Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Eleventh Meeting
November 13-14, 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.
Andrea Ferreira-Gonzalez, Ph.D.
Kevin FitzGerald, S.J., Ph.D.
Andrea Ferriera-Gonzalez, Ph.D. (appointment pending)
Barbara Burns McGrath, R.N., Ph.D.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Huntington F. Willard, Ph.D.

***Ex Officios*/Alternates Present**

Gurvaneet Randhawa, M.D., M.P.H. (HHS/Agency for Healthcare Research and Quality)
Linda Bradley, Ph.D. (HHS/Centers for Disease Control and Prevention)
James Rollins, M.D. (HHS/Centers for Medicare & Medicaid Services)
Steven Gutman, M.D., M.B.A. (HHS/Food and Drug Administration)
Elizabeth Mansfield, 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)
Alan Guttmacher, M.D. (HHS/National Institutes of Health)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Anand Parekh, M.D., M.P.H. (HHS/Office on Public Health and Science)
Michael Carome, M.D. (HHS/Office for Human Research Protections)
Martin Dannenfelser (Administration for Children and Families)
Michael Amos, Ph.D. (Department of Commerce)
Scott McLean, MC, USA (Department of Defense)
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, NOVEMBER 13, 2006

Call to Order and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, SACGHS Chair, welcomed those in attendance and stated that the public was made aware of the meeting through notices in the Federal Register, as well as announcements on the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) website and through the SACGHS listserv. Dr. Tuckson introduced Dr. Greg Downing, Project Director for Health and Human Services (HHS) Secretary Michael Leavitt's Personalized Health Care initiative; and Sheila Walcoff, staff member to the Secretary. Dr. Tuckson welcomed Debra Leonard and Emily Winn-Deen, former SACGHS members, who were serving on the Task Forces for Gene Patents and Licensing and on Pharmacogenomics, respectively.

Dr. Tuckson welcomed three new *ex officios*: Dr. Gurvaneet Randhawa of the Agency for Healthcare Research and Quality (AHRQ), Dr. Anand Parekh of the Office on Public Health and Science (OPHS), and Dr. Michael Amos of the Department of Commerce (DoC). Dr. Tuckson acknowledged new OBA staff member Dr. Yvette Seger, who was taking the lead on the Large Population Studies issue. Dr. Seger was previously a research associate for Faster Cures, a biomedical research advocacy organization. She was also a science and technology policy graduate fellow at the National Academies. Her dissertation research at Cold Spring Harbor Laboratory earned her a Ph.D. in Genetics from SUNY Stony Brook in 2004.

Dr. Tuckson briefed the Committee on his June 2006 meeting with Dr. Elias Zerhouni, Director of NIH. They reviewed the progress of SACGHS and discussed methods for enhancing the impact and public visibility of the Committee's work. Dr. Zerhouni suggested additional dissemination of the results of SACGHS deliberations and products, such as the development of manuscripts for journals. Dr. Tuckson stated that work was in progress on an article about the Committee's recommendations on coverage and reimbursement for genetic tests. He asked Committee members to consider ideas for additional products or manuscripts.

Dr. Tuckson reviewed the priorities of the Committee. He then noted the influence of SACGHS on the development of a consumer alert aimed at raising awareness of the risks of "at-home" genetic tests. He thanked Matt Daynard, FTC; Steve Gutman, FDA; Muin Khoury, CDC; and Linda Bradley, CDC for their success in collaborating to create the alert.

Dr. Tuckson described Secretary Leavitt's commitment to the development of personalized health care and noted that electronic health records (EHRs) will be an important part of this transformation and will include genetic and genomic information. Dr. Tuckson stated that he met with Ms. Walcoff and Mr. Downing the previous month to discuss how SACGHS could be helpful in advancing the Secretary's agenda in this area. He also described the Federal advisory committee known as the American Health Information Community (AHIC). AHIC is a public/private partnership aimed at bringing together the best thinkers in health care to coordinate performance assessment data, consumer decision support, and health information technology. They are working toward an interoperable health care delivery system that facilitates better health care decisions by consumers and health care professionals, while protecting privacy and security. The AHIC working group on personalized health care is charged with analyzing technological challenges. Dr. Tuckson stated that it was important for SACGHS to stay informed of their efforts.

The Secretary's Office and AHIC issued a Request for Information (RFI) in the Federal Register on November 1, 2006 to seek input from the public and private sectors on plans for developing and using health information technology (IT) and genetic and molecular medicine for evidence-based clinical practice, health outcomes evaluations, and research. A copy of the RFI was provided to Committee members and Dr. Tuckson encouraged them to respond and to share it with interested colleagues. Feedback on the RFI was due January 1, 2007. Dr. Tuckson turned the floor over to Ms. Walcoff for an update on the Secretary's Personalized Health Care initiative.

Ms. Walcoff said the work of SACGHS is highly relevant to the Secretary's initiative in personalized health care. She stated that the initiative would improve the safety, quality, and effectiveness of health care by leveraging advances in genomics and health IT. This convergence will lead to educated consumers and providers and better clinical outcomes. The Secretary's focus is primarily on improving health in a patient-centric way. Ms. Walcoff emphasized the importance of input from the science community, the provider and patient community, and the health IT community. She stated that the working group on personalized health care would be making recommendations on standards for incorporating genetic information and genomic test information into personal EHRs. They might also address the integration of databases, including genetic and medical test information for clinical decision support. The Secretary feels a sense of urgency and is accelerating this initiative during his tenure at HHS, and Ms. Walcoff said that SACGHS is the perfect forum for continuing this work in the future. She stated that she would describe the relevant issues in more detail at the next Committee meeting.

Ms. Sarah Carr then briefly reviewed the ethics rules for SACGHS members.

Session on Pharmacogenomics

Dr. Tuckson stated that the Committee was in the process of developing a report to the Secretary on pharmacogenomics (PGx) and the opportunities and challenges associated with its integration into health care and public health. In June 2006, SACGHS discussed some preliminary recommendations. Following that, The Lewin Group prepared a draft report and staff members revised initial recommendations based on the Committee's input. The Task Force met in September to further develop the report and its recommendations. Dr. Tuckson turned the floor over to Task Force Chair Kevin FitzGerald to present the results of their work and lead the Committee in discussion.

Update on the Efforts of the SACGHS Pharmacogenomics Task Force and Review of the Draft Report

Kevin T. Fitzgerald, S.J., Ph.D., Ph.D.
Chair, Pharmacogenomics Task Force

Dr. FitzGerald stated that the drivers behind personalized medicine and PGx are research and development, the health care system, public interest, and public policy. Although the promises of PGx offer improved productivity of the drug pipeline and increased safety and efficacy of drugs, there are many challenges that must be addressed before PGx can be integrated into clinical and public health care practice. SACGHS's role is to identify these opportunities and challenges and provide advice to the Secretary.

Dr. FitzGerald provided an overview of SACGHS efforts to date, including informational sessions in June and October of 2005, approval of the report outline in October 2005, a compilation of Federal PGx activities in March 2006, development of draft recommendations in March and June of 2006, and a review of the literature, also in June 2006. The Lewin Group developed the draft report, including incorporation of the recommendations that were revised by staff members based on Committee input.

The goal of the day's session was to ensure that all major opportunities and challenges associated with PGx had been identified, the draft recommendations addressed high priority issues, and the draft recommendations provided appropriate solutions. The Committee was asked to reach consensus on whether or not the draft report and recommendations were ready for public review and comment. Dr. FitzGerald said the next steps after the meeting would be to revise the report and recommendations based on the day's input. In December 2006, The Lewin Group would seek input from 15 Federal and non-Federal experts/stakeholders on various PGx issues. Public comment would then be sought in early 2007. The Task Force hoped to finalize the report and recommendations in the summer of 2007 and to release the final report by the end of the year.

The report is organized around three themes: research and development, gatekeepers, and implementation of PGx to improve outcomes in clinical practice. Dr. FitzGerald asked the Committee to consider whether the recommendations identified all the major issues and to identify recommendations that were of the highest priority for action on the part of the Secretary. He said the Task Force had conducted a preliminary ranking of the recommendations and identified 12 that they considered high priorities.

Research and Development

Research and development topics included: 1) basic and translational research; 2) clinical research; 3) the infrastructure enabling research and development; and 4) the related ethical, legal, and social (ELSI) issues. The report offered 5 recommendations on research and development, which included 14 subparts.

Dr. FitzGerald stated that more basic research is needed to advance understanding of the biochemical pathways associated with drug metabolism and drug action, the genes involved in these pathways, and the gene functions affecting the toxicity of drug treatments. In addition, more translational research is needed to apply this knowledge to the development of clinically useful PGx technologies. Translational research studies, if designed carefully, can also be a source of data for downstream studies of the clinical validity and clinical utility of PGx tests.

Dr. FitzGerald discussed the co-development of PGx drugs and diagnostics and noted the possibility of resistance by industry because of concern for market segmentation, uncertainty about FDA regulations for co-developed products, and the necessity of organizing collaborations between drug and diagnostic industries, which would mean coordination of their development processes. However, co-development could result in expedited FDA approvals, fewer label changes, and a greater likelihood of provider uptake.

Dr. FitzGerald stated that many drugs were abandoned because they failed to detect a significant treatment effect in the broader population. However, a post hoc analysis of clinical drug trial data for which genotype information is available could enable the rescue of such drugs for use by smaller populations of high responders. The incentives for pursuing identification of new indications for existing drugs are mixed. A company might have more incentive if a drug or device is still under patent and less incentive if it isn't. There also might be more incentive if adverse drug reactions are severe or if there are no alternative treatments for a condition.

Drugs and diagnostics for rare (i.e., "orphan") diseases raise other issues. Currently, the orphan drug threshold must be less than or equal to an incidence of 200,000, while the diagnostic threshold is less than or equal to an incidence of 4,000. This could favor development of PGx drugs, but not their accompanying diagnostics. It is unclear whether the FDA would consider a PGx-based drug an orphan product if it confers large benefit to an orphan-sized population, but a modest benefit to a large population. Dr. FitzGerald stated that one of the current barriers to the translation of PGx into clinical practice is the lack of evidence of clinical validity and clinical utility.

Pharmacogenomics research would benefit from a better infrastructure, including integration of research and clinical databases, repositories, and records. However, successful PGx data collection, storage, modeling, and transfer is difficult because of the variation in data formats, the fact that EHRs are in the early stages, and there are different funding streams, stakeholders, administrative protocols, and organizational cultures.

A key ELSI issue in research and development is the privacy and confidentiality of research records. Yet data access and utility is sometimes sacrificed in data protection. Dr. FitzGerald said that researchers will have to continue to balance privacy protections with access and utility. Another ELSI issue is the fact that PGx test results may reveal secondary information, which is problematic because of discrepancies in human subjects research regulations (the Common Rule) and FDA regulations. A third ELSI issue is that drug company liability could increase if PGx testing is not required as a condition of drug treatment.

Dr. FitzGerald stated that the identification of individual differences in drug response could continue to stratify subgroups into racial categories. An example often used to illustrate this problem in both the literature and the media is the approval of the drug BiDil for use by self-identified African Americans. Association of molecular subgroups with race could reinforce the idea that race is a biological construct, which could limit the availability of PGx-based drugs to certain subpopulations.

