Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Ninth Meeting
March 27-28, 2006
Bethesda, Maryland

Committee Members Present

Reed Tuckson, M.D., Chair
Cynthia Berry, J.D.
Sylvia Mann Au, M.S., CGC
Chira Chen
James P. Evans, M.D., Ph.D.
Debra G.B. Leonard, M.D., Ph.D.
Julio Licinio, M.D.
Agnes Masny, R.N., M.P.H., M.S.N.
Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Huntington Willard, Ph.D.
Emily Winn-Deen, 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)
Linda Johnston-Lloyd, M.D., M.P.H. (HHS/Health Resources and Services Administration)
Vence Bonham, Jr. J.D. (HHS/National Institutes of Health)
Francis S. Collins, M.D., Ph.D. (HHS/National Institutes of Health)
Tim Leshan, M.P.A. (HHS/National Institutes of Health)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Michael Carome, M.D. (HHS/Office for Human Research Protections)
Bernard Schwetz, D.V.M., Ph.D. (HHS/Office of Public Health and Science)
Martin Dannenfelser (Administration for Children and Families)
William Koch, Ph.D. (Department of Commerce)
Amy Turner, J.D. (Department of Labor)
Ellen Fox, M.D. (Department of Veterans Affairs)
Sherrie Hans, M.D., Ph.D. (Department of Veterans Affairs)
Peter Gray, J.D. (Equal Employment Opportunity Commission)

Executive Secretary

Sarah Carr, NIH Office of Biotechnology Activities

Monday, March 27, 2006

Welcome and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, Chair, stated that the public was made aware of the meeting through notices in the Federal Register, as well as announcements on the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) website and through the SACGHS listserv.

Ms. Sarah Carr reviewed the Committee's 12 study priorities. Dr. Tuckson commented on the extensive progress of SACGHS on these issues.

He noted that since the last meeting, the coverage and reimbursement report was finalized and transmitted to the Secretary. He indicated that the final report was being released to the public for the first time that day and described the methods in place for its active dissemination. Dr. Tuckson asked Committee members to take a leadership role in further disseminating the report. The Committee agreed that a slide presentation with the report's recommendations should be prepared and posted on the SACGHS website for Committee members to use for their individual activities. The full report has been posted on the site. Dr. Leonard suggested sending the report to in vitro diagnostic organizations such as BIO or AdvaMed. She also asked when and how the Secretary would respond to each recommendation. Ms. Carr noted that it would take time to consider all the implications of the recommendations, including cost.

Dr. Tuckson told the Committee that the letters on the incorporation of genetics, genomics and family history into the electronic health information infrastructure and on direct-to-consumer (DTC) marketing of genetic tests also have been finalized and transmitted to the Secretary of Health and Human Services (HHS). The DTC letter recommended that the Federal Trade Commission (FTC) and the Food and Drug Administration (FDA) consider developing a joint statement informing consumers about genetic tests marketed directly to consumers. Dr. Steven Gutman reported that an interagency work group on the issue was developing a final product for consumers and continues to survey the Internet for examples of websites making false claims in their marketing of genetic tests sold directly to consumers. Dr. Gutman asked the Committee to let him know of any potential targets.

Regarding the letter on the health information infrastructure, Dr. Tuckson planned to call Mr. David Brailer, National Coordinator for Health Information Technology, concerning the incorporation of genetic and family history into electronic health records.

Reviewing the agenda, Dr. Tuckson stated that on Day 1, the Committee would continue to develop the reports and recommendations on large population studies and pharmacogenomics. On Day 2, they would hear a briefing on the National Academy of Sciences' (NAS) report on the impact of genomic and proteomic patents and licensing practices on innovation in public health. They also would hear the conclusions of the SACGHS Patents and Access Task Force review of the NAS report, as well as its recommendations for the Committee's next steps. SACGHS was to be updated on the status of Federal genetic nondiscrimination legislation and hear about a new survey of public attitudes on this topic. Public

comment sessions were scheduled for both days.

He stated that the results of the October 2005 survey on the effectiveness of the Committee's activities were provided in the table folders. In general, the survey results indicated that the Committee was considered effective, with room for improvement in some areas. Some members wanted more feedback from HHS concerning SACGHS's work and priorities.

Dr. Tuckson thanked Dr. Joseph Telfair for his liaison activity with the HHS Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children and Dr. Debra Leonard for her liaison activity with the CDC Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Highlights of the recent meetings of these two groups were provided in the table folders. Dr. Tuckson also noted that written updates from the *ex officio* agencies were provided in the briefing materials.

Dr. Tuckson informed the Committee of changes in SACGHS membership, ex officios, and staff. Christopher Hook had resigned from SACGHS due to family and professional obligations. The Secretary was expected to fill the vacant seat in the near future. Dr. Tuckson reported that two *ex officio* positions also had changed. Dr. Cristina Beato, Principal Deputy Assistant Secretary of Health, was appointed to serve as the *ex officio* for the HHS Office of Public Health and Science. The Department of Defense was to be represented by Lieutenant Colonel Scott McLean, Chief of Medical Genetics at Lackland Air Force Base in Texas. Ms. Amanda Sarata, SACGHS staff, accepted another job in December and was replaced by Ms. Amita Mehrotra.

Large Population Studies Session

Overview of Large Population Study Policy Issues and Possible Approaches
Huntington F. Willard, Ph.D.
Chair, SACGHS Task Force on Large Population Studies

Dr. Huntington Willard reviewed the Committee's development of a draft report on large population studies. He reminded the Committee that the National Institutes of Health (NIH) encouraged SACGHS to weigh in on the value of a large population study on the interactions among genetic variation, the environment and common diseases nearly 3 years ago. During the Committee's priority-setting process, this issue was categorized as one that required in-depth study. In March 2005, SACGHS held a full-day meeting to hear about the policy issues a large population study would raise. In June 2005, the Committee approved an outline for a report to the Secretary to identify key policy issues, potential approaches, and recommendations. In October 2005, another day-long session was held that focused primarily on public engagement mechanisms. These activities provided the Committee with sufficient information to move forward in drafting a report and reaffirmed the notion that the public must be involved in all stages of a proposed study.

Dr. Willard noted several related developments, including the Gene and Environment Initiative (GEI); the Genetic Association Information Network (GAIN); a Request for Applications (RFA) released by the National Human Genome Research Institute (NHGRI) for the conduct of a pilot public consultation study to obtain public input on a possible large U.S.-based longitudinal cohort study of the role of genes and environment in health and disease; and progress on the National Children's Study. In addition, the Department of Veterans Affairs (DVA) announced that it was forming an advisory committee on

genomic medicine.

Dr. Willard explained that there were three steps in the Committee's charge from the NIH Director. First, they were asked to delineate the policy issues and questions policymakers would need to address. Second, they were charged with exploring the ways in which these questions might be addressed. Third, they were asked to provide an opinion on optimal approaches that would form the basis for recommendations to the Secretary. The first step was accomplished in the draft report and the latter two steps were the key topics for the day's discussion.

Dr. Willard stated that the scientific background in the draft report described the methods that would be used to identify the genetic basis of disease, discussed various biobanks created through large population studies around the world, and provided an overview of a hypothetical large population cohort study in the U.S. This approach was initially outlined in a paper by Dr. Francis Collins and subsequently addressed by an expert working group convened by NHGRI.

Dr. Willard listed the six key issues identified by the Task Force that served as the framework for the draft report:

- Need for public engagement;
- Research policy considerations;
- Research logistics;
- Regulatory and ethical considerations;
- Public health implications of research results; and
- Social implications of results.

Public Engagement. Describing why public engagement is important, Dr. Willard referred to the problems in public perception concerning the U.K. Biobank, which has many critics. Although the study was discussed in public many times, there are still misunderstandings about its purpose. He stated that public engagement matters because of the potential study's unprecedented cost, scale (i.e., one half to one million Americans), duration, and potential social implications. The Task Force identified several questions for the report, including: At what level does one engage the public? What is actually meant by "the public" (e.g., the individuals who might participate in the study, the scientific community, elected officials at the Federal, State, and local levels)? When does one engage the public? What questions might be asked? Which subgroups of the public need to be engaged? Dr. Willard said these were overarching issues to keep in mind during the discussion.

Research Policy Considerations. Five key policy topics also were identified, the first of which was research policy considerations. Questions included: Is such a study needed? What is its value and cost? What would the effects of funding this program have on other research priorities? Can existing studies be used to achieve the same goals? Should the U.S. collaborate with other countries conducting similar studies? Which agencies should be involved and which should take the lead? What role should the private sector have? What intellectual property policies should govern the study? Given that the long-term cost required to mount such a study would be unprecedented, would it be possible to sustain support at public, scientific, and political levels over such a long period of time? The Task Force identified a number of relevant research policy issues, including the need for and potential benefits of the project, its costs and effects on other research priorities, the current capacity to conduct such interdisciplinary science, the need for various partnerships, and intellectual property concerns and access.

Logistics. The second key policy topic identified related to the logistics of the study. Questions included: How will representativeness be defined and achieved? Given that the study's benefits to individual participants may be indirect, would it be difficult to recruit a broad range of study participants? What are the ramifications of using racial or ethnic categories for sample stratification? Will the underinsured or underserved be part of the study, and if so, how does one ensure that these individuals are recruited in sufficient numbers? How will non-genetic study variables be defined and studied? Will the lack of a universal health care system make a study of this scale difficult or impossible to implement? Will new technologies be required to collect environmental data? The issues that were flagged in the report concerning research logistics involved enrollment criteria and recruitment of racially or ethnically defined groups, measuring various differences in the population across many sites, and coordination across multiple institutions and health care systems in the U.S.

