackett said that if she boxed up a test and sold it to another laboratory, FDA would exert control. Otherwise, FDA is not involved. Dr. Leonard added that she is regulated by CLIA. Dr. Leonard and Dr. McCamish clarified that research funded by NIH can be patented and that many patents are obtained for Government-funded work.

Dr. Tuckson asked Dr. McCamish if the private sector was working on a solution to these problems, taking into account both the interests of commerce and the interests of health. Dr. McCamish was not aware of any private groups trying to resolve these issues.

Dr. Tuckson asked Dr. Cho if she felt it was time to conduct another set of study survey analyses. Dr. Cho said there was reason to re-analyze the work she and her colleagues conducted 5 years prior because there had been significant change, especially in the multiplex testing arena.

Dr. Tuckson asked that the full Committee focus on three questions: Should the Committee move forward on this issue? If so, what should be accomplished? What questions should be addressed to arrive at these goals? He said that based on the discussion, the Task Force on Patents and Access would either take the issue forward or disband.

Full Committee Discussion and Next Steps

Dr. Leonard suggested that the Committee explore whether testing in laboratories promotes patient access. Dr. Evans said the Committee should take up the patents and access issue and recommended a survey at the level of the patient. Dr. Leonard said one way to learn about patient access would be through public forums. The Committee could also provide a question on patient access to genetic counselors, nurses, physicians, and the public.

Dr. Winn-Deen said she interacts with technology transfer offices at universities that seem disconnected from the concept of patient care. They prefer to obtain exclusive licenses because it is easier. She said that since technology transfer officers control the licenses, they are important stakeholders, and should be brought into the discussion. Dr. Tuckson proposed that the Committee hear from industry and from university technology transfer offices. Dr. Leonard added that "industry" includes *in vitro* diagnostic test companies, the pharmaceutical industry, and the biotechnology industry. Dr. Hans also wanted to hear from the deans and university presidents who preside over the technology transfer offices.

Dr. Winn-Deen suggested making a recommendation to the Secretary on turning NIH best practices guidelines into something with "teeth" that grantees must comply with as recipients of NIH funding. Mr. Tim Leshan, NHGRI, pointed out that there are limitations on NIH's requirements of grantees because of the Bayh-Dole Act. He suggested that NIH's Office of Technology Transfer participate in the Committee's discussion.

Dr. Tuckson suggested that the Committee develop a definitive description of the science that is being made available in the public domain and its functional relevance (e.g., that it cannot then be patented).

Dr. Winn-Deen suggested that the Committee consider making recommendations about mechanisms to overcome the issue of multiple patent holders and multiple licenses. She said significant royalty stacking issues will prevent commercialization at reference laboratories and for commercial kits. She suggested encouraging a patent pooling strategy, so that different stakeholders that want to license can go to a single entity. Dr. Leonard noted that this related to recommendation 11 from the NAS report, i.e., that

NIH should undertake a study of potential university, Government, and industry arrangements for the pooling and cross-licensing of genomic and proteomic patents and research tools. She said this effort could be broadened to apply to clinical diagnostics.

Dr. FitzGerald agreed that the Committee should explore the patents and access issue and suggested hearing from someone who could present a legal analysis from the USPTO perspective. Mr. Martin Dannenfelser said an appropriate person from the House and/or the Senate could focus on NIH-funded research and could be informative in the legal arena. Dr. Leonard noted that Rep. Lynn Rivers introduced legislation on patents and access and that the College of American Pathologists might be able to address this area. Dr. FitzGerald said he would like to hear from patient advocacy groups. Dr. Leonard added that it had been suggested earlier that the Committee hear about the European and Canadian perspectives. Dr. Sylvia Au suggested involving public health programs.

Dr. Tuckson excused himself to attend a meeting with the NIH Director and asked Dr. Leonard to serve as Chair during his absence.

Dr. Leonard asked the Committee to vote on whether they should continue working on the patents and access issue. The Committee unanimously agreed to move forward. Dr. Teutsch mentioned the concept of creating a clearinghouse for patents and access information. He wanted to focus on access to tests that are clinically important to patients. Ms. Berry thought the Committee would benefit from the input of outside economists. Mr. Leshan said that very little research has been done in this area. The Committee suggested Scott Ramsey, Richard Gold, or Pat Danson as potential speakers on economics. Dr. Telfair and Dr. Leonard discussed the fact that the different stakeholder groups would need specific guidance from the Committee to provide input. A document would have to be written that outlined the areas the Committee wanted them to address.