Discussion: Research and Development

Ms. Cynthia Berry suggested that the report mention that some Federal agencies, such as AHRQ and HHS, are discussing comparisons of the effectiveness of drugs, which would allow payers and providers access to effectiveness information. Dr. James Rollins noted that CMS commissioned AHRQ to look at both the effectiveness and the accuracy of various tests for genetic cancer disorders, including sensitivity, specificity, receiver-operator characteristics, and likelihood ratios. He suggested taking into consideration measures to evaluate accuracy, in addition to looking at the clinical utility and clinical validity of PGx tests.

Dr. Francis Collins stated that the need for rapid turnaround and results should be flagged as a research and development priority because the issue of accelerating turnaround time has not received as much attention as it warrants. If test results are not returned quickly enough to influence medical decisions, the standard of care will not change. Therefore, additional research is needed in rapid turnaround, cost-effective point-of-care genotyping for PGx. Dr. Scott McLean added that pre-symptomatic testing allows providers to have results in hand quickly for an acute illness. As an example, he said that the military conducts testing before giving anti-malarial drugs and such an approach could be used with certain pre-symptomatic testing for PGx applications.

Dr. Andrea Ferreira-Gonzalez noted that it's important to state in the report that tests must be performed in CLIA-certified laboratories if results are returned to patients. She was not sure whether all Institutional Review Boards (IRBs) in the country are aware of the CLIA requirements. She suggested recommending that the Secretary work with Office for Human Research Protections (OHRP) to remind IRBs of this requirement. Dr. Debra Leonard suggested adding information on cost effectiveness research in the R&D section.

Dr. Michael Amos pointed out that the text of the report makes assumptions that the tests are accurate, yet there are only a handful of clinical diagnostic tests that have standard reference materials available. He added that the technologies that would make PGx available to everyone do not yet exist. Dr. Winn-Deen disagreed and noted that CDC is funding a technology platform that can be used in PGx. She said CDC was issuing a Request for Proposal (RFP) to develop rapid point-of-care testing for avian influenza based on genetic analysis. Dr. Amos replied that the data on rapid genetic testing must still be integrated into a

form that can be used and studied to implement new biomarker discovery. He said that no new protein biomarkers had been approved by the FDA in the last 10 years. Dr. FitzGerald suggested that these ideas could be added to the report's discussion of the goals and current status of PGx technology. He then asked the Committee to review each recommendation on research and development.

In Recommendation 1A, the Committee expanded the concept of "genes" to "gene variations and functions" to capture the importance of gene variability from person to person. In discussions about Recommendation 1B, Dr. Amos suggested adding language that would reflect the need for a change from a reductionist approach (e.g., one protein and one gene) to a systems biology approach. Dr. Collins did not agree that a systems biology approach is needed to identify potential candidates for trials and stated that full-fledged clinical validity needs to be established in prospective trials. The Committee decided to change the order of the recommendations to: 1A, 1C, and 1B. Dr. Leonard suggested expanding 1B to state that the PGx technologies being developed must provide answers in a clinically timely manner. Dr. Collins said the wording of 1B needed to be even more explicit in encouraging technologies that give rapid turnaround, cost-effective, point-of-care genotyping for pharmacogenomics.

Dr. Rochelle Long, National Institute of General Medical Sciences (NIGMS), suggested using Recommendation 1C to encourage upgrading of ClinicalTrials.gov (run from the National Library of Medicine) to collect additional fields. She said the registry could list the types of materials collected in the trials and state whether the data had been consented for PGx studies. The goal would be to enable collaborations that would allow PGx components to be added onto or designed into clinical trials at their outset. Dr. Barbara McGrath wanted to add "cost effectiveness studies and ELSI issues" under 1C.

For Recommendation 1D, Dr. Long noted that NIH doesn't give priority scores to studies, but rather, assembles review panels to do so. She said that the recommendation could be changed to state that funding decisions should favor studies that satisfy FDA quality of evidence standards. Dr. Joseph Telfair said he was under the assumption that priorities are already given to studies that are methodologically sound and statistically rigorous and Dr. Long agreed. Dr. Liz Mansfield, FDA, stated that studies are typically reviewed and funded prior to being started. However, Recommendation 1 was written in a way that made it appear that FDA advice would be sought only after studies were begun. Dr. Winn-Deen said the goal of Recommendation 1 was to encourage the publication of good studies independent from industry. The Committee agreed that this recommendation needed to be clarified.

Recommendation 2A encouraged the development of guidance documents about best practices for the co-development of PGx drugs and diagnostics. Dr. Mansfield noted that an FDA white paper on this topic was headed toward draft guidance status. The Committee accepted the draft wording of 2A and also 2B, which was written to encourage FDA to facilitate co-development of PGx products.

In discussions about Recommendation 2C, Dr. Randhawa asked where proprietary data on abandoned drugs would be housed if pharmaceutical companies agreed to submit it. He was not sure that housing it at FDA would advance the goal of making the data available to the public. Dr. Allen Rudman, FDA, agreed, stating that FDA has a voluntary genomic data submission process, but the information that is submitted is confidential. The Committee agreed to Dr. Evans' suggestion to substitute the phrase, "encourage the sharing of proprietary data" for "encourage the voluntary submission of proprietary data." Dr. Leonard made the point that some drugs have been abandoned in developmental stages, prior to FDA submission, and data on these would not be captured.

The Committee discussed whether to develop concrete suggestions for incentives for voluntary submissions. Dr. Evans cautioned the Committee against making recommendations to incentivize drug companies unless they had specific ideas on how this could be accomplished. Dr. FitzGerald suggested asking for ideas on concrete incentives during the upcoming fact-finding stage. He said that if no feasible

incentives existed, the Committee could develop an alternative recommendation. The group discussed whether this recommendation should apply only to abandoned drugs. Dr. Winn-Deen reminded the Committee that the original concept for this recommendation was rescue of abandoned drugs. Pharmaceutical companies were considered more likely to comply in these cases because the stakes are lower.

Recommendation 2D was flagged as a high priority by the Task Force. It stated that FDA should amend the Humanitarian Device Exemption Regulation so that incentives for the development of orphan drugs are extended to PGx tests intended for use in conjunction with orphan drugs. Dr. Mansfield clarified that the Humanitarian Device Exemption extends to tests that are intended to be run on a population of 4,000 or less and that no clinical validity is required. She questioned whether the Committee should recommend rewriting the regulation to extend it to a population of 200,000, the number allowed for orphan drugs. She said this would create a non-level playing field for genetics tests versus every other kind of test. The Committee agreed with Dr. Winn-Deen's suggestion that they instead recommend that the same incentives apply to orphan drugs as their companion diagnostics.

Recommendation 3A was flagged by the Task Force as a key recommendation. It stated that HHS should support efforts to address gaps in evidence for which clinical validity and utility evidence is lacking. Dr. Rollins wanted to incorporate measures of accuracy, expand the idea of utility, and add the idea of management of the patient. Dr. Linda Bradley, CDC, noted that issues about accuracy could be addressed by adding "analytic validity." Dr. Parekh felt that clinical utility already encompassed patient management because, as defined in the report, it informs clinical decisionmaking. Dr. Randhawa suggested emphasizing analytic validity in Recommendation 1 and focusing on clinical outcomes in Recommendation 3. Dr. Randhawa wanted to add the concept of mechanisms for generating new knowledge for clinical outcomes in Recommendation 3.

Recommendation 3B was also flagged by the Task Force as a high priority. Dr. Winn-Deen suggested clarifying which manufacturers (e.g., drug, device) were the subject of the recommendation. Dr. FitzGerald said the wording should be changed to specify drug manufacturers. Dr. Mansfield stated that evidence of clinical utility is not traditionally required for devices and that by requesting it, the Committee could delay tests from getting to market as quickly as possible. Dr. Rudman suggested adding that the FDA should encourage manufacturers to submit PGx data in addition to clinical utility data. Dr. Leonard noted that the Center for Drug Evaluation and Research (CDER) at FDA had recently developed a table of biomarkers and PGx tests. The CDER website could be referenced in 3B as a means of making this information available.

Discussion of Recommendation 3C raised questions about a potential conflict of interest if health plans could determine clinical utility and then base payment on their own assessments. Dr. Evans believed it should be up to providers to demonstrate clinical utility. Dr. Rollins explained that CMS sets payment by considering all data currently available and determining whether or not a treatment is considered reasonable and necessary for a specific condition. He said this practice was consistent with the draft recommendation. Dr. Randhawa noted that in addition to payers, evidence of clinical utility could be generated by federally funded programs, privately funded programs, or other entities. He said the goal of the recommendation should be to help identify gaps in knowledge and then fund knowledge/outcomes research. He said the payer's perspective was just one element of the discussion. Dr. Tuckson agreed to draft new language urging the Government to work with various entities to facilitate knowledge development.

Recommendation 4A was flagged by the Task Force as extremely important, as it related to interoperability among research, regulatory, and health record and claims databases. The Committee accepted the draft wording with no changes. Recommendation 4B was also flagged as a priority by the Task Force. It addressed the issue of finding an appropriate balance between data sharing and protecting privacy. Some Committee members felt 4B went too far in the direction of protecting privacy. Dr. Collins suggested changing the wording to state that every effort should be made to maintain confidentiality and privacy of data, while also ensuring that research can go forward by providing access to qualified scientific researchers. Dr. Telfair suggested adding examples of projects that have struck the appropriate balance.

Dr. Evans and Dr. Tuckson felt that the third paragraph of Recommendation 5 placed an extraordinary burden on manufacturers by requiring them to conduct additional studies to identify biological markers that underlie differential drug responses in racial and ethnic subpopulations. The Committee decided to delete the paragraph. They agreed that the intent of the recommendation was to move from a racial explanation of drug effectiveness to a genomic, pharmacogenomic explanation. Dr. Telfair suggested adding stronger language in the ELSI section on the fact that race is an imperfect proxy for biological factors.

Gatekeepers

Dr. FitzGerald introduced the “gatekeepers” theme in the report. He explained that gatekeepers are groups that can enable, halt, or redirect the course of PGx technologies and therefore can affect integration and patient access. They include: industry, the FDA, CMS and other third-party payers, and clinical practice guideline developers**.**

The role of industry involves the manufacturers' perceptions of risk and return on investment influence and whether and how PGx products are developed and marketed. There are disincentives to developing PGx products that can lead to a segmented market, resulting in decreased profitability. Another disincentive is the additional responsibility involved in coordinating co-developed products.

FDA approval affects manufacturing practices, the conduct of clinical trials, market clearance, post-marketing surveillance, access to PGx products, and their use in clinical practice. This raises questions about the adequacy of genetic test regulation, the extent to which genetic data submissions will be required, premarket review of co-developed products, and labeling of PGx products.

CMS and other third-party payers have the ability to obtain coverage and favorable reimbursement, which is critical to manufacturers' willingness to invest in R&D for new PGx products. The challenges include the fact that Medicare does not cover preventive services, private plan coverage may be difficult to obtain, (e.g., because of limited clinical validity and utility information), reimbursement may not be adequate, and uncertainty about and variation in plans' evidence expectations.

Clinical practice guideline developers affect the coverage of pharmacogenomic products and their uptake by health care providers through their guidelines, which are currently considered insufficient.

Discussion: Gatekeepers

Recommendation 6A was flagged by the Task Force as a high priority. Dr. Rollins clarified that CMS views PGx tests as diagnostic when patients have signs and symptoms of a particular disorder, but does not consider the tests diagnostic when patients do not have any signs or symptoms. In other words, CMS does not cover preventive services, such as a predisposition for a specific genetic disorder. Dr. Rollins noted, however, that the Secretary was investigating whether Congress could give CMS a designation for

a prevention category. This action was previously recommended by the Committee in the coverage and reimbursement report. The Committee agreed to be more specific in 6A and recommend that PGx testing should be covered for patients who have a predisposition for a genetic disorder even if they don't have any signs or symptoms of a disorder.