Regulatory and Ethical Considerations. The third key policy topic was regulatory and ethical considerations. The questions posed in the report were: What are the regulatory requirements and how would they be met? Are there unique informed consent considerations for a long-term study of this magnitude? Would the study provide health care to uninsured participants, and if so, how would that work? Are special protections needed for children or adolescents? Who will have access to study data, and under what circumstances? Are special arrangements required to give participants some measure of control over their samples and data? Would the study be able to meet participants' expectations regarding confidentiality? Will additional privacy protections be necessary and for how long? How would the research data and samples be stored? Would the study results be returned to participants and under what circumstances? What Federal laws and regulations would be needed regarding whether or not to return research results to participants and family members? How does one deal with the issue of family members who, although not be participating in the study, would be interested in the information because of its relevance to their own health? Issues flagged as a result of those questions pertain to IRB review and whether informed consent is possible. Other issues relate to the misconceptions subjects may have about the medical care they will receive in the study, privacy and confidentiality issues, control of biological samples and data, and returning research results.

Public Health Implications. The fourth key policy topic addressed public health implications. Questions identified were: Will the statistical genetic associations be robust enough to lead to new therapeutic or preventive strategies? Would a large population study widen the gap between what can be diagnosed and what can be treated? Would the data gathered at the broad population level be applicable to individual communities and groups? How would study results be implemented by regulatory health and safety agencies, given the complexity of population risk assessments and the balance between population risk and individual risk assessments? Do regulatory agencies, public health departments, and health care providers have sufficient resources to translate the knowledge that such a study would generate?

Social Implications. The fifth key policy area involved the social implications relevant to a large population study. Could such a study create new health disparities? Would the findings exacerbate existing vulnerabilities? If the study led to the identification of new vulnerable populations, would there be sufficient public health or social resources available to respond? If the study generated clinically useful information, would it benefit only those who have access to the health care system? Can study results be applied in the current decentralized and fragmented health care system? Could the findings from such a study exacerbate racial discrimination or other types of discrimination and group stigmatization? What are the views of minority communities about the study's implications? Would the

study increase risks of genetic discrimination? Would the study findings lead to reductionist explanations of the role of genetics in disease? The social implications issues identified in the report address questions that relate to elucidating and/or exacerbating health disparities, the risks of genetic determinism, and developing reasonable social and policy responses to anticipated research findings.

Full Committee Discussion

Dr. Willard stated that the goal for the session was to discuss and prioritize the policy issues he described and to ensure their completeness and relevance. The group also would discuss the possible approaches identified in each area that could provide the basis for specific recommendations to the Secretary.

Beginning with public engagement, Dr. Willard said a number of mechanisms could be employed, e.g., national or local surveys, State referendums, seeking Congressional support and funding, town meetings around the country, focus groups, and online collaborations that provide Web-based materials for the public. Each of these methods had been used in other countries to obtain support for large population studies.

To engage the public concerning design, planning, conduct, follow-up, and reporting, Dr. Willard suggested town meetings, focus groups, or Web-based collaborations. He stated that NIH created a design considerations work group in 2005 that addressed these issues and he displayed a slide showing the stages of public consultation they identified. The slide depicted the large number of groups that need to be engaged; the issues concerning protocol development, education and training (not just of the research participants, but of physicians, scientists, and policy experts); and the substantial issues related to database development, privacy, access, and structure.

Dr. Willard stated that many disease advocacy groups would want to be involved in the study and noted that their buy-in would be important. They would represent their organizations' interests and help engage the public. It also would be necessary to obtain the support of scientific and professional organizations that have experience with study design, recruitment and data collection. Various levels of public consultation would provide valuable feedback, possibly resulting in changes to the study goals or design. After multiple rounds of consultation, HHS, Congress, and other groups would be called upon to make a decision on whether to move forward with the study.

Dr. Tuckson asked for a timeline delineating the overall report development process, including the development of recommendations. Ms. Carr suggested that the report go out for public comment after this meeting. She said the final report and recommendations could be ready for the Committee's approval by the November 2006 meeting.

Regarding the RFA for a specialized center to seek public input about a large population study using surveys, focus groups, and public meetings, Dr. Collins noted that NHGRI set aside $1.55 million over the course of 2 years to fund the effort. He said letters of intent were due April 10, applications were due May 10, and that review of the applications would take place during the summer. He expects projects to be funded by the end of September 2006 and the results to be available in September 2008. Dr. Collins clarified that the RFA represented an opportunity to collect public input, but was not a commitment to undertake the study. He said that ultimately, the public may not think it is a good idea or funding may never be allocated.

Dr. Tuckson asked how the NHGRI initiative and the SACGHS effort overlapped. Dr. Collins said the RFA effort was not intended to be a full public consultation, but rather a first step. He listed some areas that would be surveyed under the RFA: the acceptability of the initiative's goals; concerns about data use; expectations for privacy protection; acceptability of open-ended consent; acceptability of a central institutional review board; optimal approaches to recruitment; the need for tailored approaches for individuals or communities with special needs; expectations about the return of research results to individuals, communities and the public at large; the need for an ongoing dialogue with participants concerning study goals and processes; the advisability of including or excluding children; and intellectual property concerns. Dr. Willard clarified that the NHGRI effort would serve as a pilot project to conduct first-round public engagement. Dr. Collins added that SACGHS input was welcome on the current grant because the specifics of the consultation were still being worked out.

Dr. Tuckson asked whether the public comment solicited through the RFA was meant to be part of a future "go/no-go" decision or to provide advice on how to conduct the study. Dr. Collins said there was no certainty about whether the public engagement effort would lead to a decision to go forward with the study and there were no funds in the FY07 Administration budget to support a large-scale U.S. prospective cohort study. He also noted that no funds were allocated in the FY07 budget to support the National Children's Study (NCS), a prospective cohort study that had been in the planning stages for 6 years. Dr. Collins felt the task at hand was to explore public receptivity to and the scientific value of the effort, while waiting to see if the funding climate changed. He noted that since budget discussions begin during the summer, a report from the Committee in June would be useful to influence funding. Dr. Tuckson agreed that SACGHS needed to make a statement on the issue by June.

In response to a question from Dr. Telfair, Dr. Collins responded that the proposals would be reviewed by an internal or external committee.

Dr. Willard asked why the grant was a U01 rather than an R mechanism. Dr. Collins said there was debate about which of the two mechanisms to use, but they ultimately decided to use the U01 mechanism, which allows for more involvement of staff in the ongoing conduct of the program, because the agency had success in similar circumstances.

Ms. Cynthia Berry wondered whether NHGRI or the NIH Task Force had considered conducting a comprehensive media campaign to educate the public prior to conducting focus groups and surveys. Dr. Collins expressed concern that a large media campaign could be misleading since the agency does not know whether there will be a study.

Dr. Julio Licinio read from the announcement for GEI, which said there would be two components to the project, a genetic aspect and a technology development program to devise new ways of monitoring personal environmental exposures that interact with genetic variations and result in human disease. He said this approach does not account for the psychosocial components of the environment, such as poverty, death, separation, trauma, or abuse. He asked if that also would be true for the proposed large-scale study. Dr. Collins agreed that the environment consists of more than toxin exposure and said they are sensitive to these other components as they design the $40 million-a-year GEI effort. However, he said there is a great need to develop better technologies for measuring specific environmental exposures, which also would be relevant to a large-scale population study.

Dr. Emily Winn-Deen asked Dr. Collins if NIH had identified a specific level of acceptance that would

be needed on the part of the public to move forward. Dr. Collins said they had not defined a threshold; they were depending on the RFA applicants to develop these specifics. He said he did not expect the public engagement efforts to raise strong objections to the concept, but rather to identify areas of concern so the study design could be adjusted. He felt the public would be mostly positive about the study as long as certain protections were included.

Ms. Agnes Masny asked if NCS (or other studies) conducted public engagement in the development of their programs and whether there lessons had been learned from those efforts. Dr. Collins replied that NCS conducted extensive public engagement efforts in various settings. He said these data could be made available to the Committee.

Dr. Telfair asked Dr. Collins what information would be provided to potential participants of the public consultation activities, given that there would be no media campaign. He also asked what the next step would be after the pilot study. Dr. Collins stated that those who participate in the consultation process would receive some initial educational materials on large population studies, followed by a discussion in a focus group or survey format. He did not know what the next steps would be after the pilot. If the arguments in favor of the study did not create budgetary enthusiasm, NHGRI may not conduct any further activities. If there were momentum based on the scientific value of the study, they would likely start actual collection of clinical information and DNA samples on a pilot scale. Only later would they contemplate scaling the study up to a half- or 1 million participants.

Dr. Debra Leonard expressed concern about the difficulties of engaging uninsured and underserved populations. She also stated that the terminology used should be clear about whether the study would create a biobank, a biorepository, medical data, or an environmental data repository. She said it is important to distinguish whether the plan is to build a repository that could be used for any type of gene/environment disease studies or whether it is intended to target specific diseases. Dr. Collins agreed with her first comment about engaging the underserved. He stated that perhaps they should not use the word "study." They are planning to create a resource for discoveries about every disease that is common enough to have sufficient incident cases during the lifetime of the project. Dr. Collins said the goal ought to be creation of a community resource to which hundreds or even thousands of scientists will have access.

Dr. Jim Evans commented on the difficulties that would arise because of the fragmentation of the health care system, especially for minority populations. He asked about the possibility of coupling ongoing electronic health records efforts with the pilot study. Dr. Collins replied that there had been discussion about whether an electronic health record system could be used for the study. Dr. Evans suggested that the public be asked about this in the NHGRI consultation process. Dr. Collins agreed that this would be a useful question to ask the public.