Mr. Dannenfelser noted that pandemic flu is a high priority concern for the Secretary. Several Committee members agreed that since SACGHS has a broad mandate that includes bioterrorism organisms, they should consider exploring patents on viruses, such as Hepatitis C.

Public Comments

Michelle Schoonmaker, Ph.D.
Association for Molecular Pathology (AMP) Professional Relations Committee

Dr. Schoonmaker reported that members of the AMP have had to cease or alter clinical laboratory testing due to restrictive gene patents for an ever-growing list of diseases. The AMP believes that the human genome sequences are in the public domain and there should be open access to them for any clinical application. They believe genetic test services are medical procedures and, as such, should be widely available to promote optimal patient care, medical education, and medical research. Dr. Schoonmaker said the restrictive use of patents and exorbitant licensing fees prevent physicians and clinical laboratories from performing genetic tests, limit access to medical care, jeopardize quality, and raise costs. She urged the Committee to develop recommendations on steps that can be taken so that patients have broad access to the benefits of ongoing and future research on the genetic basis of disease. Dr. Schoonmaker made the following recommendations on behalf of AMP:

- All clinical laboratories should be exempt from gene patent restrictions for diagnostic testing in the practice of clinical medicine.
- Research funding agencies should oppose patent licensing agreements that inappropriately limit

clinical care, the use of medical procedures, medical education, and medical research.
- Organizations, including universities, that hold patents and require licenses for use of their technology for genetic testing should offer non-exclusive licenses and make these available to any qualified clinical CLIA-certified high complexity laboratory on an equal basis.
- To ensure that testing remains widely available and affordable, financial terms for test licenses should be reasonable. License agreements should also be free of any terms that limit the number of tests that can be performed by a laboratory or regulate the technical performance or clinical use of the test.
- License agreements should likewise be free of terms that inappropriately limit research related to the testing or the public dissemination of the resulting research findings.

SACGHS was invited to contact Dr. Wayne Grody, Chair of AMP's Professional Relations Committee, for further information.

Elissa Levin, M.S.
Clinical Director, DNA Direct

Ms. Elissa Levin said DNA Direct is a web-based company that offers genetic testing and genetic counseling services directly to consumers. She stated that genetic testing services can be offered responsibly and reliably through a DTC approach, although it will not replace traditional models of testing. She highlighted several reasons why some consumers have chosen DTC services:

- Limited access to genetic services by qualified professionals.
- Concerns about privacy, confidentiality, and genetic discrimination.
- Genetic interpretation and support services.
- The cost of testing and services.

Ms. Levin emphasized that DTC companies must be responsible for developing and maintaining standards of practice. She said there are key factors that currently distinguish reputable companies. These include the selection of tests offered, the laboratories utilized, and the level of services provided. DNA Direct offers clinical genetic tests that are routinely offered through most genetic centers. They evaluate each test option in light of its clinical validity and utility and use renowned experts in the medical and genetics fields.

Ms. Levin said it is not up to the DTC industry to defend the validity of laboratory testing. She said that must be resolved through CLIA, FDA, and other relevant agencies. Since FDA is not currently regulating genetic tests, she said consumers should be made aware that reliable testing can be obtained directly, often using the same laboratories as their primary care physician. Ms. Levin stated that providers of tests must be more transparent about where their laboratory testing is done and that DNA Direct partners only with large, reputable CLIA-certified laboratories.

Ms. Levin said that some DTC companies allow consumers to test or order online, providing no human contact or support by genetics professionals. In such cases, pre-test education may be unavailable or incomplete, informed consent may not be required, and post-test results may be disclosed without interpretation. She stated that DNA Direct has a website that offers patient-oriented information. She said all test orders are reviewed and authorized by a board-certified medical geneticist and signed informed consent is required. Test results are conveyed via personalized reports that include interpretation by genetic counselors and a medical geneticist based on the individual's personal and family history. Disclosure protocols are test-specific, so some test reports are only released once they've been disclosed through a post-test discussion with a genetic counselor and the patient. Genetic counselors are available

to patients at any point and all clinical interactions are HIPAA compliant. Ms. Levin said genetic counselors working for DTC companies are able to maintain their professional standards.