The Committee accepted the draft wording of Recommendation 6B with no changes. However, Ms. Berry stated that she might later submit a related recommendation on the impact of PGx on the development and use of health plan formularies.

Recommendation 6C was deleted because it was considered too broad to be useful and it overlapped to some degree with Recommendation 11B.

Implementation

Dr. FitzGerald reviewed the implementation section of the report, which described education and guidance, information technology, economic implications, ELSI issues, and the coordination of HHS PGx activities.

Concerning provider education and guidance, Dr. FitzGerald noted that genetics education and training by health professionals, payers, and regulators is currently insufficient. There is limited information available through labeling and practice guidelines about how to interpret PGx test results and use them to inform treatment decisions. Genetics education is also needed by consumers so they can make informed treatment decisions. However, direct access to PGx testing through over-the-counter sales or direct-to-consumer marketing could increase inappropriate use of these tests. This could lead to increased health care costs, the potential for misinterpretation of test results, misinformed health decisionmaking, and adverse health consequences.

Dr. FitzGerald stated that the uptake of EHRs is still in the early stages and there is no consensus on how genetic information should be stored in EHRs or who should have access to the data. There is a lack of harmonized standards for storing and exchanging genomic data and a need for PGx decision support tools and reminder systems.

One of the economic implications of PGx is that the use of such technologies will likely add to health care costs in the short term. There is a need to examine the benefits and costs of investment in PGx technologies, but there is currently little research on their cost effectiveness. The Committee agreed that this section of the report should be reworded to balance the idea of possible initial increases in health care with the longer-term possibility of savings due to a decrease in the number of adverse reactions.

ELSI issues include the financial barriers to PGx products (e.g., high co-payments, underinsurance, no insurance) that could result in access disparities; concerns about genetic discrimination; and liability risk if the provider fails to administer recommended tests.

Dr. FitzGerald said that many coordinated activities were ongoing in HHS agencies and listed in Appendix A of the report. However, there is no single coordinated Federal framework or action plan to address PGx challenges or share information about these activities.

Dr. FitzGerald then opened up the floor for discussion.

Discussion: Implementation

Ms. Berry commented on the possibility of initial increased health costs of PGx technologies, with savings realized downstream. She stated that the Federal budget does not recognize downstream savings, such as fewer hospitalizations or adverse drug events. She suggested crafting a recommendation that would press for consideration of these types of data, which could lead to enhanced health care coverage by Federal programs. The Committee agreed that the text on this issue should be re-worded in the report and discussed under Recommendation 9. Dr. Sherrie Hans noted that all medical technology is affected by the limited way in which the cost savings are calculated in the Federal budget.

Recommendation 7A was flagged by the Task Force as a high priority. Dr. Rollins suggested changing "meta-analysis" to "systematic reviews that look at how test results were used in the management of patients."

The Committee accepted the draft wording of Recommendation 7B with no changes.

For Recommendation 7C, the Committee discussed changing "provide resources to professional organizations" to "work with professional organizations." Dr. Telfair suggested the wording, "provide a mechanism for coordination." The Committee agreed that examples of collaborative efforts of HHS with professional organizations should be added. Ms. Berry suggested adding the concept of creating incentives to encourage providers to report data (e.g., enhanced Medicare reimbursement). Dr. Tuckson said this idea fit well with AHIC's goals. The Committee considered whether to include industry, as well as professional organizations in 7B and 7C. Dr. Hans noted that the Veteran's Administration (VA) published two reports on the motivations of industry in providing information to practitioners. The reports were issued through the National Center for Ethics in Health Care.

During discussion of Recommendation 7D, which was flagged as high priority by the Task Force, Dr. Long stated that "dosing decisions" should be changed to "decisions" and the term dosing should be deleted throughout. Dr. Evans and Ms. Leonard suggested adding "specific" prior to the phrase "guidelines based on test results" and adding, "such as dosing or drug selection." Dr. Winn-Deen agreed to provide the language concerning labeling information.

The Committee accepted the draft wording of Recommendations 7E, 7F, and 7G with no changes.

The Committee decided to combine Recommendation 8A with 8C.

The Committee accepted the draft wording of Recommendation 8B with no changes.

Dr. Telfair suggested that Recommendation 8C be changed to emphasize the use of existing mechanisms to enhance public awareness and public consultation, such as the efforts ongoing at Health Resources and Services Administration (HRSA). Dr. Tuckson stated that is was important to connect this recommendation with the Personalized Health Care agenda that HHS was already implementing.

Recommendation 9 was flagged as a priority by the Task Force. Dr. Leonard was concerned about the emphasis on the economic value of research and development versus the use of PGx technologies. Dr. FitzGerald suggested adding, "investments in pharmacogenetics relative to investments in other health and non-health-related areas." Dr. Evans stated that this was the appropriate place to say that PGx holds the possibility of lowering health care costs and that this issue should be looked at globally. He agreed to develop new wording.

The Committee agreed that new text should be added to the report on the Federal budget's assessment of economic value. Ms. Berry felt this topic should be included in Recommendation 9, i.e., directing HHS to drill down into the types of data that the budget office might be receptive to examining. Ms. Berry agreed to develop new wording.

Because of NIH budget constraints, Dr. Collins felt that Recommendation 10 should state that NIH should continue to encourage research on the ELSI implications of PGx, rather than recommending funding of new research. Dr. Telfair added that several mechanisms within HHS are looking at these issues and these programs should collaborate on cross-cutting, high quality research. The last sentence in the recommendation was deleted because it was too broad.

Dr. Evans wondered if the possibility of litigation as a driver for the adoption of pharmacogenomics into medicine should be addressed in the ELSI recommendations. Dr. Winn-Deen stated that this issue was addressed in the report, although it did not have a related recommendation.

Dr. Hans suggested that Recommendation 11A add language stating that HHS should consider inviting participation of other Federal agencies as appropriate.

Dr. Bradley suggested that Recommendation 11B include specific examples.

Next Steps

Dr. FitzGerald discussed next steps in revising the report and the recommendations based on the input received from the Committee. He suggested that staff members and the Task Force draft wording for the revised recommendations and email them to the Committee for review. Any additional comments by Committee members were to be sent to staff. The Lewin Group was to conduct the stakeholder and expert interviews, followed by the public comment process.

Session on Gene Patents and Licensing Practices

James P. Evans, M.D., Ph.D.
Chair, Task Force on Gene Patents and Licensing Practices

Dr. Tuckson stated that in March of 2004, the Committee identified gene patents and licensing practices as a high priority issue. However, because the National Academy of Sciences (NAS) had begun a study on this topic for NIH, a decision on whether to undertake a SACGHS study was postponed until the NAS report was completed. The report, titled, "Reaping the Benefits of Genomic and Proteomic Research," was published in the fall of 2005. A SACGHS team appointed to review the study found that its recommendations sufficiently addressed intellectual property concerns in the research realm, but did not fully examine the impact of patents and licensing practices on patient access. In June 2006, SACGHS gathered more information on the topic and concluded that the Committee should conduct an in-depth study of the effects of gene patents and licensing practices on patient access. The Committee developed a scope for the study, discussed investigational approaches, and established a Task Force, appointing Dr. Jim Evans as Chair. Dr. Tuckson turned the floor over to Dr. Evans for an update on the recent activities of the Task Force.

Dr. Evans introduced Mara Aspinall, president of Genzyme, who was assisting the Task Force, and Brian Stanton, from the NIH Office of Technology Transfer (OTT). Dr. Evans stated that the goal of the day's session was to reach Committee consensus on the draft scope, study questions, and next steps that had been developed by the Task Force. He began the session by making a distinction between the concepts of "patient access" and "clinical access" as used in the study documents. Patient access refers to full patient

access to emerging technologies. Clinical access refers to a broader view of patient access, including the development of tests and the integration of genetic testing into patient care.

Dr. Evans led discussion of the draft scope. Dr. Stanton suggested deleting the phrase, “adverse effects,” which would open the study up to both the positive and negative effects of gene patenting and licensing practices. Dr. Evans added that removal of the introductory phrase, “While recognizing the benefits and importance of patenting in innovation and technology development… ” would help eliminate the negative focus. He also explained that the study scope assumes that the tests in question are legitimate, because the charge to the Task Force was not to determine which tests have a good outcome.

Dr. Evans introduced the first study question, which concerned the overall effects of patenting on clinical access. Dr. Tuckson felt the question was too broad and he suggested addressing the positive and negative issues separately. He also said the level of evidence for what constitutes a “significant” impact on access should be indicated in quantitative and qualitative terms (e.g., numbers of people, drug prices) for each subpoint.

The next question addressed the loci of possible problems, i.e., where barriers are found in the health care system. Dr. Tuckson suggested developing a “chain of evidence” that illustrates system barriers, starting from basic research and moving to the point at which patients try to access and receive reimbursement for tests. Dr. Randhawa asked what the comparator would be for the chain of evidence and Dr. Evans stated that there was no clear answer. There might not be a basis of comparison for many years, i.e., until some genes are off patent. He suggested looking at other systems in which patents and licensing are not as restrictive. Dr. Leonard stated that they could look at the relative effects of various licensing practices. Dr. Stanton suggested identifying how various components of the intellectual property system affect specific parts of the health care system.

The next study question addressed the positive and negative impacts of licensing practices. Dr. Tuckson asked what criteria would be used to determine whether licensing practices are having an effect. Dr. Evans stated that the study would try to capture quantitative and qualitative data on licensing practices, gene patents, and the prices of genetic tests. He noted that cost is integrally related to patient access because some tests are extraordinarily expensive. During discussion of the question on cost, Dr. Amos asked the Task Force to identify whether there are specific examples of limited licensing practices or patents that have prevented a product or test from reaching a clinic.

The next question dealt with the effect of development on tests. Dr. Winn-Deen made the point that that the study questions should not be structured to produce “yes or no” answers and Dr. Evans suggested changing the wording to read: “In what ways do gene patents and/or licensing practices enhance or create barriers… ”.

Dr. Evans asked the Committee if they thought the next study question, on quality, fell within their purview. The discussion began with Dr. Hans asking if the following scenario would be included in the study question: There are seven different genetic changes responsible for a certain condition. One lab holds patents on three and another lab holds patents on four. One lab decides not to pursue test development, but does not license their information on mutations. She stated that a test based on only four of the mutations would not be of very high quality. Dr. Evans saw this situation as an access issue more than a quality issue.

Dr. Collins expressed support for including the concept of quality in the study because tests that are exclusively licensed to a single provider are not receiving any other independent assessment of quality. Dr. Stanton disagreed, stating that he thought quality was not under the purview of the Task Force and that they should focus on the issue of whether or not there is access to the genes that allow testing to take

place. After some discussion, Dr. Evans decided there was consensus from the Committee on including the question on quality so that the issue did not "fall through the cracks."

The next question concerned feasible alternative models that could be applied to the patent and licensing system that would preserve its inherent incentives. Dr. Amos stated that the Committee can only propose policy for NIH, not for industry, but Dr. Evans clarified that recommendations can be made to entities other than the Secretary when warranted. Dr. FitzGerald suggested examining global approaches for alternatives and Dr. Evans said the Task Force planned to cast a wide net and convene a roundtable to learn about many other models. The word "adverse" was deleted from the question.