Ms. Chira Chen described a similar, smaller-scale, prospective study of the high incidence of breast cancer in Marin County, California driven by patient advocates. Ms Chen said it is important to find out if patient advocates would support a large population study. Dr. Collins agreed that the study must engage advocacy groups, particularly for common disorders such as heart disease, cancer, diabetes, obesity, asthma, and hypertension. He stated that NIH typically conducts research of this sort through a prospective study on a specific disease, e.g., the Framingham Study or the Jackson Heart Study. He said a large population study might incorporate some of the work of these existing studies, but with no more than 25 to 30 percent of their subjects. The rest of the participants would have to be recruited *de novo* to

obtain a valid snapshot of the population.

Dr. Licinio raised the issue of the tight budget climate. He said it would be important to explain the study to Congress so they understand it will serve many purposes.

Ms. Sylvia Au asked to what extent input from the various NIH institutes and HHS agencies would inform the pilot study. Dr. Collins replied that during NHGRI's 18-month study design effort, input was received from a large number of NIH institutes, many HHS agencies, and other agencies outside the Department, such as the Environmental Protection Agency (EPA). When developing the RFA, they obtained input from several NIH institutes and were planning to draw on the discussions of SACGHS.

Dr. Ellen Fox updated the Committee on a genomic medicine program that DVA is developing that builds on ongoing genetic and genomic research. The plan is to make use of DVA's unique assets, which include a comprehensive and sophisticated electronic health record system and a very large, stable, patient population of almost 8 million enrolled veterans. They have a centralized and integrated national health care system that is not fragmented and a robust intramural research program that allows them to apply uniform standards across the country. DVA's genomic medicine program will be the largest adult genomic medicine research and clinical resource in the United States. It will involve the collection and storage of over 1 million patients' specimens, with relevant demographic data and links to individual clinical records. It will managed by their Washington, DC central office, which will coordinate with the Department of Defense, HHS, and other agencies and resources in DVA's central office. The genomic medicine activities will be conducted at multiple sites throughout the VA health care system. Dr. Fox said a Federal advisory committee also had been established, which will assess the potential impact of a VA genomic medicine program on existing VA patient care services; make recommendations on policies and procedures for tissue collection, storage and analysis; make recommendations on a research agenda; and recommend approaches by which research results can be incorporated into routine medical care. Ms. Fox said she would keep SACGHS updated on this effort.

Discussion of Possible Approaches

The Committee discussed possible approaches that could provide the basis for recommendations to the Secretary.

Dr. Willard first asked the Committee if they were comfortable with the depth, breadth and comprehensiveness of the draft report and the goal of finalizing it at the June meeting. Dr. Telfair suggested prioritizing the issues as a first step and then addressing timeframes for each. Dr. Kathi Hanna, primary author of the report, explained that issues discussed in the report were organized temporally. Ms. Carr suggested that the recommendations section of the report provide advice to the Secretary concerning which issues should be addressed first. Ms. Au wondered if the report could be broken into smaller, more accessible sections. Ms. Carr said an Executive Summary that highlights key points would be developed before it was finalized.

Ms. Au suggested developing a series of shorter reports over a period of time, adding information from the pilot and other studies as data emerged. She suggested that the first report be prepared by June and address the key priorities decided on by the Committee. Ms. Carr felt it was important to create one large report to make the Secretary aware of the large number of issues involved. Dr. Leonard agreed that the big picture should be presented to the Secretary in one report. Dr. Robinsue Frohboese agreed and added

that other efforts, such as the VA project, should be highlighted in the report, along with suggestions for coordination with other studies. Dr. Winn-Deen said the Secretary should be informed of both the arguments for and against a large population study. She agreed that the Secretary should receive a comprehensive report that includes lessons learned from past efforts.

Dr. Willard displayed slides listing four research policy approaches for discussion. The first was the need for consultation with the broad scientific community, not just the public. Dr. Willard explained that a large number of people in the scientific community know little or nothing about the study.

Dr. Telfair wondered if this was a redundant recommendation; he felt this step had already been taken.

Dr. Leonard asked if a detailed review of scientific data on large population studies exists. She said two versions were needed, one for the scientific community and one for the public. Dr. Collins said Dr. Teri Manolio, a well-regarded genetic epidemiologist, was writing such a review for *Nature Reviews Genetics* that would be available soon.

Ms. Masny asked whether existing case-control and cohort studies could be pooled together to answer some clinical utility questions. Dr. Collins noted that case-control studies do a poor job of identifying environmental contributions and biomarkers that might predict disease before it is diagnosed. He said that both case-control and prospective study designs are needed.

Dr. Leonard moved to accept the first approach and it was passed with no opposition.

Dr. Willard described the second approach for consideration. It noted the value of a highly collaborative model of project leadership and management on the part of the Federal agencies and departments that have an interest in the study. Dr. Telfair thought it would be helpful to examine other projects that involved multiple institutes and agencies. The Committee agreed to accept the second approach.

Dr. Willard explained that the third approach related to the need to consult with the international community and the private sector. Dr. Leonard agreed and stated that one benefit of collaborative arrangements with other biobanks would be cross-validation of the markers studied. The Committee agreed that the spirit of the approach was to encourage the Secretary to take advantage of the knowledge available from other sources.

The fourth approach under the category of research policy urged the Secretary to ensure that there is widespread and ongoing support for the study to sustain a long-term, stable investment. Dr. Collins noted several studies that were consistently funded for many years, such as the Framingham Study and the Human Genome Project. The Committee agreed on the fourth approach.

Dr. Willard reviewed approaches for addressing research logistical issues. The first approach dealt with the issue of developing clear definitions and parameters for stratifying the projected sample population. A related statement asked the Secretary to seek public input on the best approaches for identifying subpopulations for recruitment. Dr. Leonard added that she wanted to ensure that an approach to environmental stratification was well thought out. Dr. Telfair said it would be necessary to have clear and consistent definition parameters for systematically identifying and ensuring adequate representation. Dr. Collins stated that the NIH Work Group identified age, gender, race and ethnicity, urban versus rural, geographic location, socioeconomic status, and level of educational achievement as the parameters that

would be logistically possible.

The last point under research logistics stated that the Secretary should consult with health care providers to develop uniform and secure approaches for collecting, storing, tracking, and centralizing clinical information to be gathered over the course of the study. Dr. Winn-Deen suggested adding language to allow for the use of new technologies as they are developed, including electronic health records.

To address regulatory and ethical considerations, Dr. Willard said one approach would be to encourage the Secretary to convene Federal agency representatives to develop regulatory and ethical best practices. He stated that public input also should be sought on these issues. Dr. Fox commented that because regulations do not address ethical issues, the two concepts should be described separately.

The next approach for discussion recommended that project leadership consult with study participants on an iterative basis about the adequacy of confidentiality protections. Dr. Telfair noted that this recommendation affects the power relationship between researchers and subjects. Dr. Willard and Dr. Telfair agreed that there are models for this type of subject participation that should be taken into consideration.

The Committee moved to a discussion of public health implications. The first approach stated that the Secretary and project leadership should disseminate findings with the public health and health care communities as they emerge. Dr. Collins said that it was NIH's intent that anyone who agreed to the database's privacy stipulations would be able to access the data collected on study participants. Those interested in a particular disease would be able to mount a sophisticated analysis using a type of case-control model, identifying incident cases and possibly conducting additional laboratory studies. Dr. Licinio felt that in the initial engagement process, participants should be told that anonymity could not be guaranteed. Dr. Collins agreed that there would always be some risk of identification.

Dr. Willard described the second possible approach, which stated that project leadership would convene on a regular basis to review research results and allow for public input.

The last approach recommended that the Secretary consider establishing a standing advisory committee for the duration of the project to periodically assess social implications and routinely seek public input. Dr. Telfair pointed out that the mechanism under which the project would be funded would in part determine to whom the committee was accountable and how it functioned. Dr. Willard asked the *ex officios* if there was value in having this type of independent, freestanding committee. Dr. Collins felt there should be oversight from the outside, and suggested that this might be a function of SACGHS or another committee that already exists.

Dr. Willard concluded the overview of strawman approaches and asked if the Committee had anything to add. Dr. Leonard said the collection of environmental data had not yet been addressed. She also felt there were gaps concerning specimen handling and storage, methods for accessing the biobank, translating results into clinical practice, and internal oversight. Dr. Bernard Schwetz identified the need to work through the infrastructure to protect minority populations from research abuses, the need to address regulatory issues early in the process by forming an advisory group, and the need to develop guidance on sample use.

Next Steps

The Committee discussed methods for proceeding with development of the draft report. They agreed that Dr. Hanna and OBA staff would incorporate the Committee's comments and put the next draft out for public comment. Staff members would summarize the public comments for the Task Force, which would decide how to address them. A revised draft would incorporate public comments and be ready for final action by the Committee at the June meeting.

Pharmacogenomics Session

Update from the Pharmacogenomics Task Force
Dr. Emily Winn-Deen, Ph.D.
Chair, SACGHS Pharmacogenomics Task Force

Dr. Winn-Deen reviewed the Committee's work on pharmacogenomics (Pgx) to date. SACGHS heard presentations on pharmacogenomics (Pgx) in June and October 2005. Based on this information, the Pgx Task Force developed a report outline. Also, staff assembled information on reports and recommendations on this topic from other groups such as The Nuffield Council on Bioethics and the Royal Society. In addition, the Task Force compiled a table of efforts related to Pgx underway within the Federal agencies. Dr. Winn-Deen reviewed the findings of this effort. Within the area of research and development, Dr. Winn-Deen remarked that NIH and VA support investigator-initiated research on new and post-market therapeutics, and FDA has been proactive in working with diagnostics companies and drug companies to understand their respective viewpoints. She also mentioned several specific research and development initiatives supported by the agencies, including NIH's Pharmacogenomics Research Network, CDC's EGAPP program, and the Agency for Healthcare Research and Quality's (AHRQ) DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network. Dr. Winn-Deen stated that there is a need for extensive research in Pgx, including a novel research team approach, incentives to study post-market and generic drugs, evidence of effectiveness, pharmacoeconomic models, and coordination between the drug companies and test developers.