Ms. Levin said that society is moving toward more virtual services and consumers must be able to distinguish between valid testing services and those that do not maintain high standards of practice. She stated that the DTC industry, health care providers, and policymakers should be collaborating to set the bar so that testing is provided safely and effectively.

Dr. FitzGerald asked Ms. Levin whether there are disadvantages to conducting genetic counseling over the phone, without face-to-face interaction. Ms. Levin said the DTC model is not for everyone and that if a caller is highly anxious and does not understand the core information being conveyed, they are referred to a regional medical center.

Dr. Telfair asked how the DTC industry could move in the direction Ms. Levin was advocating. She said DNA Direct created their own standards and guidelines, which are posted on the website www.dnadirect.com. She said they are trying to move others toward their standard. She asked the Committee to consider how they could play a role in setting the bar.

JoAnn Boughman, Ph.D.
Executive Vice President, American Society of Human Genetics (ASHG)

Dr. JoAnn Boughman said ASHG is very concerned about patents and licenses and is having discussions with its member researchers, clinicians, and genetic counselors on the downstream effects on clinical testing from the research laboratory perspective. She stated that member scientists must be educated on these issues so they can address them from a scientific perspective and play an active role with their technology transfer and licensing departments.

ASHG is also asking questions about their rights as a third-party organization and their limitations concerning advertising and publication. They want to help their members differentiate between sound practice guidelines and the practices of certain organizations or individuals. Dr. Boughman said that bringing these issues to the forefront and making people aware of these differences is a step in the right direction. Their leadership is concerned about the actions of the few and the impact they may have on the patient community in the long term.

Joanna Rudnick
Kartemquin Films

Ms. Joanna Rudnick's testimony was being videotaped as part of a documentary film she was producing. Ms. Rudnick said she was speaking both as a filmmaker and as a woman at high risk for hereditary breast and ovarian cancer. She tested positive for the BRCA mutation 5 years previously and went to great lengths to keep her status a secret. She worried about privacy and discrimination issues. She slowly began revealing her BRCA status to those around her and sought information to help inform her decisions. She learned more about the BRCA mutation and interviewed more than 50 women for a film about predicting breast and ovarian cancer and the consequences of living with risk.

She said the documentary she was making chronicled the stories of other high-risk women, such as Martha Haley. Martha is a three-time breast cancer survivor who tested for a variant of unknown significance on the BRCA2 gene. She wonders why so few African American women have tested for the BRCA mutation and pleads with women to be tested so there is a better understanding of the role of genetics in African American women's breast cancer.

Linda Pedraza, also in the film, is a 43-year old BRCA positive mother of two who was diagnosed with both breast and ovarian cancer. She is losing her battle with cancer and worries about the fate of her 16-year-old daughter.

Ms. Rudnick said the women who live with this information have much to teach public policymakers, other high-risk women, and health care providers about the implications, fears, and concerns of living with predictive genetic knowledge. She said her film, "In the Family," is the first comprehensive documentary dedicated to telling their stories while asking larger questions about the legal, social, and ethical implications surrounding genetic testing for adult onset diseases. She hoped the Committee would see the film's potential as a resource for public education and professional development. The filmmakers formed a coalition for outreach and education and want to find partners with expertise in the field and establish networks to help create and distribute targeted video modules and workbooks. Ms. Rudnick showed a 2-minute clip from the film and said an 18-minute sample would be shown during lunch.

Updates from Working Groups on Direct-To-Consumer Marketing of Genetic Tests and Services

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Tuckson stated that in 2004, the Committee wrote to the Secretary urging FTC, FDA, and other HHS agencies to collaborate on the regulation of advertisements for genetic tests marketed directly to consumers. SACGHS encouraged relevant HHS agencies to collect data and conduct an analysis of the public health impact of DTC marketing of genetic tests. In response to these recommendations, two interagency work groups were formed. One was composed of staff from FTC, FDA, CDC, and NIH, which assessed the scientific accuracy of claims made by companies advertising genetic tests on the Internet. The second work group, composed of staff from FDA, CDC, NIH, and HRSA, was exploring mechanisms for collecting data on the public health impact of DTC marketing of genetic tests.