The Committee then discussed the proposed study plan, which included four components: an in-depth study, a public consultation process, consultation on international perspectives, and development of a report to the Secretary.

In-Depth Study

Dr. Evans stated that the in-depth study would begin with the commissioning of a literature review that would be completed in the spring of 2007. Following that, a roundtable would be held to discuss gaps that are amenable to additional study in the near-term. The Task Force might commission limited studies in these areas.

Committee members pointed out the limitations in the literature, i.e., some is outdated and failures are not published. The group emphasized that the literature review should focus on current situation, rather than historical information. Dr. Evans suggested commissioning an update to examine how the field is changing and noted that most of the factors that can be measured will be proxies for patient access (e.g., the ability to develop a test, the ability to offer a test, cost). He said there might be a body of economic literature that used modeling to assess the ultimate effects of gene patents and licensing on access.

Dr. Amos suggested development of a survey that could be distributed through a professional organization (such as the College of American Pathologists) to evaluate health care providers' abilities to provide genetic technologies to patients. The providers surveyed could include genetic counselors, pathologists, laboratory directors, and those in academic settings. Mr. Stanton noted the importance of determining a benchmark against which to measure results. Dr. Winn-Deen noted that if commissioned studies are necessary, the researchers should not be biased in favor of a particular result. Dr. Ferreira-Gonzalez suggested looking at the effects of licensing on cost and delayed access to testing from the perspectives of academia, independent laboratories, and industry. Dr. Amos and Dr. Evans agreed that the final report on access should include a vision for navigating the barriers uncovered by the study. This might involve recommending changes in patent laws, but also working within the constraints of current laws. The Committee agreed that communication should take place between the NIH committee that was analyzing the NAS report and SACGHS.

Public Consultation

Dr. Evans described the timeline for the public consultation process, stating that the Task Force planned to solicit public comments on the effects of gene patents and licensing practices on patient access over a 2-month period early in 2007. Key stakeholders would be invited to a SACGHS meeting in the summer of 2007 and a final product would be developed documenting these comments in the fall of 2007.

Dr. Tuckson suggested providing the public with criteria to help them determine whether it was actually patenting and licensing practices that affected access, rather than cost or other factors. Dr. Leonard and Dr. FitzGerald suggested that the public consultation process be used to help define the patient access

problem and establish the language used to solicit comments from the public. This language should be neutral, however, and would have to be reviewed by the Committee. Dr. Evans clarified that the qualitative data collected from the public was important because of the lack of quantitative research that demonstrates, in a controlled manner, the effects of patents and licensing. The Committee would therefore have to rely to some extent on the qualitative experiences and comments of various stakeholders. It was decided that consultation would be sought primarily from three groups: advocacy organizations, the public at large, and health care providers. Dr. Leonard suggested that it be called a public data-gathering process or information-gathering process.

International Perspectives

Dr. Evans said the Task Force felt that they could learn from models in other countries if the comparisons were germane and feasible. They planned to develop questions for international experts in the summer of 2007 and invite these experts to a roundtable session that would take place in the fall of 2007. The Committee had no changes to this part of the work plan.

Discussion of Proposed Study Plan

Dr. Evans asked for feedback on the overall study plan, including the timetable, the stakeholders included, and public consultation methods. The Committee felt that the timeline for the research process was too ambitious and that more time should be allowed. Dr. Hans suggested that the scope of work for a contract include the option of conducting case studies after the public consultation process. Dr. Tuckson stated that, because of the difficulties inherent in trying to quantify and characterize the impact of patents and licensing on patient access, additional expertise might be required to gather information in areas such as health economics.

Dr. Evans clarified that development of the study hypotheses would have to wait until it was clear what the gaps are, although he felt the study should have a large degree of neutrality and not be hypothesis driven. Dr. Randhawa asked how the Committee intended to define “genetic test” for the purpose of the study. He wondered whether the Task Force planned to explore the patenting of testing platforms and methodologies, as opposed to specific genes. Dr. Stanton suggested that the Committee define “gene patent” as a starting point, so that the questions would be formulated with concrete algorithms. After some discussion, the Committee agreed that the study should focus on the patenting of gene sequences and their allelic derivatives. Dr. Leonard added that the recommendations that are relevant to gene patents could easily be translated and applied at an earlier phase to prevent exclusivity in clinical practice concerning proteomics.

Public Comments

Llana Suez Mittman, Ph.D., M.S., CGC

Dr. Mittman stated that in the past, scientists focused on ethnically defined groups for the study of rare or recessively inherited conditions, but a new paradigm shift is targeting more common afflictions (e.g., diabetes, hypertension and asthma). She said that the Jewish case in genomic research is particularly troubling and that the Ashkenazi Jewish population received disproportionate attention with respect to genomic studies. Jewish community leaders are concerned that this focus will revive the fallacy of the inferiority of the Jewish people and lead to stigmatization and discrimination. In spite of the racial, ethnic, cultural, and economic diversity of Jews, they are often viewed as a monolithic group and stereotypically portrayed as a model minority of affluent and well educated people. Often, no distinction is made among various subgroups. As an example, she said that a recent study in the American Journal of Public Health portrayed Ashkenazi Jews as an advantaged group receiving preferential treatment in genetics and

enjoying easy access to BRCA testing at the expense of other less advantaged groups. However, she said that as many as 600,000 Jews are recent immigrants to the U.S. and face linguistic, economic, and cultural barriers to health care. Dr. Mittman identified serious issues related to within-group discrimination. These issues seem to emerge from misconceptions within the Jewish community with respect to its genetic endowment and linking Jews with common disorders, as well as inherited mental disorders. She recommended that when studying public perceptions related to large population-based genetic studies, the definition of vulnerable populations should be explained and Federal officials charged with eliminating health disparities should conduct public deliberations.

Dr. Debra Leonard
Association of Molecular Pathology (AMP)

Dr. Leonard provided AMP's perspective on the draft guidances from FDA on ASRs and IVDMIAs. She said that "Commercially Distributed Analyte-Specific Reagents (ASRs): Frequently Asked Questions," defined a much narrower interpretation of the ASR rule than was currently in practice. AMP was concerned that a narrow interpretation would limit the availability of ASRs, which provide high quality reagents for the validation of laboratory developed tests by clinical laboratories under CLIA regulations. If ASRs become more limited, laboratories will find other sources for these reagents that are of poorer quality or will stop performing many tests that are standard of care. This could lead to decreased patient access to molecular testing services. The second draft guidance, "In Vitro Diagnostic Multivariate Index Assays (IVDMIAs)," defines FDA's regulatory approach to complex multivariable tests. Dr. Leonard stated that the use of an interpretive algorithm is routine in medical practice and should not in and of itself raise specific concerns with the FDA.

She also stated that AMP was very concerned by the CMS decision not to incorporate a genetic specialty into CLIA regulations. She said that CLIA regulations define genetic testing in terms of classical cytogenetics only. Defining genetic and molecular diagnostic testing explicitly would allow for appropriate regulation and oversight of these tests. A genetics specialty within the CLIA regulations would promote expansion of proficiency testing programs, provide better oversight of genetic tests, and reassure the public and members of Congress about the quality of genetic testing performed in CLIA-certified laboratories. Dr. Leonard presented AMP’s position on the assessment of coverage and reimbursement for genetic testing services. The organization was concerned that the CPT codes and reimbursement levels set for them are less than the cost to perform them. AMP applauded SACGHS for its recommendations on this issue and asked the Committee to follow up to determine whether action will be taken. AMP also wanted SACGHS to give full consideration to the negative impact of exclusive licensing and enforcement practices for gene patents on the future of genetic testing. They believe that gene patent enforcement limits the tests that can be performed by clinical laboratories and they urged SACGHS to develop recommendations to the Secretary of HHS to address the clinical impact.

Dr. Tuckson noted that public comments from the International Society of Nurses in Genetics (ISONG) were provided in the Committee’s table folders.

Oversight of Genetic Technologies and Genetic Testing Laboratories

Session Overview

Reed Tuckson, M.D.
Chair, SACGHS

Dr. Tuckson stated that oversight of genetic tests had been a public policy concern for over a decade. Both FDA and CMS have responsibility for regulating genetic tests and genetic testing laboratories. Genetic tests developed in-house by individual labs are subject to less regulation than commercially distributed genetic tests. He stated that the quality and validity of genetic tests has always been a high priority for SACGHS and for its predecessor committee, the Secretary's Advisory Committee on Genetic Testing (SACGT). Dr. Tuckson stated that the Clinical Laboratory Improvement Amendments (CLIA), which regulate clinical laboratories, do not have specific provisions for laboratories performing genetic tests. CMS had reported to the Committee in June 2006 that plans were underway to add a genetic testing specialty to the CLIA regulations. Dr. Tuckson said that this session would allow for an in-depth discussion about whether gaps in oversight persist. After presentations by CMS and FDA representatives, the Committee would discuss whether SACGHS should move beyond a monitoring role and undertake fact-finding and analysis.

Developments at FDA

Steve Gutman, M.D., M.B.A.
Director, Office of *In Vitro* Diagnostic Device Evaluation and Safety, FDA

Dr. Gutman stated that FDA has been involved in the regulation of medical devices and *in vitro* diagnostic devices (e.g., lab tests) since passage of the Medical Device Amendments of 1976. The amendments introduced general controls for lab tests, including requirements that makers register their products, follow good manufacturing practices, and report adverse events. FDA works collaboratively, and if necessary, coercively, to resolve any problems that arise. The framework is a risk-based regulatory process.

The 1976 law also introduced a requirement for premarket review to demonstrate that new medical devices are analytically reliable before entering the marketplace. For some tests (e.g., a new genomic marker of unknown significance), clinical performance must also be demonstrated. FDA regulates labeling for all products and ensures that there are adequate instructions for use. However, FDA regulations are not the only path for a new test to come to market. Laboratory developed diagnostic tests (sometimes referred to as "home brew" tests) are created in a single lab for use at that lab. This practice is very well established, but not entirely trouble free. For laboratory developed tests, there is no requirement for premarket review, no clear separation between the research phase and the clinical phase of product use, and no explicit requirement for demonstrating clinical validity.

In 1997, FDA published an analyte-specific reagent (ASR) rule intended as an incremental increase in the regulation of laboratory developed tests. ASRs are the building blocks or active ingredients of the laboratory developed test. The regulation required general controls, such as registration and listing, good manufacturing practices, and adverse result reporting, but did not require general premarket review. The ASR rule was developed to create a safe harbor for laboratory developed tests so that the practice could go on unimpeded, but with increased quality and transparency. Dr. Gutman pointed out that the preamble to the ASR rule codifies the fact that that FDA has always seen laboratory developed tests as falling within the definition of medical devices, and that laboratories creating those tests are within the definition of sponsors or manufacturers and therefore subject to FDA jurisdiction under the 1976 Act.

The ASR rule had some unintended consequences. Some ASR manufacturers began promoting products as ASRs that were inconsistent with the rule's definition to skirt FDA oversight. The draft ASR Q&A Guidance (2006) was not intended to eliminate legitimate laboratory developed tests, but to better clarify the definition of an ASR and limitations on marketing. From the FDA perspective, there was nothing new in substance, spirit, or meaning in the Guidance, although it provided new examples. The labs have the same responsibility as they did when the rule was published. Dr. Gutman said comments on the Guidance document were in the process of being received and an extension of the public comment period was being considered. Dr. Gutman noted that the ASR rule provides a Class I exempt status to the building blocks of home-brew assays. FDA has generally exercised enforcement discretion over laboratory developed tests.