In addition to gathering scientific evidence, Dr. Winn-Deen said that clinical practice must change, or the desired result of improved health care will not be achieved. She discussed barriers to integrating new science into clinical practice, including a lack of relevant evidence, the cultures of different medical specialties that make them unreceptive to change, lack of awareness by providers and the public, and a lack of coverage and reimbursement for Pgx testing.

The key infrastructure issues include the need for electronic health records and data standards, which affect whether a healthcare provider has the information necessary to guide clinical decision making. The Office of the National Coordinator for Health Information Technology, Health Resources and Services Administration (HRSA), and DVA are very active in addressing these issues.

The oversight issue addresses how and when pharmacogenomics should be utilized. Dr. Winn-Deen noted CDC's new program to develop quality control materials for genetic tests as well as an interagency effort involving FDA, NIH, Environmental Protection Agency, and National Institute of Standards and Technology on microarray data quality, so datasets from different studies can be pooled. Dr. Winn-Deen said FDA has been extremely proactive in working with the pharmaceutical companies by encouraging them to submit their research data related to biomarkers. FDA recently issued a guidance document that

serves as a model for public/private collaborations. Dr. Winn-Deen said there is still a need for guidance on labeling changes for existing and newly released drugs.

Education is another key issue. Dr. Winn-Deen said patients need information that allows them to make educated decisions about Pgx testing, and healthcare providers need education to help them understand when Pgx testing is appropriate. Toward this end, NIH has produced brochures to help inform the public about Pgx, NIH and HRSA provide funding to the National Coalition for Health Professions Education in Genetics for educational efforts, and AHRQ's Centers for Education and Research on Therapeutics (CERTs) help to educate providers.

Effective surveillance systems also are necessary. Dr. Winn-Deen noted FDA's Adverse Event Reporting System (AERS), CDC's mission to protect Americans' health and safety, and AHRQ's Integrated Delivery System Research Network (IDSRN). She questioned whether these surveillance systems were effective or sufficient. She noted that pharmaceutical companies have good data on utilization patterns but that these data are proprietary.

Dr. Winn-Deen said better coordination across Federal agencies and more mechanisms for data sharing like NIH's PharmGKB database and CDC's Human Genome Epidemiology Network (HuGENet) are needed. The inclusion of personalized medicine in Secretary Leavitt's 500-Day Plan and FDA's Critical Path Initiative indicates that the issue is receiving high-level interest.

Finally, ethical, legal, and social implications (ELSI) of Pgx also are important to bring to the Secretary's attention. Key topics include allocation of resources, health disparities, informed consent, privacy protections, the role of race, psychosocial harms, gene patents, and genetic exceptionalism. Federal efforts include NIH's ELSI programs, HRSA's work on improving access to care, and the Office of Minority Health's focus on protecting ethnic and racial populations.

Dr. Winn-Deen explained that the goal for the Pgx session was to identify broad areas on which to focus recommendations, including an assessment of whether the Task Force had identified all relevant issues.

Dr. Winn-Deen also informed the Committee that The Lewin Group, through its contract with Office of the Assistant Secretary for Planning and Evaluation (ASPE), is preparing a review of the Pgx literature for review at the June meeting.

FDA Draft Guidance for Industry and FDA Staff on Pharmacogenetic Tests and Genetic Tests for Heritable Markers
Steven Gutman, M.D., M.B.A.
Director, Office of *In Vitro* Diagnostic Device Evaluation and Safety, FDA

Dr. Gutman described FDA's draft guidance on pharmacogenetic tests and genetic tests for heritable markers. The draft guidance was developed by the FDA Office of *In Vitro* Diagnostics and released in February 2006. Public comments are currently being sought on this draft guidance. This draft guidance replaces a broad document on multiplex testing that was issued in February 2003. Public comments on the multiplex testing document indicated that it was too ambitious and should be divided into two documents - one on less complex testing and the other on more complex testing. Based on that advice, FDA prepared the current pharmacogenetic tests draft guidance with updated information and a narrowed focus. The second guidance has not yet been developed.

The purpose of the draft guidance on pharmacogenetic tests and genetic tests for heritable markers is to help shorten development and review timelines by creating a roadmap for sponsors that describes FDA's data expectations for new products. The agency is anxious to facilitate rapid transfer of new technology from the bench to the clinical laboratory and to encourage the informed use of pharmacogenomic and genetic diagnostic devices. The draft guidance is directed at manufacturers, particularly diagnostic device companies; traditional sponsors of new diagnostic devices; FDA review staff; venture capitalists; pharmaceutical companies; academics; government researchers; and entities that might fund translational research.

The foremost element emphasized in the draft guidance is intended use. Intended use determines the types of risks FDA attributes to a device, the regulatory threshold needed to bring a device to market, and the types of data the agency expects to see. The clinical purpose and target population for the new product also are key. FDA acknowledged in the guidance the challenge of addressing rare events and defining the performance of predictive tests when the predicted outcomes occur far in the future as well as the low prevalence of some diseases.

The document describes device design and explains the information needed for a quality submission, including a description of and information on samples, methods and controls. FDA ensures quality through a comprehensive program, including device authority for ensuring minimum data and labeling thresholds prior to the marketing of new diagnostics, quality system regulations to ensure consistency in the manufacture of the product over time, and mandatory and voluntary reporting obligations for laboratories and health care users. A good FDA review will focus on the analytical performance of the assay, including core studies that demonstrate analytical performance, issues of accuracy and precision, levels of detection or measurement, and thresholds, as well as its clinical performance, referring to the Standards for Reporting of Diagnostic Accuracy statement. FDA also carefully examines labeling according to the relevant Code of Federal Regulations, including intended use, quality control, interpretations and precautions, stability, and performance parameters. In addition, FDA is interested in data processing and validation of instrumentation that will drive the methodology.

The draft guidance defers in part to a draft concept paper on co-development of drugs and diagnostics, which was being revised for issuance as draft guidance. This co-development draft guidance would clarify regulatory routes and continue to promote informal or formal early interactions with sponsors, which would allow FDA to understand what is coming down the pipeline. These interactions would ensure that the agency has the requisite expertise to evaluate submissions.

Full Committee Discussion

Dr. Winn-Deen and Dr. Leonard asked about FDA's role in making dosing recommendations for individuals who are slow or rapid drug metabolizers, as there are no guidelines for healthcare providers or pharmacists. Dr. Gutman said FDA recognizes the problem but does not believe that it is his agency's sole responsibility. He said the hope is that some work will be initiated through the Critical Path Initiative, by pharmaceutical companies, and by academics. Dr. Gutman asked for suggestions on how this issue could be addressed in the guidance. Dr. Winn-Deen suggested using warfarin as a model. In this example, people were optimized to the most effective dose of warfarin and genotyped to see if their HER-2C9 and VCOR1 variants were predictive of this dose. The conclusion was that the correct dosages could be predicted based on those two genotypes. She suggested that drug manufacturers who know that

their drugs are metabolized by CYP2D6 do the same kind of look-back studies and that dosing guidance be developed based on their findings. Dr. Gutman thought that was reasonable.

Dr. Gutman asked whether his colleagues who are responsible for labeling should be asking for more data before making labeling changes or whether they should be more conservative in labeling. Dr. Leonard said that from a liability perspective, it would be disturbing to have labeling that warns about polymorphisms that affect dosing.

Dr. Evans said an important recommendation that could be made to the Secretary would be for FDA to have the ability to conduct prospective clinical outcome studies. He stated that it would be hard to argue for the adoption of Pgx testing without them. Dr. Collins said the National Heart, Lung, and Blood Institute was actively mounting such a study. He asked Dr. Gutman about the nature of discussions within FDA about how the AmpliChip P450 would enter clinical practice when it was approved. Dr. Gutman said Strattera served as their model and that an analysis of the literature on psychiatric neurologic diseases was performed, noting that some publications make tentative dosing recommendations. Based on Strattera and the literature review, FDA expected two things of AmpliChip: there would be a long transition before the necessary information was available and a tremendous educational burden because healthcare providers would not know how to use the information.

Dr. Leonard pointed out that the Federal efforts table stated that the National Institute for General Medical Sciences obtained approval to solicit proposals to fund research on ethical, economic, legal, and social issues related to pharmacogenetics research, specifically the hurdles of translating basic research into clinical practice. She wondered if they could be encouraged to fund the prospective outcome studies that might be needed. Dr. Collins said they were not planning to conduct clinical studies; rather, these would have to be done by the respective institutes interested in the topic areas. Dr. Collins added that they are complicated, expensive studies to undertake. Dr. Winn-Deen suggested encouraging the Secretary to ask NIH to make broader use of their funding to take on this challenge for one or more drugs related to their remit. Dr. Collins said that although that was an option for SACGHS, there was no extra funding to conduct such studies, and that if they did so, some other effort would have to be cut. Dr. Julio Licinio thought it was important to recommend dedicated funding for such an effort in the report. Dr. Willard agreed that since this is an important priority, the Committee should consider recommending that it be considered a special initiative that merits specific funding. Dr. Evans agreed that the demonstration of efficacy in pharmacogenetics looms very large and should be considered a priority. Dr. Winn-Deen commented that this was an opportunity for SACGHS to influence the health of the American people in the near-term. She suggested recommending some actions that are immediately applicable as well as activities that will yield results in the future. Dr. Evans said it was reasonable to try to shift some of this burden to the companies that develop the drugs by asking them to conduct studies that demonstrate clinical outcomes. Dr. Gurvaneet Randhawa stated that given limited resources and the large number of drugs developed, it is not feasible to mount observational studies *de novo* to determine the efficacy of new drugs and their interaction with genes. He suggested that the Committee instead focus its attention on improving ongoing hospital-based data collection systems and conducting studies that utilize existing databases. He indicated that this would help determine the genes and conditions that require new studies. Dr. Linda Bradley agreed and said that the EGAPP Work Group is discussing the use of databases that already exist.