FDA-FTC Collaboration

Matthew Daynard, J.D.
Senior Attorney, Federal Trade Commission

Mr. Matthew Daynard remarked that Secretary Leavitt's recent letter to the Committee summarized the status of the work group's activities by stating that FDA, CDC, and FTC were developing a consumer alert that will encourage consumers to talk to their health care practitioners about DTC tests. Consumers would be encouraged to question claims made by these companies. Mr. Daynard said the CDC approved the content of a draft of the consumer alert and that the FDA and FTC were in the process of clearing the document. FTC, FDA, and CDC would disseminate the consumer alert in the form of a press release, along with a variety media alerts to ensure that it is picked up. Consumers would be directed to the websites for the agencies and to hotline numbers for more information and guidance, as well as to their health care practitioners. Mr. Daynard expected that the final approvals would be received within the following month. Dr. Tuckson noted that this effort was an excellent example of Government agencies

working together in an expeditious manner. He asked that SACGHS staff draft a letter to the Secretary commending these organizations for responsiveness.

Data Collection and the Public Health Impact
Scott Bowen, M.P.H.
Deputy Director, National Office of Public Health Genomics, CDC

Mr. Scott Bowen reported on efforts to collect data on DTC marketing of genetic tests, including levels of awareness among the general public and practicing physicians. He stated that at the national level, CDC would be collecting data in 2006 using the Health Style Survey, targeted at consumers, and the Doc Style Survey, targeted at primary care physicians. Questions would address knowledge of the genetic tests available and the type of media by which this knowledge was gained. Physicians would be surveyed about the number of patients who asked about these tests and that brought tests results to them for interpretation. At the State level, Michigan, Oregon, and Utah, three of the CDC-funded Capacity Improvement States, added questions on awareness and use of DTC genetic tests to their behavioral risk factor surveillance system modules for 2006. Results from these efforts were expected by mid-2007.

Mr. Bowen stated that Myriad Genetics launched an intense media campaign in Denver and Atlanta in 2003 to promote the availability of DTC tests to detect the presence of BRCA1 and BRCA2 mutations. CDC conducted a study of the public health impact of this campaign using Raleigh-Durham and Seattle as control sites. The results were published in the *Journal of Genetics and Medicine*. The study found that physicians' knowledge did not differ between pilot and control cities on a statistical basis, but that more physicians in pilot cities reported interest in using the tests. They increased the number of times they ordered genetic testing for breast and ovarian cancer during the previous 6 months, largely because their patients were coming to them to ask about testing. Many physicians responded that they needed more information about available genetic tests. The researchers concluded that, given the complexity and limitations of genetic testing for the risks of breast and ovarian cancer, development and broad dissemination of clinical guidelines and education of physicians is needed.

Dr. Hans pointed out that the CDC study was conducted prior to the release of the United States Preventive Services Task Force recommendations regarding testing for BRCA1 and 2. She asked if the CDC would follow up on their impact. Mr. Bowen said CDC will be looking at the response to these recommendations. He also said the CDC did not have plans to research the outcomes of the "Tell Someone" campaign on HPV testing, but would consider helping States if they asked for assistance.

Genetic Discrimination

Update from Key Stakeholders on the Status of the Federal Genetic Information Nondiscrimination Legislation

Dr. Tuckson introduced the session by noting that Dr. Elias Zerhouni, NIH Director, was extremely responsive to the Committee's agenda on genetic discrimination and had several ideas on enhancing the value of SACGHS work in this area. Dr. Zerhouni had personally worked to ensure that the issue was receiving visibility within the Department and planned to provide the Committee with a report on the actions taken by the Government in this regard.

Dr. Tuckson stated that SACGHS had a number of conversations with the advocacy community, the business community, and the health insurance community on genetic discrimination. He said these constituency groups had been willing to negotiate their positions to reach consensus for the public good.

Michael J. Eastman
Director of Labor Law Policy, U.S. Chamber of Commerce

Mr. Michael Eastman stated that the Chamber's position was that any legislation dealing with discrimination based on genetic information should be narrowly drafted to ensure that it accomplishes its goals without inviting frivolous or unnecessary litigation or causing undue burdens on employers. He stated that such legislation appears to serve a different purpose than traditional civil rights legislation. From the Chamber's perspective, Title VII of the Civil Rights Act, the Americans with Disabilities Act, and the Age Discrimination Act were created to remedy a long history of pervasive discrimination. He said that in the case of genetic discrimination, it appears that the primary purpose of the proposed legislation is to deal with the fear that prevents people from taking genetic tests. He stated that because those purposes are different, the ways in which the law is implemented might need to be different. He pointed out that most of the Chamber's involvement in the issue concerned employment discrimination (Title II), not insurance discrimination (Title I).