Dr. Gutman then addressed the draft Guidance on *In Vitro* Diagnostic Multivariate Index Assays (IVDMIAs) (2006). He said IVDMIAs are a growing category of tests that include elements that are not standard ingredients of in-house tests, and they therefore raise safety concerns. IVDMIAs do not fall within the scope of the laboratory developed tests over which FDA has generally exercised enforcement discretion. Dr. Gutman stated that although the draft Guidance sends a signal, it is a much narrower signal than the laboratory community or the community in general was interpreting it to mean. FDA was concerned about one or two dozen products that might be headed to market in the next 5 to 10 years, not hundreds or thousands of submissions. The Guidance was targeted to a narrow niche of devices that use complex software, algorithms, or formulas to create patient-specific scores or indexes that a well trained health care provider would not be able to interpret. FDA did not intend that all algorithms or software would fall into this category. He stated that just because a device is multivariate, it is not automatically an IVDMIA. Dr. Gutman closed by stating that FDA's mission is to promote public health by getting good products out quickly and keeping bad products off the market.

Dr. Tuckson asked if Dr. Gutman felt there was a gap in oversight, and if so, to define it. Dr. Gutman stated that there is a partial gap and he listed three specific problems. First, although CLIA, CAP, COLA, and JCAHO provide some protections, they can't fully analyze data in 2 or 3 days. He said he has seen a great deal of bad data manipulated in odd ways. Second, he stated that in a competitive arena, labs and companies answer to their hospital administrators and stockholders, respectively, and public health is not their first concern. Economic pressures affect their decisionmaking processes. The third gap he mentioned lies in the differences in the regulation itself, because there is an inability to go after clinical validation. He said that is a basic limitation of CLIA.

Developments at CMS

Judith A. Yost
Director, Division of Laboratories and Acute Care
Centers for Medicare & Medicaid Services

Thomas E. Hamilton
Director, Survey and Certification Group
Centers for Medicare & Medicaid Services

Ms. Judith Yost stated that the CLIA regulations were published in 1992 and that they cover all testing in the United States, including genetic testing. She provided a history of recommendations for changes to CLIA and stated that a comprehensive final quality control regulation was published in 2003. A number of recommendations were made by various advisory bodies and many were still unresolved, including the issue of whether a specialty area is needed for genetic testing.

Ms. Yost provided an overview of the current scope of CLIA, beginning with quality control. She said that there is no genetic testing specialty; tests that are considered genetic are dispersed throughout the various laboratory specialties. She discussed proficiency testing (PT), which is a measure of the long-term accuracy of laboratory testing, and said there is no formal PT required for genetic testing in the CLIA regulations. In the area of personnel education and training, there are a number of personnel positions required in the laboratory for high complexity tests (and most genetic tests are considered high complexity). Competency checks for personnel are required annually. CLIA also requires quality assurance, which is an overall plan in the laboratory for assessing the quality of testing, solving problems, and communicating with patients and staff. Quality assurance encompasses all of the CLIA quality standards. Ms. Yost described the CLIA sanctions that are imposed against laboratories cited for deficiencies and that fail to correct problems. Based on the seriousness and scope of the problems, labs can be fined $10,000 a day, be denied Medicare reimbursement, or lose CLIA certification. She stated that the CLIA survey process is very effective overall.

To shed light on the recent decision not to propose a regulation for a genetic testing specialty, Mr. Thomas Hamilton described the process by which an administrative rule is considered. Internal deliberations take place among the major agencies of HHS to determine whether there would be an absolute benefit. The questions asked are: Is there a problem for which the proposed rule is a remedy? Is it a significant problem? Does the rule effectively address the problem? How strong is the evidence that the proposed rule will address the problem?

Mr. Hamilton then discussed these questions as they related to the benefit of a genetic testing specialty. He said there was a lack of evidence that there was a problem solvable by CLIA that was currently unaddressed. He said a genetic testing specialty would not provide clinical validity or solve the problem of a lack of proficiency testing. CMS is not directed, authorized, or funded to create proficiency tests; that is the responsibility of professional societies. CMS merely approves the tests. He added that prescriptive standards in a Federal rule could become outdated and lock the field of genetic testing into an outmoded system of compliance.

The second part of the analysis determines comparative benefit, i.e., whether the benefit exceeds the costs or outweighs alternative approaches that might be less costly, more effective, or take less time. Mr. Hamilton stated that laboratories are already covered by CLIA, including genetic testing laboratories. He said a new rule would cause disruption to the existing infrastructure and specialties and would take about 3 years to implement. CMS explored whether other avenues would be faster and just as (or more) effective. They tried to identify how the existing CLIA regulations and law could be used as effectively as possible to address any issues that emerged, and Mr. Hamilton acknowledged that there were issues. For example, CMS has identified some laboratories conducting genetic testing that thought they were exempt from CLIA. CMS is working with FDA and CDC to collaborate on surveillance. When they find a laboratory that does not have a CLIA certificate (or the appropriate CLIA certificate for the tests they are conducting) they direct the State survey agencies to take action. Labs that refuse entry or refuse to apply for a CLIA certificate can be sanctioned. CMS wants to identify the genetic testing laboratories that are not fulfilling the responsibilities currently required in the regulations and make sure that they are brought into full compliance.

The third element of the analysis of the burden of a proposed regulation is that, even if it has a comparative advantage over other regulations, how does it fit into the overall scheme of the priorities of all the regulations (i.e., the burden of priority)? What infrastructure would be needed to implement a new rule and how does that investment compare with other needed investments? When the Department and CMS looked at all the potential regulatory changes that they could effect and the extent to which they could address some issues through current regulations, they decided to put their efforts into applying and strengthening the existing regulations. Those actions could be taken immediately, in contrast with a proposed regulation.

Dr. Tuckson opened up the floor for discussion. He asked the speakers if any issues were not being addressed by any Federal agency, leaving gaps that could harm the public. Mr. Hamilton noted that CLIA is only concerned with analytic validity, not clinical validity. FDA has a role in the clinical validity of test kits, but not in laboratory developed tests. He stated that all the agencies must work together to create an effective system. Dr. Gutman acknowledged that there are gaps in the system, some of which may cause little or no harm; others could cause great harm.

Dr. Leonard stated that a gap exists because laboratory developed tests don't go through a premarket review at FDA and because the CLIA regulations are weak in their evaluation of these tests. She stated that CAP instituted a list of questions for genetic tests that must be answered by an inspector and that oversight can be effective, but it depends on the quality, education, and training of the specific inspector. She stated that, in deciding not to create a genetic testing specialty, some problems are falling through the cracks. However, these could be addressed by creating general rules in CLIA that look at test validation for laboratory developed tests.

Ms. Yost agreed that CLIA does not cover clinical validity, but rather asks whether tests are accurate and precise, what the reference range is for tests, and what the reportable range is for specific laboratories. For new tests, CLIA looks at sensitivity and specificity. In some cases, CMS surveyors don’t have the expertise to evaluate the data. CDC and FDA have agreed to evaluate this data if CMS collects it.

Mr. Hamilton stated that a genetic testing specialty would not solve all the problems in the system. He described the regulations that provide overarching authority and responsibility for the laboratory. Title 42 of the Code of Federal Regulations at 493.801(a)(2)(i)(i) states that each laboratory must establish and maintain the accuracy of its testing procedures (both laboratory developed and test kits). Title 42, 493.1236(c) states that at least twice annually, the laboratory must verify the accuracy of any test that is not subject to proficiency testing. He noted, however, that these regulations deal with analytic validity, not clinical validity.

Ms. Chira Chen asked Mr. Hamilton if anyone regulates laboratory developed assays. He stated that if the assay is not producing accurate results, it falls in the analytic validity area and is subject to CLIA. Dr. Tuckson said it is a problem that there is no requirement concerning the assessment of clinical validity. Dr. Winn-Deen said it is necessary to accept that this is an imperfect system and she questioned whether laboratory developed tests would ever be required to meet the same standards as manufacturer-developed tests. However, because new information is emerging in the field all the time, the lab developed tests and IVDs play an important role.

Dr. Ferreira-Gonzalez said that, even though it might take years, efforts should be made to develop proficiency testing for genetic tests so that people can have complete confidence in them. She also asked Ms. Yost to elaborate on specific requirements for individuals performing genetic testing for inherited disorders. She asked whether a high complexity, CLIA-certified laboratory director could currently start offering an FDA CLIA product for cystic fibrosis carrier screening that would be interpreted by someone with adequate training. Ms. Yost stated that because there are no specific requirements for genetic testing

personnel, the laboratory director has the overall responsibility for hiring the right people. If a new test is added that takes specific expertise, the laboratory director must either retain on contract or hire individuals who can perform and oversee the test. In this case, it would be a physician or Ph.D. with board certification, a certain number of years of experience, and specific training. If a lab does not have the appropriate individuals to perform specific testing, CMS cites the lab director and the lab can lose its certificate to conduct testing. Ms. Yost said that there is a comprehensive series of checks and balances built into CLIA, and although problems sometimes occurs that are unanticipated, the labs are doing the best job they can under the circumstances.

Dr. Tuckson asked if any entity has data on labs that aren't doing a good job. Dr. Randhawa stated that even if all lab tests were done accurately, that would not be sufficient to improve public health. He felt it was important to discuss clinical utility and the outcomes of testing, which CMS and FDA had not addressed in their presentations.

Dr. Evans asked if a problem exists with CLIA inspectors who do not have the expertise to evaluate in-house developed tests. Ms. Yost said it is a problem, but CMS is actively working on it. They plan to either train a core of people so that they have the necessary expertise and investigative skills to look at all the laboratories in the country (rather than the local surveyors), or to contract with people who already have the expertise. These specially trained personnel will know what questions to ask and will have individual labs explain their technology if they don’t understand it. She said this need would not be solved by a genetic testing specialty, because the new technologies that are arising are in a number of areas, some of which can’t be anticipated at this time.

Dr. Ferreira-Gonzalez noted that the Clinical Laboratory Improvement Advisory Committee (CLIAC) planned to look at the issues related to a genetic specialty at its next meeting in February. Since CLIAC is advisory to CDC and CMS, she suggested waiting for their recommendation on the issue, which could be discussed at the March SACGHS meeting.

Ms. Yost provided a brief update on a Government Accounting Office (GAO) investigation and Congressional hearing on direct-to-consumer (DTC) testing. GAO is the investigative arm of Congress and they were requested to look at DTC testing and follow up on the status of the proposed rule at CMS. They identified a number of labs that were providing nutrigenomic testing, i.e., evaluation of lifestyle through analysis of diet, sleep, smoking habits, and other behaviors. She noted that most DTC concerns are not CLIA issues, but CMS is responsible for oversight of the laboratories. The nutrigenomic tests are laboratory developed and CMS is closely monitoring them in collaboration with CDC and FDA.