Public Comment

Ms. Gail Javitt
Law and Policy Director, Genetics and Public Policy Center, Johns Hopkins University

Ms. Gail Javitt addressed the Committee on genetic testing quality and pharmacogenetics. She stated that the success of pharmacogenetics is predicated on a robust pipeline of genetic tests that reliably detect variations in DNA. The laboratories that do the testing need to be capable of performing the tests accurately, the tests must provide clinically valid information, and healthcare providers must know how to interpret the results. She expressed concern that current regulation of genetic testing is not strong enough. There is no specialty area for genetic testing laboratories under the Clinical Laboratory Improvement Amendments (CLIA), even though there was significant support for it. In November 2005, the Genetics and Public Policy Center sent a white paper to the Centers for Medicare & Medicaid Services' (CMS) Administrator Mark McClellan, urging him to issue a proposed regulation for a genetic testing specialty under CLIA. The Genetic Alliance sent a similar letter.

Ms. Javitt's second point was that there are gaps in oversight for the genetic tests themselves. A genetic test can come to market through genetic testing laboratories supplying a test kit or they can make the test themselves in-house. She stated that the vast majority of tests are performed using in-house technologies, which are not subject to pre-market FDA review. Of the more than 900 genetic tests available, only a few are sold as test kits. In addition, once a test kit is approved for a particular indication, a laboratory can offer its own proprietary test for the same indication. She felt FDA's intention to regulate pharmacogenetic tests will be undermined unless FDA's requirements apply to all pharmacogenetic tests, regardless of how they are produced.

Ms. Javitt commented that the absence of adequate oversight means that healthcare providers and the public are hard-pressed to distinguish between good and bad tests, and they have little assurance that the tests they are using to make profound healthcare decisions are reliable and relevant predictors of disease risk or treatment outcome. She asked that the Committee recommend that CMS issue a proposed regulation for a genetic testing specialty under CLIA and that the Secretary establish a regulatory framework for genetic tests to ensure that they are clinically valid, regardless of whether they are performed using a test kit or an in-house developed method.

Pharmacogenomics Session (continued)

Development of Recommendations

Dr. Winn-Deen introduced two questions on translational needs for the Committee to discuss: 1) Do the current research activities meet the needs identified by SACGHS; and 2) How should research to determine the effectiveness of pharmacogenomic-based drugs and tests be conducted, especially in a diverse population? She stated that the Committee agreed earlier in the day that funding is deficient for translational research and suggested adding a recommendation to address it. She opened the floor for discussion of the two proposed recommendations for addressing this issue: the first urging FDA to promote the inclusion of diverse populations in Pgx studies; and the second encouraging healthcare organizations to become active in Pgx research.

Dr. Leonard questioned the feasibility of the first recommendation, stating that FDA is not required to

conduct Pgx studies. Dr. Gutman believed the recommendation would apply to some products. Dr. Winn-Deen suggested rewording the recommendation with the caveat that when Pgx data is utilized as part of a drug review, it should be gathered from a diverse population. Dr. Randhawa pointed out that "diverse populations" was not defined. Dr. Winn-Deen said they could clarify the language to make it clear that it refers to genetically diverse populations.

Ms. Berry suggested a recommendation be crafted that would provide an incentive for companies to conduct Pgx research and submit data. The Committee agreed that HHS can influence trials but does not have control over private industry. Dr. Leonard suggested that a representative of FDA Center for Drug Evaluation and Research (CDER) participate in future SACGHS meetings. Dr. Gutman said he would convey that request to CDER.

Dr. Telfair asked for clarification on the types of healthcare organizations referred to in the second recommendation. Dr. Winn-Deen gave the example of Kaiser Permanente, i.e., healthcare organizations that manage a great deal of data. The Committee agreed that Secretary Leavitt could be asked to take steps to foster public/private partnerships.

The Committee discussed a potential recommendation to increase funding of translational studies, either by encouraging each of the NIH institutes to fund translational research within their scope or by designating a separate source of funding for such studies. Dr. Tuckson stated that it was not practical to recommend new funding streams because NIH is already short on funding. Dr. Winn-Deen agreed, but said she would like to see each agency charged with funding Pgx research as much as possible within their various components. Dr. Collins suggested narrowing the types of studies for which the recommendation would apply. He said the Committee had previously said they would like to see more funding of prospective Pgx trials. Dr. Winn-Deen noted that part of SACGHS's mandate is to teach the field that work in genetics must take place across all NIH research areas.

Dr. Winn-Deen moved on to regulatory issues for drug/diagnostics co-development. The Task Force had identified several specific needs: better coordination between those conducting research and those regulating the technology, incorporation of Pgx into the design of clinical trials, and guidance from FDA on how and when Pgx will influence labeling practices.

Dr. Licinio stated that a national registry or database for adverse drug reactions is needed. Dr. Gutman noted FDA's MedWatch program, which has both required and voluntary reporting mechanisms. In addition, CDER was being reorganized to provide the group examining adverse drug events with greater independence. Dr. Licinio pointed out that these efforts are not equivalent to a network that would share information among researchers. Dr. Gutman explained that MedWatch has a mechanism for contacting companies, hospitals and laboratories, and for directing inspections. He said the regulations might be flexible enough to allow samples to be collected and analyzed, although such an effort would be difficult operationally.

Dr. Collins noted that the AERS database is not an easy or uniform solution because it is voluntary and captures only about 10 percent of adverse drug events. He felt the time was right to work with health maintenance organizations that have a large number of members and computerized systems for tracking adverse events. Dr. Tuckson noted that he works with a company called Ingenix that collects post-marketing, adverse event information based on a database of over 70 million people. They monitor new drugs and provide feedback to FDA and others.

Dr. Winn-Deen summarized by stating that there should be a recommendation addressing the need for surveillance of adverse drug reactions, through MedWatch or any private adverse drug reaction databases. Dr. Randhawa asked if the Committee was considering making a separate recommendation for using such databases to identify non-responders who could participate in Pgx studies.

Dr. Winn-Deen moved on to the topic of incentives and barriers for companies to co-develop drugs and Pgx tests. The first issue identified by SACGHS was the different designation thresholds for orphan drugs and orphan devices. Dr. Winn-Deen asked if FDA had addressed this disconnect. Dr. Gutman said he was not aware of any internal discussions on the issue. Dr. Winn-Deen suggested that the Committee ask FDA to look into this. The Committee acknowledged that the Orphan Drug Act does not facilitate development of therapeutics for subpopulations with genetic variations that affect the progression of conditions and their response to treatments.

Dr. Winn-Deen addressed infrastructure, noting that surveillance had already been discussed. She said the Committee posed a recommendation to incorporate genetic analysis in both the drug approval and the post-marketing process to encourage broader utilization of pharmacogenetics. She noted some overlap of this idea with the recommendation on translational studies. Several Committee members agreed that the two recommendations should be incorporated into one.

On the topic of direct-to-consumer marketing, Dr. Winn-Deen said FDA and FTC were working together to examine false claims about genetic tests. She asked if the Committee wanted to propose that these agencies develop consumer alerts concerning genetic tests. Dr. Gutman said FDA was working on a consumer alert process that would be completed in the near future. Dr. Winn-Deen said that the language of the report would be modified to reflect that a consumer alert was imminent.

The Committee discussed the possible need for a consumer alert when a drug label changes. Dr. Gutman said current efforts in this area are directed at healthcare providers unless the labeling change involves an over-the-counter drug. Dr. Leonard was concerned that consumers who know about a labeling change will take the information to their healthcare providers, but the healthcare providers will not know what to do. Dr. Evans was more concerned about the momentum of individualized medicine, including the cottage industry of unethical salesmen who sell ineffective or dangerous DNA-based products. Dr. Winn-Deen explained that FDA and FTC were investigating such products.

The next topic addressed was coordination of international, Federal, and private efforts. Dr. Winn-Deen stated that there had been some discussion about the appointment of a "genetics czar" or coordinator within HHS. Dr. Collins believed it was better to continue the current coordination efforts among agencies. He said that appointment of a czar would make it someone else's problem and could create a disincentive for the agencies to work together. The Committee and *ex officios* agreed. Dr. Collins added that the international lines of communication concerning genetics also are working well, citing the success of the Human Genome Project and the HapMap project.

The Committee moved to the next topic of education. Dr. Winn-Deen stated that SACGHS has developed a resolution on the need for continuing genetics education. She asked the Committee whether they wanted to consider additional ways to move information about genetics into society more broadly. The Committee agreed that it was important to provide information to healthcare providers who might be prescribing Pgx drugs but felt it was too soon to educate the general public about Pgx. Such an effort

should not be started until efficacy has been established and there are good studies that support the drugs' claims. Dr. Randhawa asked who will provide the education and at what stage. He said that there was a need for buy-in from professional organizations at the outset so that they could be involved in crafting the message.