Mr. Eastman said that in 2005, there were about 75,000 charges filed at the Equal Employment Opportunity Commission (EEOC). The agency found no reasonable cause in 62 percent of those cases and reasonable cause in 5.7 percent. (Because of settlements, the numbers don't add up to 100 percent.) He said that data provides evidence that many cases are filed without merit. Employers spend between $30,000 to 50,000 to defend a typical case, which he said is a significant burden.

The Chamber's three fundamental concerns have been: 1) the appropriate scope of relief for true victims; 2) whether or not the bill has preemption of State law; and 3) the extent to which the bill goes beyond discriminatory conduct and addresses the collection and flow of information held by employers.

Mr. Eastman said that over a 6-month period of discussion with advocates for genetic nondiscrimination, common ground principles were agreed on in eight categories. The first was to acknowledge that "fear" is affecting the use of new technologies in health care and participation in clinical studies. In addition, employers fear the unknown, such as the consequences of new legislation and the potential for new litigation. Category two was "standard and scope." Both groups agreed that legislation should be enacted to create a single national standard, providing the same protections, obligations, remedies, enforcement, and exceptions from State-to-State. The third category was the "enforcement process." The process for an individual bringing forth a claim should be filtered in some way to weed out non-meritorious cases. The fourth category was "remedies," which included injunctive relief, equitable relief, and additional remedies for egregious cases. Category five was "the definition of family member." Family members covered under legislation should be limited to three generations: grandparents, parents, siblings, spouses, and children, including adopted children. Category six was "permissible exceptions and HR compliance." An employer should not be punished on occasions when it is reasonable to take action based on the employee or prospective employee's genetic information (e.g., compliance with other laws, such as the Family and Medical Leave Act; employment benefit counseling; or direct threat situations). Category seven was the "sunset clause and independent study commission." An independent review of any new law should take place within 6 years by an independent commission. If the legislation is narrow and there's an independent commission, they do not believe there's a need for a sunset clause in the legislation. Category eight was "communication and education." An education and communication campaign aimed at employees, employers, and health care participants would be necessary to carry out the purposes of the law, reduce fear, and educate constituents.

Sharon F. Terry. M.A.
Chair, Coalition for Genetic Fairness

Ms. Terry said she worked closely with Mr. Eastman on the eight categories of common ground, which were presented to Rep. Judy Biggert, sponsor of the legislation. Rep. Biggert arranged a meeting for them with the Education and Work Force Committee, which had positive results. The Education and Work Force Committee planned to look at the possible effect of the common ground principles on the pending legislation.

Dr. FitzGerald asked how closely the common ground principles mirrored the current legislation. Mr. Eastman said some principles were already included in the current legislation, some would require minor changes, and some provisions would be extensive and difficult to draft. Ms. Berry asked about time frames for the legislation and whether it would coincide with Health Week. Ms. Terry said they were continuing to work on the number of co-sponsors and were not sure how quickly the Education and Work Force Committee would address the new principles.

Dr. Leonard asked for an update on the status of the legislation. Ms. Terry said it was the same bill that passed in the Senate, 98 to 0, in January 2005. The bill was currently in three committees: Education and Work Force, Commerce, and Ways and Means. Ms. Terry said it was up to the Education and Work Force Committee to move the legislation forward so the other two Committees could sign off, as they had agreed to do. The bill could then go to the floor of the House for a vote. If the bill changed substantially in the process, but passed in the House, the House and Senate would have to make decisions together about the final signed law. If it was to pass in its current form, the process would be a simple one. Ms. Terry said they had a Hill briefing scheduled later in the week to build momentum for passing the law before the November elections.

Dr. Collins asked if they were staying in regular communication with the Senate about the proposed changes. Ms. Terry said they were staying in touch with staff in the Senate, but had not presented the common ground principles because they didn't know what effect their recommendations would have. They had asked Congresswoman Biggert and her office to keep the Senate informed.

Dr. Licinio asked Ms. Terry if she felt the legislation would be too restrictive if it included the recommendations in the eight categories. She replied that neither the advocates nor the Chamber were completely happy with the compromises they made, but said they needed to work together to help eliminate fears without placing a great burden on employers. She said both sides were comfortable with their decisions. She acknowledged that some within the Coalition for Genetic Fairness did not renew their membership because they wanted to see stronger remedies and stricter provisions in the legislation.