Dr. Tuckson asked Ms. Yost to speak about the New York State (NYS) Genetics Program and stated that Ann Willey, Director of Policy for the program, was present. Ms. Yost said that New York has the most stringent State laboratory standards in the United States, with an extensive infrastructure. She contrasted that with the economy necessary in CMS, which is self-funded. Under the NYS program, there are two types of tests: FDA-approved and every other type of test (e.g., research use only, investigative use only, in-house developed ASRs). The latter types of tests must be approved by the NYS program before they can be offered. NYS has conducted approximately 450 reviews overall, which include both analytic and clinical validity. They also provide laboratory guidance on the materials needed for review. Ms. Yost noted that all reference laboratories in the country probably have a site somewhere in the State of New York, because any testing on a New York resident, regardless of where it takes place, is covered under NYS law and their tests must be submitted to the State for approval. She estimated that 75 percent of the genetic testing in the United States is subject to New York State oversight.

The program in New York is divided into two segments: cytogenetics (in place since 1972) and genetics (in place since 1990). Cytogenetics includes clinical information about test selection and interpretation, patient consent, confidentiality, specimen retention times, and turnaround time. There are requirements for reports to be signed by a cytogeneticist, that there be an interpretation suitable for a non-geneticist, and prenatal and pre-implantation outcome verification. Labs are subject to the New York State Proficiency Testing program.

There are similar requirements for genetic testing, including clinical information about test selection and interpretation, patient consent, confidentiality, specimen retention times, and very detailed QC procedures, with method documentation and retention of records. The reports must be signed by a geneticist. There must be an interpretation suitable for a non-geneticist M.D. and prenatal and pre-implantation outcome verification. In this case, proficiency testing requirements are the same as CLIA. When PT material is not available, particularly for rare diseases, the laboratory is subject to external PT, if available, or biannual review. Although there is a very detailed definition of “genetic test” under State law, some tests are disposed through the laboratories, just as in CLIA.

Dr. Tuckson stated that the Committee had an ethical obligation to follow through on the issue of genetic testing and find a suitable answer, since SACGHS, as well as SACGT, raised the issue. His concern was that people's health could be compromised and he said the Committee should think about whether there is a problem, and if so, whether it is significant.

Mr. Matthew Daynard, FTC, asked Dr. Willey what the response had been to their program and the effect of the New York law on industry and consumers. Ms. Berry asked her what prompted New York to act in the first place. Dr. Willey replied that a New York State statute from 1964, which predated CLIA (1967), requires the State to oversee the practice of laboratory medicine for the testing of all specimens derived from the human body for all purposes. When cytogenetics (the examination of human chromosomes) became a practice of laboratory medicine, it required oversight. When biochemical genetic assays for enzymes or PKU or DNA markers for genetic assays became the practice of laboratory medicine, it was required that they establish science-based standards for laboratory practice.

Dr. Willey said the statute requires that all tests performed by a permitted laboratory be generally accepted (i.e., FDA-cleared as an *in vitro* diagnostic device) and approved by the Department. The NYS process for validation review of non-FDA-cleared tests is not unique to genetics; it applies to any laboratory test, whether clinical chemistry, microbiology, or virology. The standards require that the laboratory submit validation data and clinical validity data, and for genetics, only a very small number of cases are involved. There must be a known clinical association with the genetic marker. She said that all in-house developed assays using ASRs require departmental approval, whether for genetics or microbiology.

Concerning the response to the NYS standards, Dr. Willey said that consumers are not well informed about the oversight of laboratory tests. Physicians are only slightly better informed. Many are told by the patient’s insurance company where they should order tests. She stated that 95 percent or better of all labs are good labs. The biggest objection from industry is that the office is slow because there are only two technical persons on staff who review all submissions. If a laboratory has a critical clinical need to offer a test, the office issues a non-permitted lab approval for that patient, that purpose, and that time only. Labs are allowed only about 50 such requests.

The surveyors do not attempt to review technical data at the time of a survey. They ask labs which tests are offered. For laboratory developed tests that are not FDA-approved and with no package insert stating that it's an IVD, the surveyors ask to see a letter of approval from the Department of Health. If the lab can't produce that letter, they are cited and the deficiency is corrected by submission of the validation

data. Dr. Willey noted that there are labs offering clinically useless tests that are having adverse consequences for pregnant women. They are told to cease and desist, and if they continue, they can be charged $2,000 a day.

Dr. Tuckson asked if it was burdensome for labs to have to meet NYS requirements, as well as those of CLIA and FDA. Dr. Willey said New York State is CLIA-exempt because the State has higher standards. Labs located outside the State obtain their CLIA certificates from their local State entity. She said that, to her knowledge, no one else reviews the actual validation data.

Ms. Berry wondered whether some of the procedures used in New York State could be implemented at the Federal level. She stated that she was not convinced that genetics is unique and requires a specialty under CLIA, because the problems that arise could apply to many tests in many labs. Dr. Tuckson asked Dr. Willey if there a special need in the area of genetics. She replied that, in her opinion, the success of the New York State program is that it does not treat genetics differently. It makes no exceptions for genetics, but simply holds it to the same standards.

In answer to a question from Dr. Winn-Deen, Dr. Willey said that some vendors are concerned that if they obtain FDA clearance for an IVD, a lab will use it as their gold standard to validate their in-house developed assays, because the in-house assay is cheaper.

Dr. Winn-Deen asked Ms. Yost if there was a plan to work with CAP to develop full process controls for proficiency tests for genetics; Ms. Yost said there was not. She stated that PT is not approved by CMS, except for the 83 analytes that are in the regulation. Dr. Ferreira-Gonzalez noted that there have been major efforts by CDC in the areas of PT and QC for genetic tests. Ms. Yost said CMS was working with them and hoping to develop educational materials for genetic testing laboratories.

Dr. Ferreira-Gonzalez stated the core of the problem being considered by the Committee was that the CLIA regulation does not include a requirement for the demonstration of clinical validity.

Ms. Yost stated that CLIA provides the minimum standards for laboratory quality and that some approved accrediting organizations have more stringent standards. The CLIA program was developed so that it would dovetail with FDA without duplication of effort. CLIA looks at whether lab tests provide the right answers, while FDA decides whether the tests are useful.

Dr. Tuckson asked the Committee to decide on the steps that should be taken by the Committee, if any. He suggested writing a letter to the Secretary stating that the public should expect that appropriate oversight is in place for the diagnostic and therapeutic interventions they receive. He said the letter could also state that SACGHS understands that burdensome rules and regulations are not helpful. It could state that the Committee heard from several HHS agencies on the issue and that questions remained as to the adequacy of the oversight of genetic testing. In addition, the letter could request that the Secretary bring together representatives of FDA, CDC, and CMS to report on whether there is a significant problem and what remedies might be taken to address it. Ms. Berry asked if this step had already been taken. Mr. Hamilton clarified that the process he described did not look at the entirety of genetic testing, but only at the question of a proposed regulation. Although it was discussed with CDC and FDA, the process took place primarily within CMS.

Dr. Ferreira-Gonzalez suggested waiting to take action until after the CLIAC meeting in February.

Ms. Berry did not object to a letter to the Secretary if the Committee could define the problem in concrete terms. Dr. FitzGerald suggested focusing on an approach that addressed clinical utility. Other suggestions included greater use of the FDA option, changing CLIA's authority for all testing to include clinical validity, and focusing on a genetics testing specialty.

Dr. Phyllis Frosst suggested writing a letter to the Secretary that included an example of a gap that could affect a specific individual. Dr. Tuckson asked the Committee to vote on the options before them. After some discussion and clarification of the options, a subcommittee was appointed to write a letter that would define the problem and note that CLIAC was meeting in February. The expectation was that the letter would go to the Secretary on or before January 1.

TUESDAY, NOVEMBER 14, 2006

Opening Remarks

Reed Tuckson, SACGHS Chair

Dr. Tuckson stated that the first session would focus on the report to the Secretary on policy issues associated with a large population cohort study of genes, environment, and disease in the U.S. The goal was to reach consensus on whether the report was ready for transmittal to the Secretary. He pointed out that the Institute of Medicine (IOM) had provided copies of "Genes, Behavior, and the Social Environment," which addresses the importance of including behavioral factors and the social environment in studies of gene/environment interaction. Dr. Tuckson turned the meeting over to Task Force Chair Hunt Willard to lead discussion of the Large Population Studies report.

Session on Large Population Studies

Hunt Willard, Ph.D., Chair, Task Force on Large Population Studies

Dr. Willard stated that the purpose of the session was to review the public comment process and discuss the changes that were made to the draft report since the last meeting. He described the milestones in report development and said that NIH Director Elias Zerhouni asked the Committee to focus on identifying the key policy issues that should be addressed before undertaking a new large population study in the U.S. and outline possible approaches to address them. Dr. Willard emphasized that SACGHS was not asked to come to a conclusion about whether a new large population study should move forward.

Dr. Willard stated that the draft was sent out for a 60-day public comment period in May of 2006. In addition to postings on the SACGHS website, the Federal Register, and the NIH Guide for Grants and Contracts, a substantial targeted email outreach tapped a variety of different groups. Media outreach took place through the NIH Office of Communication. In addition, a "Dear Colleague" email was sent to a variety of listservs. In all, approximately 48,000 individuals were informed that the draft report was ready for review. In response, 69 sets of comments were received. Approximately 60 percent of the comments came from three groups: about 25 percent from academically based researchers, 19 percent from professional societies, and 17 percent from Federal Government agencies. A variety of other constituencies and sectors accounted for the remaining comments. Although there were 69 responses, many were quite comprehensive, with a total of about 600 different comments. Groups of two to three Task Force members analyzed comments about each of the report's key sections. They identified the comments' major themes and decided which changes to incorporate.

Dr. Willard listed the major themes of the public comments; i.e., the tone of the report was not neutral; more information was needed on existing cohort studies in this country and abroad; more discussion was

needed on the types of interdisciplinary research that would be necessary to mount a large population study; issues of socioeconomic status and cost factors were not sufficiently addressed; more information was needed on the complex ethical, privacy, and confidentiality issues involved; greater ethical oversight would be necessary for such a project; and more emphasis was needed on public engagement.

Staff worked with the Task Force to revise the report in response to these comments. A major revision made to the report's format involved the integration of two separate sections on public engagement into one chapter. The tone of the report was changed to reflect a more neutral perspective throughout. The report's introduction was expanded to better describe the role of SACGHS in report development, to provide background information on the NHGRI-led effort to examine design considerations, and to provide an overview of the public comment process. In Chapter 2, scientific background, more detail was added on the Human Genome Project. The section on existing cohort studies in the United States was substantially expanded. In Chapter 3, the Women's Health Initiative and the National Children's Study were added as examples of interdisciplinary research. The sections describing the need for partnerships and access to data and materials were expanded and information was added on the NIH Genome Wide Association Studies (GWAS) Initiative. Significant feedback was incorporated from the public comments to ensure that the report used a broad operational definition of "environment." Dr. Barbara McGrath suggested adding the concepts of geographic diversity and gender to this definition.

In Chapter 3, the section on recruitment and enrollment was expanded to include information on socioeconomic and lifestyle factors and to incorporate material from a presentation by Dr. Charles Rotimi. New sections were added on "Multidisciplinary Research Teams" and "Coordination Across Multiple Institutions and Health Care Systems." In Chapter 3, under "Regulatory and Ethical Issues," the section on privacy and confidentiality was significantly expanded based on comments from the World Privacy Forum and others. The Task Force also added a recommendation for an independent ethics review committee. The public health and social subsections in Chapter 3 were integrated into one new section: "Public Health, Social, and Economic Implications." A text box was added to emphasize the Committee's support for genetic nondiscrimination legislation. Dr. McGrath suggested that the health disparities section address the possibility of competition for funds between public health researchers and those who might conduct a new large population study. In response, Dr. Willard proposed adding the topic of health disparities research to the overall discussion of the impact of a new large population study on the funding of other biomedical research.