The next proposed approach dealt with healthcare providers' acceptance of Pgx in their clinical practices. Dr. Winn-Deen asked Dr. Gutman to describe the system he mentioned previously for educating healthcare providers. Dr. Gutman stated that, depending on the level of risk involved, information might be communicated through a mailing or through drug firms, as it is their responsibility to provide it. In the case of a significant labeling change in a high-risk situation, FDA would create a communication plan in collaboration with the relevant drug company. Dr. Evans said it was important to explore the potential for existing and novel partnerships that can relay information to healthcare providers. Dr. Leonard suggested that Pgx testing be included in recertification processes for healthcare providers. Dr. Licinio suggested talking to the American Board of Medical Specialties to request that questions on Pgx be included in board examinations. The Committee also discussed electronic reminders, such as pop-up alerts and emails, which could provide healthcare providers with new information. Dr. Evans stated that drug formularies at hospitals could be used to alert providers about Pgx information. Ms. Berry commented on clinical decision support tools used by various organizations.

Dr. Winn-Deen moved to the next topic on the influence of liability on standards of clinical practice. This topic addressed whether healthcare providers leave themselves open to malpractice suits if they do not use new Pgx tests. Ms. Masny stated that healthcare providers who participated in a conference she attended felt that once information about a test appears on a label, they are liable for providing it. Ms. Berry felt that trial lawyers would devise innovative ways to create legal liabilities related to this issue. She said the Committee should recognize the phenomenon but not let it interfere with the best practice of medicine. She felt that there is no way to shield the medical profession from lawsuits.

The Committee also discussed the effect of health insurance coverage on whether patients receive certain tests and therapies, noting that coverage decisions may not be consistent with FDA actions. Dr. Winn-Deen suggested that SACGHS highlight the disconnect between FDA approval of tests or changing of labels and coverage decisions. Dr. Leonard asked Dr. James Rollins whether CMS would provide Medicare reimbursement for Pgx testing if a healthcare provider determines that a patient needs a drug and the label states that certain genetic variants predict proper dosing. Dr. Rollins stated that to his knowledge, Medicare does not address the threshold for proper dosing. Dr. Randhawa explained that because FDA looks at safety and effectiveness and CMS looks at what is reasonable and necessary, there is no way to achieve 100 percent agreement between the two agencies.

Tuesday, March 28, 2006

Genetic Discrimination Session

Dr. Tuckson introduced the session on genetic discrimination in health insurance and employment, which is the Committee's top priority. SACGHS had closely monitored Federal legislative activities on the issue. In May 2005, they sent Secretary Leavitt a compilation of public comments, a DVD of testimony highlighting public perspectives, and a legal analysis of the adequacy of current law. He introduced Ms. Christy White of Cogent Research, who reported on recent survey results on public attitudes toward genetic technologies and discrimination.

Survey on Public Attitudes toward Genetic Technologies and Genetic Discrimination
Christy White
Principal, Cogent Research

Ms. White previously presented data from a 2005 survey on genetic technologies to SACGHS. She reported at that time that a follow-up study was underway. Based on SACGHS input, the follow-up survey included questions on Americans' awareness of current laws and protections and their feelings about them. Since the new data was received so recently, Cogent Research was still in the process of analyzing it. From preliminary results, however, the data appeared to remain fairly stable since the previous year. She focused her presentation on the new questions, which related to awareness of specific protections, perceptions of those protections, and feelings about what should happen concerning the pending nondiscrimination legislation.

Cogent interviewed a random sample of 1,000 Americans over age 18 through an online survey. The sample was representative of the U.S. population by age, education, gender, income, and ethnicity. The data were weighted by education and ethnicity to ensure that it accurately represented the U.S. adult population.

Ms. White said that about one quarter of survey respondents are aware that genetic information can be used to understand and optimize health, and almost half are interested in using genetic information to understand their own health. Concern about misuse, however, was still very high. Seventeen percent of respondents mentioned genetic discrimination as a drawback of genomics. Sixty-six percent were concerned about how their personal genetic information would be stored and who would have access to it. Thirty percent said this fear would prevent them from having a genetic test.

Numerous entities were implicated by survey respondents in terms of who might try to gain unauthorized access to personal genetic information. Ms. White stated that, as with the previous survey, the extent of mistrust was extreme. Sixty-five percent of respondents suspected life insurance companies, the government, or health insurance companies. About half of Americans expressed concern about banks, financial institutions, or their employers. Sixty-five percent said insurance companies will do everything possible to use genetic information to deny coverage, and a similar number said insurance companies will use information to deny coverage for drugs to those whose genetic profile indicates a low chance of responding. Only eighteen percent of respondents believe there are currently laws that protect them, twelve percent hold the viewpoint that there are not any protective laws, and seventy percent have no awareness of any current laws or protections.

Those who thought there were laws protecting them were asked whether current medical and health privacy laws are sufficient or whether more protection is needed. Only one-fourth of respondents believed that current laws are sufficient.

Ms. White reported that the desire for protections is very high. Seventy-two percent agreed that the government should establish laws and regulations to protect the privacy of individuals.

The researchers then educated participants and told them that Congress is considering new legislation that would specifically prohibit employers from using employees' personal genetic information to make hiring decisions or set insurance rates. The researchers presented two views and asked participants which they agreed with more. Only fifteen percent agreed with the first view that business owners would not misuse their employees' personal genetic information and therefore the new law would only add costly and unnecessary burdens for businesses. Eighty-five percent agreed with the second view that, without amending current laws to prohibit employers from misusing their employees' personal genetic information, it is only a matter of time before they use this information to discriminate against some individuals.

Cogent also asked questions about a national databank. Participants were told that a major public health initiative has been proposed to create a national databank that would include detailed DNA and environmental information on up to one-half million individuals. They were told that this information would provide a powerful tool for scientists to understand links between genes, other factors, and specific diseases affecting millions of Americans. Only twenty-four to thirty-one percent agreed that a national database should be created.

Questions and Answers

Dr. Tuckson asked if there was a mechanism for determining whether people knew more about genetics, genetic discrimination, and genetic legislation than in the previous survey. Ms. White said there was very little change in awareness about the field of genetics and a slight increase in the number of people familiar with the idea of genetic discrimination.

Dr. Collins asked if there was a way of assessing the correlation coefficient between the people who are most worried about access to information and those who oppose the databank. Ms. White said Cogent would analyze this correlation.

Dr. Evans wanted to know if the survey asked whether the thirty percent of people who would not have a genetic test would be reassured by passage of legislation. Ms. White said that sixty percent of participants would be more interested in genetic testing if legal protections were in place.

Dr. Frohboese asked which ethnic categories were used in the survey and what the response rates were for each category. Ms. White said they used the key Census demographic categories. She explained that because Hispanics and African Americans are typically underrepresented in Web surveys, these two groups were oversampled.

Ms. Au wanted to know if a question was asked about participants' general feelings toward the government and whether it was cross-matched with the negative databank responses. She wondered

whether individuals' opinions of government affect their viewpoints about the need for a national databank. Ms. White said they did not ask about general feelings toward the government, but noted that only one percent of the respondents indicated they would want the government to have their genetic information. These numbers jumped to twenty-four and thirty percent if the respondents knew there would be a benefit and that their identity would remain anonymous.

Update on the Status of the Genetic Information Nondiscrimination Act 2005 (S. 306/H.R. 1227)
Sharon F. Terry, M.A.
Chair, Coalition for Genetic Fairness

Ms. Sharon Terry displayed a timeline of events since 1996 related to genetic discrimination. She stated that H.R. 306 passed unanimously in the Senate for the second time in a second Congress. H.R. 1227 was introduced and referred to three committees in March 2005, and since then had acquired 170 sponsors. Ms. Terry said that Republicans were usually signing on once the legislation was on their radar screens. She stated that the Coalition believes that if an equal number of Democrats and Republicans sign on, the committees will move the legislation forward.

The Coalition also had been engaging the Chamber of Commerce, National Association of Manufacturers (NAM), and Society of Human Resource Managers in dialogue to find common ground. She felt they would soon be able to give Congress an indication that the legislation could move forward because of the substantial dialogue these parties engaged in. The Coalition also was working with trade associations and companies such as IBM, which established a policy endorsing the principles of the legislation company-wide on an international level.

Ms. Terry presented a list of steps that SACGHS could take to encourage legislative action, including:

- Requesting a meeting with the Coalition for Genetic Fairness, Chamber of Commerce, and National Association of Manufacturers;
- Asking the Secretary to invite these same organizations and the White House Domestic Policy Office to a meeting;
- Reminding the Secretary that as he works with Congress on funding for GEI, he should explain the importance of H.R.1227 and its potential impact on this initiative;
- Making a strong statement expressing concern about the chilling effect that the lack of Federal legislation is having on research and its impact on the country's investment in biomedical research;
- Sending the genetic discrimination public comments to the new chairman of the Education and Workforce Committee, Howard McKeon (R-CA); and
- As individuals, working with their constituencies as knowledgeable experts on this issue.

Q&A and Committee Discussion

Dr. Tuckson reviewed these recommendations and commented that the Committee spent a considerable amount of time the previous year with the Chamber of Commerce and America's Health Insurance Plans (AHIP), although not NAM. He said that the time may be right for the Committee to talk with these organizations again. Dr. Tuckson said AHIP's concerns related to the unintended consequence of being unable to use information to coordinate care for complex cases that required a variety of medical and non-medical social supports. Ms. Terry reported that AHIP has stated while they would not actively

endorse the legislation, they would not actively oppose it.