Ms. Au asked for more information about the category concerning State pre-emption. Mr. Eastman and Ms. Terry explained that one national standard would be better than the current mix of State laws, some of which are good and some of which are poor.

Dr. Telfair asked Ms. Terry how she planned to bring those who wanted stricter provisions back "into the fold" after the legislation passed. Ms. Terry didn't foresee a problem working with these groups and expected that they would want to participate in the education campaign. She said the differences were not as great as they had been several years ago.

Presentation of Certificates

Dr. Tuckson described the contributions of Debra Leonard, Agnes Masny, and Emily Winn-Deen in service to the Committee. He presented each with a certificate and a letter from Secretary of HHS Michael Leavitt. He stated that they would continue to serve as *ad hoc* members on the Task Forces.

Next Steps and Concluding Remarks

Dr. Tuckson asked Ms. Carr to lead a discussion on adding members to the SACGHS subcommittees. Mr. Leshan announced that he was accepting a position at Brown University to head the Office of Government Relations and Community Affairs.

Ms. Carr stated that Cynthia Berry had agreed to chair the Genetic Discrimination Task Force. Reed Tuckson, Peter Gray, Robinson Frohboese, MK Holohan, and Joann Boughman were serving as members, with Agnes Masny staying on as an *ad hoc* member. Dr. Collins suggested that Mark Rohrbaugh, head of the Office of Technology Transfer, be contacted to serve as an *ex officio.*

Ms. Carr said Kevin FitzGerald would chair the Task Force on Pharmacogenomics to fill the vacancy left by Emily Winn-Deen. Andrea Ferriera-Gonzalez, Jim Evans, Julio Licinio, Hunt Willard, Gurvaneet Randhawa, Muin Khoury, Steven Gutman, Steven Teutsch, Joseph Hackett, Allen Rudman, Alan Guttmacher, and Rochelle Long are serving as members, with Emily Winn-Deen staying on as an *ad hoc* member.

Jim Evans agreed to serve as Chair of the Task Force on Patents and Access. Members include Andrea Ferriera-Gonzalez, Sylvia Au, Cynthia Berry, Chira Chen, Scott Bowen, James Rollins, MK Holohan, Denise Geolot, and Martin Dannensfelser, with Debra Leonard serving as an *ad hoc* member.

Hunt Willard was chair of the Task Force on Large Population Studies, with Barbara McGrath, Sylvia Au, Chira Chen, Julio Licinio, Kevin Fitzgerald, Joseph Telfair, Steven Teutsch, Muin Khoury, Francis Collins, Alan Guttmacher, Ellen Fox, and Sherrie Hans serving as members.

Dr. Tuckson stated that he would meet with the Task Force chairs soon. He said he would like to find ways to enhance the visibility of the work the Committee and wanted to hold a meeting on this topic with representatives from each subcommittee. They could present their ideas to the full Committee at the next SACGHS meeting. Dr. Tuckson then asked Ms. Carr to summarize the results of the current meeting.

She said the Committee asked SACGHS staff to develop a document that describes the current CLIA regulations, outlines gaps in oversight, and reviews the components to be addressed in the Notice of Proposed Rulemaking. Dr. Tuckson asked that the introduction to the document define the problem and link it to the patent issue. This document would help the Committee decide whether further action was warranted.

Ms. Carr reported that in the area of pharmacogenomics, the Committee agreed that the Task Force should continue developing a draft report based on the literature review. As part of this effort, the recommendations discussed by the Committee would be refined and consolidated. The draft report would be presented for discussion at the November meeting. Committee members were encouraged to identify any gaps or omissions in the literature review.

The Task Force on Patents and Access would consider the effects of gene patents on clinical practice for single and complex gene diseases, including, but not limited to, patient access, the use of genetic/genomic services, and the economic impact and quality of those services. They would also consider legal issues, industry perspectives, economic considerations, and the processes of granting and licensing medically relevant patents.

The Committee decided to write a letter to the Secretary to commend the collaboration between FDA and FTC on DTC marketing of genetic tests.

Dr. Tuckson said that Greg Downing, from the Office of the Secretary, assisted in bringing the work of the Committee to the Secretary's attention. The Committee agreed that all issues under discussion had been adequately addressed. Dr. Tuckson adjourned the meeting.

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

Reed Tuckson, M.D.
SACGHS Chair

Sarah Carr
SACGHS Executive Secretary