Discussion of Recommendations

Dr. Willard led a discussion of the report's recommendations and stated that all but three recommendations were unchanged. A recommendation was added to make an overarching statement that the Secretary should consider the full range of policy issues in the report as part of the process for determining whether to undertake a new large population study. After some discussion, the Committee agreed to accept the wording of the overarching recommendation, which was neutral in tone. They agreed that the executive summary and conclusion would be the appropriate sections to describe the enormous potential of the study with respect to advances in science and health. They also decided to delete the phrase, "and prior to a decision being made" from the overarching recommendation.

The Committee discussed the five recommendations under "Research Policy." Recommendations 1 and 2 were accepted with no changes. In Recommendation 3, the Committee changed "the Secretary may wish to establish" a highly collaborative model of leadership to "the Secretary *should* establish a highly collaborative model of leadership." They also decided to add examples of agencies that are well suited to participate in the collaborative leadership of the study (e.g., NIH Institutes and Centers, CDC, and VA). Recommendations 4 and 5 were accepted with no changes.

The Committee discussed the four recommendations under “Research Logistics.” Recommendation 1 was accepted with no changes. In Recommendation 2, the word “assessment” was added, as follows: “Project organizers should be encouraged to consult with community-based organizations as part of their recruitment, *assessment*, and enrollment strategies." Recommendation 3 addressed the need for new methods for measuring environmental factors. Dr. Amos asked that more information on this topic be added to the body of the report. The recommendation was changed to clarify that consultation on this issue should take place with both HHS and non-HHS agencies. Recommendation 4 was accepted with no changes.

The Committee discussed the four recommendations under “Regulatory and Ethical Considerations.” Dr. Frohboese suggested that Recommendation 1 promote technical assistance and guidance from a Federal work group, rather than recommending that this work group develop ethical best practices and standard operating procedures. She also suggested substituting the phrase, “health information privacy” for “medical privacy.” The Committee agreed that the proposed Federal work group should not be charged with ensuring regulatory compliance by all research sites, as this would not be feasible. Several Committee members agreed to provide new language for Recommendation 1. Recommendation 2 was new and was developed in response to public comments. It stated that an independent ethics committee should be established to serve in an advisory capacity to the IRB and project management. Additional research questions might be raised over time and one of the functions of the ethics board would be to assess those questions and determine whether the initial consent was valid for future projects or whether a re-consent process would be required. Other functions would include drafting a statement describing the informed consent process and the development of policies on data access. The Committee agreed that an ethics board would not weaken or duplicate the functions of an IRB and accepted the new recommendation. Recommendation 3 was accepted with no changes. For Recommendation 4, Dr. Frohboese suggested changing the word "promote" to "ensure." The Committee also agreed to change “guidance” to “policy.”

The Committee discussed two recommendations under “Public Health, Social, and Economic Implications.” Recommendation 1 was significantly reworded to ensure that interim findings would be disseminated at the point where they might contribute to clinical knowledge. Recommendation 2 was accepted with no changes.

The Committee discussed two recommendations under “Public Engagement.” Recommendation 1 was edited to eliminate redundancy. The following sentence was added to Recommendation 2: “It will also be important to obtain feedback from participants following the conclusion of a study in order to determine the impact of the study on their health and lifestyle.” Dr. McLean suggested adding information in the text about the role an ombudsman could play in ethical oversight. The Committee agreed to this change.

Dr. Willard asked if there were other comments on the report. The Committee discussed the conclusion, which had not yet been written. They agreed that it should acknowledge the substantial potential benefit of a new large population study. In addition, it should state that the process of conducting a rigorous exploration of the issues raised in the report would have numerous benefits and should be pursued by the Secretary. It was agreed that the conclusion would be disseminated to Committee members via email for final approval.

Dr. Tuckson asked the Committee to decide whether the report would be ready for transmittal to the Secretary once the revisions were completed by staff. The members voted unanimously to accept the report and recommendations.

Public Comments

David Mongillo, American Clinical Laboratory Association (ACLA)

Mr. Mongillo stated that ACLA represents local, regional, and national hospital and independent clinical laboratories across the United States and all of its members perform genetic testing. He stated that CLIA explicitly requires that laboratory directors ensure that, "the test methodologies selected have the capability of providing the quality of results required for patient care." ACLA believes this responsibility is consistent with clinical validity. CLIA also requires that labs have clinical consultations on the appropriateness of the testing ordered and interpretation of test results for the purpose of clinical validity. Mr. Mongillo said there are some labs performing direct-to-consumer tests with questionable clinical validity, as described in a recent GAO report and in Congressional hearings. He said that all ACLA members are CAP-accredited and most are licensed in New York and therefore subject to the highest level of regulation, inspection, test validation, and accreditation. Since 75 percent of all genetic testing is performed in labs that are licensed by the State of New York, he asked that the minority not drive regulations for the well-meaning majority.

Mr. Mongillo said the FDA guidance on IVDMIAs defines a new category of laboratory developed test that will be subject to FDA approval and would essentially make laboratories into manufacturers. He said CLIA regulates labs and FDA regulates tests and there are fundamental differences and redundancies between these regulatory approaches that would make compliance with both sets of regulations burdensome. He said FDA requires quality system regulations to produce essentially identical products from the first kit to the last. CLIA, however, operates as a QA/QC package, so that each individual laboratory can responsibly perform thousands of different laboratory tests daily with an assurance of quality. He said the new FDA guidance will include package insert requirements consistent with the need to perform the test in multiple laboratories. However, laboratory developed tests' standard operating procedures can be quickly modified and validated in a particular laboratory consistent with CLIA quality assurance. He said there are also major differences to ensure compliance with test modifications. Most importantly, CLIA explicitly allows for the timely ability to modify tests to incorporate the latest medical knowledge and enhancements. Mr. Mongillo said FDA stresses the importance of smart regulation and that the future of genetic testing will include numerous IVDMIA test applications. ACLA is concerned with the ability of FDA resources to keep pace with not only the initial approvals, but with the ongoing approval of valuable test modifications that contribute to medical innovation and improved patient care.

Dr. Tuckson asked what set of standards are used by the certified consultants who are supposed to address clinical validity in CLIA labs. Dr. Ferreira-Gonzalez said CLIA has specific standards for these consultants and Dr. Tuckson asked how CLIA determines whether they are doing a good job. Dr. Ferreira-Gonzalez said that CAP's inspectors can investigate clinical validity going back any period of time. Dr. Tuckson noted that CAP guidance might be specific enough to be used as a performance assessment tool for the quality of the consultation by a particular person.

Federal Developments and Updates

Update on Collaboration, Education, and Test Translation (CETT) Program

Steven C. Groft, Pharm.D.
Director, Office of Rare Diseases, NIH

Dr. Steve Groft updated the committee on the Collaboration, Education, and Test Translation Program (CETT). CETT promotes the translation of tests for rare genetic diseases into the clinic and works actively to encourage clinical lab and research collaborations. Dr. Groft stated that the program's

partnerships with CDC, HRSA, and CMS have strengthened. In addition to moving genetic testing from research to practice, CETT would like to improve education about rare genetic disorders and find ways to collect and store clinical and genetic information so that genotype/phenotype correlations can be made.

Dr. Groft listed several recent meetings on genetic testing. One focused primarily on molecular genetic testing and another addressed biochemical genetic testing. At the biochemical meeting, a recommendation was made that the CETT program be expanded to include biochemical genetic testing and that an effort should be made to determine why some tests are only available in non-U.S.A. labs. It was also recommended that a laboratory consortium be developed for biochemical genetic testing, similar to the successful consortium that formed on molecular genetic testing. Dr. Groft said that a group was beginning this effort. Other recommendations were: training of both laboratory and clinical personnel should be encouraged; guidelines should be developed to ensure the quality of testing, result interpretation, and diagnosis for inherited metabolic disorders and other genetic diseases; quality assurance measures should be enhanced for various laboratory tests; international collaboration in research efforts should be improved; and information resources should be enhanced to provide easy-to-access, user-friendly information on biochemical testing.

Dr. Groft reported that the Office of Rare Diseases was expanding the CETT program by adding several advisors to help review biochemical genetic tests when they come in for consideration. GeneTests, led by Bonnie Pagon, was to provide specific information, either by expanding the current capacity or by setting up a companion site through subcontracting. This would give CETT an equal emphasis on biochemical and molecular diagnostic testing. ACMG made a commitment to develop testing guidelines needed by users and providers, in collaboration with other professional organizations. CDC staff was preparing a report about the meeting for the Web. The Steering Committee planned to review the recommendations to refine roles and responsibilities and undertake additional collaborations, as needed. A follow-up meeting was planned for the next year to review progress and make further recommendations.

Dr. Groft listed several tests that were approved for translation through CETT by various laboratories and commercial organizations using multiple methodologies. Dr. Groft added that about six to eight leaders of patient advocacy groups came together and completed a training program. They now serve as a resource to other patient advocacy groups to explain the CETT program and the benefits of having genetic tests developed and made available.

Some of the needs identified by the CETT program are templates of educational materials for clinicians, individuals, and families on understanding genetic tests and rare diseases; report forms that are interpretable to non-genetic clinicians; and ways for test results to be made understandable by everyone.

In response to questions, Dr. Groft said the program had not delved into patent issues yet and that the CDC was helping extensively with quality control issues. Dr. Ferreira-Gonzalez encouraged Dr. Groft's team to work closely with the professional organizations that were trying to standardize the reporting of genetic testing so that the results would be understandable by clinicians. Dr. Randhawa asked for a description of the criteria for prioritizing tests for translation. Dr. Groft said a team of reviewers determines whether a test is ready for translation by asking such questions as: Has the laboratory involved completed the test in the research laboratory? Has it been useful? What are the cost considerations? The review team then makes recommendations to the Steering Committee. Dr. McLean asked if the availability of information on biochemical testing would increase the demand for these services and create a problem. Dr. Groft stated that there had been some legal problems and that a few labs had shut down. However, he said that it was important that biochemical genetic tests remain available and they were looking at ways to increase training, which would hopefully reduce the number of problems.

NIH Proposed Policy on Genome Wide Association Studies (GWAS)

Susan Shurin, M.D.
Deputy Director, National Heart, Lung, and Blood Institute (NHLBI)

Dr. Tuckson stated that NIH wanted the Committee to be aware of an important policy proposal from NIH on genome wide association studies (GWAS) and that Dr. Susan Shurin would provide an update. He said the GWAS proposal had an important component on facilitating the sharing of genome and clinical information generated by NIH research, including the creation of a central database at NIH to house the data. NIH was seeking public comment on the proposal and was eager to receive input and advice.

Dr. Shurin stated that a genome wide association study is defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (e.g., blood pressure or weight) or the absence of a disease or condition. The goal of this research is to devise better ways of predicting risk, implementing preemptive therapies, preventing the development or progression of disease, and developing new diagnostics and therapeutics. She said that since NIH is the steward of the American public's investment in research, the agency is responsible for obtaining the maximum benefit from studies. They have long encouraged the wide sharing of data, including published papers on the Web. However, scientists are now generating far more data than they can analyze. Genetic data, especially related to association with disease states, is a very valuable resource. The participants in such research deserve to have their privacy protected and their contribution maximized.