Dr. Licinio asked Ms. Terry what roadblocks are preventing passage of the legislation. She said the employer community currently has the most concerns about the legislation. She said Congress does not like to be at odds with entities such as the Chamber of Commerce or NAM. However, she believed that in the next few months, their concerns would be minimized. Another roadblock is that there are many bills waiting to be processed and the genetic nondiscrimination legislation was a low priority for most people.

Dr. Tuckson asked if the legislation had been changed to address concerns about frivolous lawsuits. Ms. Terry replied that there would be slight changes to the language of the bill. She explained that the bill is moderate in that it requires those who feel they are experiencing discrimination will have to go through a step-by-step process to seek a remedy prior to bringing a lawsuit.

Dr. Frohboese agreed with the Coalition that another meeting should take place with the groups that still have concerns about the legislation. Dr. Tuckson suggested sending a letter to the Secretary as expeditiously as possible urging him to bring these organizations together with the White House Domestic Policy Office and the chairs of the committees that are responsible for the legislation. The Committee agreed that the meeting should take place quickly.

Dr. Leonard suggested adding to the letter information on the effect of H.R.1227 on GEI and a strong statement about research concerns. Ms. Masny suggested the letter also ask the Secretary to send the compilation of public comments and DVD to those in new positions in Congress. In addition, the Committee decided to add some of the new survey data to the letter once the data analysis has been completed.

The Committee also agreed that the section of the large population studies report on privacy and confidentiality should include a stronger statement supporting genetic nondiscrimination legislation.

Public Comments

Anthony Lakavage, J.D.
Preserve the Research Use Exemption Coalition

Mr. Anthony Lakavage stated that he was representing the Preserve the Research Use Exemption Coalition. He explained that the Coalition consists of life sciences and biotechnology companies and organizations dedicated to maintaining the fundamental objectives of the patent system. The Coalition strongly supports preserving the existing research use exemption.

Mr. Lakavage said the fundamental policy underlying the patent system is to provide exclusive rights for a limited time period to investors in new and useful technologies, in exchange for those technologies being fully disclosed to the public. He said that disclosure promotes further innovation by allowing newer technologies to be developed building on the disclosed information. Mr. Lakavage said there are only a few limited circumstances under which the use of a patented invention is in the broader public interest. The research use exemption allows conduct that would otherwise constitute infringement of the patents when that conduct is purely for philosophical and non-commercial inquiry.

In its report, the National Academy of Sciences' (NAS) Committee on Intellectual Property Rights in

Genomics and Proteomic Research and Innovation diverged from the current application of the research use exemption by recommending that it be expanded and codified to provide a regulatory or statutory exemption from infringement for research on a patented invention. However, he said the committee acknowledged that there has been little evidence to suggest that the research use exemption as currently applied imposes a significant burden on biomedical research.

The Coalition believes that any expansion of the research use exemption, such as that proposed in the NAS report, would be counterproductive, discourage innovation, and have serious consequences for those who would have traditionally invested in the innovative research tools industry. Mr. Lakavage stated that expanding the research use exemption would diminish the value of research tool inventions, undermine innovation, increase litigation, delay access to technologies while litigation is in the courts, and limit access to valuable research. He said that the committee's research use exemption recommendation is not based on sound public policy or legal reasoning. He asked that SACGHS consider the Coalition's views and not support any expansion or codification of the research use exemption.

Jaydee Hanson
International Center for Technology Assessment

Mr. Jaydee Hanson stated that the International Center for Technology Assessment opposes gene patents. They believe there are ethical, scientific and health reasons for not patenting genes and are concerned that developments in gene therapy could be significantly limited by gene patents.

He noted that recent estimates suggest that approximately 20 percent of human genes have been patented. Mr. Hanson said that patents covering human genetic material claim exclusive control over naturally occurring human genes and limit how they can be used in research and diagnosis. He stated that this exclusivity could hinder health care and the advancement of scientific technology. He said that gene patents are being challenged in courtrooms and legislatures. International organizations, such as the United Nations Educational, Scientific and Cultural Organization and the Council of Europe's Committee on Legal Affairs and Human Rights, view genes as belonging to the common heritage of humanity. Mr. Hanson said that as we learn more about the human genome and how genes interact, we need the ability to look at all genes together. He said there also is concern that the current monopoly over genetic testing will inevitably lead to a loss of expertise and information among researchers and healthcare providers, which will hinder improvements in current testing mechanisms.

Mr. Hanson said that in the United States, 35 percent of geneticists reported that sharing basic data and research material substantially decreased between 1992 and 2000, and 21 percent claimed that their inability to access data from another researcher resulted in the abandonment of a promising line of research. A 1998 survey of 200 genetic testing laboratories found that 25 percent had been prevented from offering a test due to the enforcement of a patent or license. In addition, approximately 50 percent reported that they did not attempt to develop new tests due to the patent constraints. Mr. Hanson recommended that the U.S. follow Europe's example in protecting its citizens by denying broad patent claims on genes that correlate with particular diseases.

Joann Boughman, Ph.D.
Executive Vice President, American Society of Human Genetics

Dr. Joann Boughman reported that the Board of the American Society of Human Genetics (ASHG) met with eight House offices and ten Senate offices to express their views on genetic nondiscrimination. They received commitments from four representatives to co-sponsor H.R. 1227.

Dr. Boughman also provided an update on ASHG's educational efforts, stating that they have greatly expanded their educational resources for K through 12 through a Web portal called GenEdNet, (the Genetics Education Network). GenEdNet contains teaching standards and genetic content for every grade in every State and province. Dr. Boughman said Phase 2 of the website's development was underway, in which every standard was being related to at least one vetted website with age-appropriate and accurate information. Phase 3 will add active teaching and hands-on activities for the classroom. ASHG also is developing undergraduate education activities.89

In addition, ASHG is working with NHGRI on DNA Day, which was to take place on April 25th. DNA Day sponsored an essay contest that received almost 400 submissions. A special DNA Day initiative was taking place in the Northeast, with 50 to 100 geneticists planning to go into classrooms.

Patents and Licensing Session

Session Overview and Framing the Topic
Debra Leonard, M.D., Ph.D.
Chair, SACGHS Patents and Access Task Force

Dr. Leonard stated that in March 2004, SACGHS ranked DNA-based patents and licenses as a high-priority issue. However, around that time, NIH had commissioned NAS to review the patenting and licensing of human genetic material and proteins and the impact on research and clinical practice. The Committee decided to defer its consideration of the topic until NAS completed its work. In November 2005, when the NAS Committee published its final report, SACGHS charged the Patents and Access Task Force with reviewing the NAS report and determining whether there were still areas that warranted the Committee's attention.

Some of the original questions identified by SACGHS were: Do DNA-based patents blur the distinction between natural phenomena and invented products? Are DNA-based patents too broad? Have the changes in the U.S. Patent and Trademark Office's (USPTO) utility guidelines been effective in reducing DNA-based patent submissions whose utility is questionable? Which licensing terms are creating the majority of problems for genetic/genomic test providers (e.g., high royalty fees, the field of use, sublicensing, reach-through rights, exclusivity clauses)? Do exclusive licenses raise particular concerns for genetic/genomic test providers? How prevalent are exclusive licenses?

SACGHS also raised questions about the impact on research: Do gene patents and licensing practices inhibit research progress? To what extent do delays in publication due to patent submissions affect the progress of science? Does patent stacking inhibit scientific discovery and technology development by making it difficult for a researcher to obtain all the licenses necessary to carry out specific research projects? Is the impact of the 2000 amendment prohibiting federally funded researchers from imposing undue restrictions on future research and discovery being monitored and analyzed, and if so, has it had an

effect?

In the area of clinical practice, SACGHS questions included: Do patents facilitate or inhibit the translation of scientific information into medical practice? Are patent incentives needed for the translation of genetic/genomic discoveries into genetic/genomic technologies? How do patent and licensing policies affect the availability of and equitable access to clinical genetic tests? Do current patenting and licensing practices for genetic technologies affect the training of laboratory clinicians? Is exclusive licensing in the best interest of public health, given the difficulty of sending samples to multiple laboratories, lack of competition for testing, and absence of independent test validation? Do DNA-based patents and licenses reduce access by either increasing costs due to licensing fees, reduced availability, or other reasons? Is there a mechanism for balancing the protection of an inventor's intellectual property with the broad utilization of gene discoveries for health care purposes? Do DNA-based patents require special consideration due to their potential to improve public health?

In the area of economic impacts of patents and licenses, the questions raised included: Do patent and licensing policies increase the cost of medical products, including genetic tests and gene technology-based treatments? Are current patenting policies and practices critical to the success of the biotechnology and pharmaceutical industries? Could changes in current law undermine innovation, doing more harm than good?

Briefing on the Report of the National Academy of Sciences Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation
David Korn, M.D.
Member, NAS Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation

Dr. Korn stated that NAS was asked to form a committee to examine how well the U.S. patent system is working with regard to technologies in genomics and proteomics, to evaluate U.S. systems compared with those of Europe and Japan, and to investigate whether the application of patent law and practice is inhibiting research and innovation. The study was conducted primarily by NHGRI and the National Institute of General Medical Sciences.

The committee found that patenting practices vary greatly among biotechnology categories; that patent numbers has leveled off in most categories but pendency has increased, creating a large backlog of genomic and proteomic applications at USPTO; and that U.S. inventors and their signees dominate patents in almost all categories of interest. Dr. Korn stated that this is a U.S. problem, rather than an international problem.