At the beginning of 2006, the National Heart, Lung, and Blood Institute (NHLBI), one of the NIH institutes, began receiving an increasing number of applications for genome wide association studies on persons with heart, lung, and blood disorders. Both NHLBI and the National Human Genome Research Institute (NHGRI) felt it was important to develop policies to ensure that investigators share their data widely, consistent with the consent provided by subjects. A discussion began between these two Institutes and eventually led to meetings with all the NIH Institutes and Centers about developing one consistent policy. Dr. Shurin commented that wide sharing of these data is already taking place, but NIH is trying to change the culture in the investigator community so that instead of having a proprietary sense of their data, researchers will be willing to let other people see it to maximize the benefit. She said a single portal of entry would be helpful and would provide optimal protection for privacy and intellectual property issues.

The guiding principle of GWAS is that the greatest public benefit will be realized if the data are available under terms and conditions consistent with the informed consent provided by individual participants, in a timely manner, to the largest number of investigators. The elements of the proposed policy include data management (expectations for submission of and access to data); publication (a defined period of publication exclusivity for investigators submitting data); and intellectual property (patenting approaches that enable both research and the downstream discoveries necessary to develop public health related products). The proposal states that the repository would be located at the National Library of Medicine (NLM), National Center for Bioinformatics (NCBI).

Applicants for the genome wide association research funding will be peer reviewed at NIH and those funded will have to submit data for broad sharing, consistent with the consent given. The repository will also accept data from non-NIH-supported investigators if they meet the standards and are interested in sharing. The submitting investigators and the institutions at which they work will be responsible for submitting coded data without identifiers and for noting any limitations on data use. The codes will be maintained at the institution, so that neither NCBI nor NIH will know the identities of participants. The coded linked genotype and phenotype data will then be entered in the repository. For access to anything

but basic descriptive information and aggregated data, the researchers will have to go through a controlled access process. Pre-computed data will be posted on the Web. Dr. Shurin said this system was designed so that the obvious associations are immediately available, making them non-patentable. Patenting could take place downstream after manipulations of the data by secondary investigators.

Investigators who submit data will have to provide extensive information about their studies, the quality of the data they are submitting, any issues related to subjects, and assurances of compliance with applicable laws. Investigators who want access to data will have to submit a request, state what they plan to do, agree not to identify individuals, and provide annual progress reports. A Data Access Committee will have dataset-specific access rights and they will consider each request.

Dr. Shurin said they met with the Office for Human Research Protections (OHRP) to discuss whether this secondary use of data constitutes human subjects research. OHRP determined that it does not constitute human subjects research because the data is stripped of identifiers and NIH and subsequent users will not have access to the identifiers. OHRP suggested that NIH customize oversight to specific situations.

The issues for participants include consent, security of data, and the inherent risks of identifiability and genetic discrimination. The issues related to the protection of the data include the long-term responsibility for the coded submissions, the return of results, and computer security.

In August 2006, NIH issued an announcement for a public comment period on the draft policy that was to continue until the end of November 2006. A town hall meeting about the policy was to be held on December 14, 2006.

In response to a question, Dr. Shurin stated as part of GWAS, NIH would like secondary users, some of whom will be experts in statistics, to share their methods in bioinformatics.

Dr. FitzGerald expressed concern about the possibility of identification of subjects who come from small patient pools. He asked how this risk would be explained in the informed consent process, as well as the possible risks from the use of data in future studies. Dr. Shurin said they expect to deal with retrospective studies differently from prospective studies and will do the best they can to assess and explain the potential risks. She acknowledged that the data will be subject to Freedom of Information Act (FOIA) disclosure.

Dr. Randhawa asked if the de-identified data will be available at the individual level or the aggregate level. Dr. Shuring replied that it will be available as individual data. She stated that NIH was currently involved in establishing the standards for the phenotypic information, which was challenging.

Dr. Ferreira-Gonzalez asked how the policy would deal with the development of intellectual property. Dr. Shurin said they would like to see scientists protect intellectual property as they begin to find targets that might be useful for diagnostics and therapeutics. They are not discouraging patents, but are trying to ensure that patenting does not occur too early. One way to prevent early patenting is by posting the data so that it is in the public domain.

Dr. Tuckson asked where the ethics expertise in the initiative is located. Dr. Shurin replied that it is within NIH. Dr. FitzGerald suggested that ethical oversight should come from an outside group so it is clear to the public that the project is accountable. Dr. Shurin said NIH asked for guidance on this issue in the public consultation process.

Update on Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Activities

Linda Bradley, Ph.D.
Geneticist, National Office of Public Health Genomics, CDC

Dr. Tuckson introduced Dr. Linda Bradley, who provided an update on EGAPP's activities. The goal of EGAPP is, "to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to practice." Dr. Bradley stated that EGAPP is a CDC-funded pilot project that began in October of 2004. It is non-regulatory in approach and is focused around an independent, non-federal, multidisciplinary working group. They integrate existing processes for evaluation and appraisal, including the knowledge gained through the SACGT, SACGHS, and the U.S. Preventive Services Task Force. Dr. Bradley stated that EGAPP's methods are still under review and most of their products are not yet final, i.e., it is a "work in progress."

The EGAPP Working Group, which consists of 13 members, has met six times since May 2005 in 1½ day forums and has also held many subcommittee teleconferences. Three standing subcommittees address Topics, Methods, and Products. In addition, each member sits on topic-specific groups that work on evidence reviews. During the first 2 years, they received support from AHRQ through an interagency agreement so that the agency's evidence-based practice centers (EPCs) could conduct five reviews as part of the pilot project. EGAPP staff members come from the CDC National Office of Public Health Genomics and technical consultants and contractors are used as needed. Other support comes from the CDC-funded Centers for Genomics and Public Health. EGAPP's interagency Steering Committee was planning to provide extensive input on the project's evaluation phase beginning in the spring of 2007. They will also be looking at the sustainability of the project.

The scope of topics for the pilot phase focused on applications recognized as important or common, e.g., tests used in clinical scenarios to guide intervention, screening tests, and tests with the potential for a broad population application.

The EGAPP approach started with lessons from the CDC's ACCE project, which conducted a formal assessment of analytic validity, clinical validity, and clinical utility and relevant ethical, legal, and social implications as part of evidence reviews. EGAPP is using questions to organize and synthesize information to determine where knowledge gaps exist. They are integrating a number of gold standard methods from existing evaluation processes, starting with reviews from the EPCs because of their credibility and experience. EGAPP uses formal analytic frameworks with key questions and explicit search strategies. They assess the quality of individual studies and the strength of evidence, providing recommendations with clear links to evidence.

Dr. Bradley listed some of EGAPP's new approaches, such as attempts to shorten the time frame between reviews and clinical practice. They are also focusing on medical outcomes (e.g., morbidity and mortality), but they consider specific family or societal outcomes when appropriate. They've commissioned modeling in some evidence reviews and are addressing cost effectiveness in a formal way.

EGAPP commissions evidence reports from AHRQ or other contractors that are peer reviewed, posted on the Web, and, in some cases, published. Dr. Bradley stated that recommendations based on the evidence were being written by the Working Group. These recommendations were slated to undergo peer review, publication, and posting. The publication of methods and evaluation, including the results of the stakeholder surveys, were to follow quickly.

Topics in the EGAPP pipeline include: genetic testing for detection and management of ovarian cancer, testing for cytochrome p450 polymorphisms in adults with depression treated with SSRI drugs, testing for

hereditary nonpolyposis colorectal cancer in newly diagnosed colorectal cancer patients and family members, UGT1A1 mutation analysis in colorectal cancer patients treated with the drug irinotecan, the impact of gene expression profiling tests on breast cancer outcomes, screening for CYP450 polymorphisms to predict response to pain management with codeine, and the use of genomic profiling to assess risks for cardiovascular disease and identify individualized prevention strategies.

Dr. Bradley said the next steps for EGAPP were focused on maintaining momentum; publishing on methods and lessons learned; publishing and disseminating products to professional organizations, health plans, and other groups; initiating project evaluation over a 1-year period; and translating the knowledge gained from the evidence reports and recommendations into informational messages for different target audiences. She stated that the EGAPP Working Group requested an independent website from CDC and recently received approval. The new site (www.egappreviews.org) will enhance interaction with stakeholders and allow the Working Group to post topic lists, methods and processes, evidence reports, recommendations, and informational materials as they're developed. It will also allow for more input from stakeholders on suggested topics for review.

During the next year, the Steering Committee and CDC planned to look at building a sustainable process and addressing the future composition of the Working Group, the role of consumers and industry, possible expansion of the scope of topics and range of stakeholders, and the need for a post-market data collection process.

Dr. Tuckson asked how EGAPP's work relates to clinical validity. Dr. Bradley said that clinical validity is the crux of the matter, i.e., Are we getting to what we think we're getting to when we run certain tests? How useful is that information? How will it impact management and outcomes for patients and their families? She said she hoped that EGAPP would be able to show where some of the knowledge gaps are and determine whether they can be easily resolved. Dr. Bradley agreed that the EGAPP process needed a mechanism for continued review of tests that are initially determined not to have enough data. This would include a way to identify relevant new studies.

Dr. Ferreira-Gonzalez asked how topics are selected. Dr. Bradley said the first set of topics was selected deliberately to test different methodologies in different clinical scenarios. Going forward, they will look at how new tests can be brought into the pipeline. Dr. Ferreira-Gonzalez recommended that EGAPP seek extensive public advice on their topics from stakeholders and professional organizations.

Update on Genetic Information Nondiscrimination Act

Sharon F. Terry
President and CEO, Genetic Alliance
Chair, Coalition for Genetic Fairness

Ms. Sharon Terry said that the changes in the make-up of Congress after the November 2006 election led to changes in the leadership of the committees responsible for the Genetic Information Nondiscrimination Act (H.R. 1227). The co-sponsors were almost evenly split between Republicans and Democrats, but she predicted only a 10 percent chance that the bill would pass during the lame duck session. The sponsors were Rep. Biggerts, Eshoo, and Slaughter.

Ms. Terry said the 110th Congress would begin in January, with new chairs and new committee structures. Senator Barack Obama was on the HELP Committee, which she felt would be helpful in the Senate. However, the advocacy groups would need to reevaluate the chief co-sponsors again in both Houses. She said it was the 11th year for the Genetic Alliance in leading this cause and they were still hopeful.

Next Steps

Dr. Tuckson recapped the decisions made during the course of the meeting:

The PGx Task Force was to revise the report and recommendations based on the input received during the session. The revised recommendations would be sent to SACGHS for review prior to seeking public comment. The Lewin Group was to obtain input from 15 Federal and non-Federal experts and stakeholders and public comment would then be solicited on the revised draft report and recommendations.

The Gene Patents and Licensing Task Force would revise the study questions, scope, and timeline based on input received during the session and initiate a literature review and public consultation process.

The new Oversight Task Force would prepare a letter to the Secretary expressing concerns about the adequacy of oversight, noting the forthcoming November meeting of CLIAC, and including a case study illustrating the risks to the public's health due to current gaps in oversight. They were also charged with organizing a fact-finding session for the March meeting.

The Large Population Studies Task Force was to revise the report and recommendations based on input received during the session and develop the report's conclusion and executive summary. The final report would be circulated to SACGHS via email and then transmitted to the Secretary.

Ideas proposed for the March meeting included updates on LPS, PGx, gene patents and licensing, the Personalized Health Care initiative, and AHIC. It was to be determined whether there would be another session on oversight. Presentations from CLIAC and CAP were being considered.

The Committee agreed that all issues under discussion had been adequately addressed and 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