The committee found that the chief difference in approaches to patenting among the U.S., Japan and Europe relates to "non-obviousness," i.e., that a claim to a patent must not be obvious. In Europe and Japan, this is called the "inventor's step," which implies that the inventor has done something creative. This concept relates to the difference between discovering something and inventing something, which Dr. Korn said is respected more in Europe and Japan than in the U.S. Also, most other countries have a statutory provision for compulsory licensing and shield research on patented inventions from infringement liability.

Dr. Korn described the concerns that were raised by the NAS committee. First was "anti-commons,"

referring to the inhibiting effect of numerous patents on valuable research and the commercialization of new therapies resulting from having to marshal licenses or permission for projects from many different patent owners. The second concern was access. Dr. Korn said that in 1980, the Supreme Court ruled that anything made by man is patentable, which opened up floodgates of biotechnology patents. The courts have been trying since then to determine the limits on patenting, if any. The last concern related to the possibility of an erosion of the norms of open science that would inhibit research and create restrictions on sharing research materials.

To address this concern, a survey by Walsh et al. asked about motivations for research among academics that were involved in substantial commercial activity. Twenty-two percent of respondents had personally engaged in patenting their own discoveries during the previous two years. Thirty-five percent of these academic researchers had been involved in business activities, such as start-ups. When asked about the main reasons why they were conducting the research they were involved in, the most frequent responses were scientific importance, interest, feasibility, and sufficient funding. Health benefit was a priority for only sixty percent. Patentability and personal income also were found to be very low motivators.

Reasons for not pursuing projects included no funding, being too busy, lack of feasibility, lack of scientific importance, not being interesting, and little social benefit. Only a tiny fraction of respondents thought there were too many patents being held or that they would not be able to patent their work or obtain income from it. The economics of research did not seem to be predominant motivators for either pursuing or not pursuing projects. Only eight percent of respondents thought they needed knowledge or information that was covered by patents.

About seventy-five percent had requested materials from some other person or institution during the previous two years, and nineteen percent said they did not receive the last requested input. This caused some delay in their research, especially when the request involved pure intellectual property. Dr. Korn explained that about forty percent of such transfers require a material transfer agreement (MTA), a legal document that describes the terms under which the recipient may use the research tool. MTAs usually restrict dissemination.

Dr. Korn stated that the NIH has been very concerned about MTAs for years. In 1999, a report to NIH pointed out that this kind of restriction was very threatening to research. The report proposed a simplified one-page agreement for material transfers and urged NIH to enforce it. Although NIH urged grantees to use this agreement, the agency did not enforce it. Dr. Korn said problems have arisen because of the "reach-through rights", which requires the recipient to share a portion of the returns of any commercialized project with the patent holder. Multiple MTA projects, each with its own research rights, can result in most or all of the benefits going to others. Royalties and manuscript review are other frequently terms of MTAs. Dr. Korn said that when scientists do not provide requested materials it is usually because of scientific competition.

The NAS committee concluded that access to patents or information inputs into biomedical research rarely impose a significant burden for academic researchers. However, the committee agreed that the patent landscape could become much more complex and burdensome in the future. Their reasons for concern about the future included the following:

1. A lack of substantial evidence for a patent thicket or a patent blocking problem is clearly linked to a general lack of awareness or concern among academics about existing patents. This could change

dramatically, however, if institutions, aware that they have no protection from legal liability, become more concerned about their potential patent infringement liability and take more active steps to raise researchers' awareness or even to try to regulate their behavior. Patent holders, equally aware that universities are not shielded from liability by a research exception, could take more active steps to assert their intellectual property rights.

2. As scientists increasingly use high-throughput tools to study the properties of many genes/proteins simultaneously, the burden on the investigator to obtain intellectual property rights to these genes/proteins could become insupportable, depending on how broad the scope of claims is and how patent holders respond to potential infringers. The large number of issued and pending patents relating to gene-expression profiling and protein-protein interactions contributes to this concern.

3. Survey data revealed substantial evidence of another, potentially remediable burden on private and public research stemming from difficulties in accessing proprietary research materials, whether patented or unpatented. Impediments to the exchange of biomedical research materials remain prevalent and may be increasing.

Dr. Korn stated that after almost a year of difficult deliberations, the NAS committee agreed on the following recommendations:

Recommendation 1: NIH should continue to encourage free exchange of materials and data. NIH should monitor the data and material sharing actions of grantees and contractors and, if necessary, require grantees and contractors to comply with their approved intellectual property and data sharing plans.

Recommendation 2: NIH should adapt and extend the "Bermuda Rules" (which were the basic operating agreement for the human genome sequencing project) to structural biology data generated by NIH-funded centers for large-scale structural genomics efforts, making data promptly and freely available via the protein database (PDB) at Rutgers University.

Recommendation 3: The PDB should work with USPTO, the European Patent Office, and the Japanese Patent Office to establish mechanisms for the efficient transfer of structural biology data in published patent applications and issued patents to the PDB for the benefit of the larger scientific community. To the extent feasible within commercial constraints, all researchers, including those in the private sector, should be encouraged to submit their sequence data to GenBank, the DNA Databank of Japan, or the European Molecular Biology Laboratory and to submit their protein structure data to the PDB.

Recommendation 4: The committee endorses NIH's *Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources and Best Practices for the Licensing of Genomic Inventions*. Through its *Guide for Grants and Contracts*, NIH should require that recipients of all research grant and career development award mechanisms, cooperative agreements, contracts, institutional and individual National Research Service Awards, as well as NIH intramural research studies, adhere to and comply with these guidance documents. Other funding organizations (such as other Federal agencies, nonprofits, and for-profit sponsors) should adopt similar guidelines.

Recommendation 5: Universities should adopt the emerging practice of retaining in their license agreements the authority to disseminate their research materials to other research institutions and to

permit those institutions to use patented technology in their nonprofit activities.

Recommendation 6: In cases in which agreements are needed for the exchange of research materials and/or data among nonprofit institutions, researchers and their institutions should recognize restrictions and aim to simplify and standardize the exchange process. Agreements such as the Simple Letter Agreement for the Transfer of Materials or the Uniform Biological Material Transfer Agreement (UBMTA) can facilitate streamlined exchanges. In addition, NIH should adapt the UBMTA to create a similar standardized agreement for the exchange of data. Industry is encouraged to adopt similar exchange practices.

Recommendation 7: USPTO should create a regular, formal mechanism, such as the formation of a chartered advisory committee or a regularly scheduled forum, comprising leading scientists in relevant emerging fields, to inform examiners about new developments and research directions in their field; NIH and other relevant Federal research agencies should assist USPTO in identifying experts to participate in these consultations.

Recommendation 8: In determining non-obviousness in the context of genomic and proteomic inventions, USPTO and the courts should avoid rules of non-obviousness that base allowances on the absence of structurally similar molecules, and instead should evaluate obviousness by considering whether the prior art indicates that a scientist of ordinary skill would have been motivated to make the invention with a reasonable expectation of success at the time the invention was made.

Recommendation 9: Principal investigators and their institutions contemplating intellectual property protection should be familiar with the USPTO utility guidelines and should avoid seeking patents on hypothetical proteins, random single nucleotide polymorphisms and haplotypes, and proteins that have only research, as opposed to a therapeutic, diagnostic or preventive, functions.

Recommendation 10: Congress should consider exempting research "on" inventions from patent infringement liability. The exemption should state that making or using a patented invention should not be considered infringement if done to discern or discover: a) the validity of the patent and scope of afforded protection; b) the features, properties or inherent characteristics or advantages of the invention; c) novel methods of making or using the patented invention; or d) novel alternatives, improvements or substitutes.

Recommendation 11: NIH should undertake a study of potential university, government and industry arrangements for the pooling and cross-licensing of genomic and proteomic patents as well as research tools.

Recommendation 12: Courts should continue to decline to enjoin patent infringement in those extraordinary situations in which the restricted availability of genomic or proteomic inventions threatens the public health or sound medical practice. Recognition that there is no absolute right to injunctive relief is consistent with U.S. law and with the Agreement in Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement).

Recommendation 13: Owners of patents that control access to genomic- or proteomic-based diagnostic tests should establish procedures that provide for independent verification of test results. Congress should consider whether it is in the interest of the public's health to create an exemption to patent

infringement liability to deal with situations in which patent owners decline to allow independent verification of their tests.

Questions and Answers

Dr. Licinio asked whether biotechnology companies or rich universities are at a greater disadvantage because of patent restrictions. Dr. Korn stated that large research universities often have thousands of faculty members, each pursuing his or her own research. This, combined with the spontaneity needed for basic research, makes it difficult for universities and academic researchers to plan ahead for the patent clearance process. A company, however, has a centrally managed research plan, and they know up front whether they will need to check on patents. These companies have sufficient time and a team of lawyers to facilitate the process. He stated that those who invent and market research tools are entitled to make money from them, but there must be an appropriate mechanism for doing so. In the past, NIH has negotiated license agreements with the makers of important research tools on behalf of the agency and its awardees.

Ms. Masny asked whether any actions on the recommendations are anticipated. Dr. Collins said that the report came back primarily to NIH as a key sponsor of the initiative and that Dr. Elias Zerhouni, NIH Director, formed a committee to review all thirteen of the recommendations. The NIH committee is in the process of developing a report, but Dr. Collins was not sure when the review would be complete.

Perspectives of the Task Force on the NAS Report and Proposed Recommendations
Debra Leonard, M.D., Ph.D.
Chair, SACGHS Patents and Access Task Force

Dr. Leonard explained that the Patents and Access Task Force was charged with reviewing the NAS report and assessing whether the questions raised by SACGHS had been sufficiently addressed by the report or warranted further exploration. She said that the gene patenting and licensing issue also was raised by the Secretary's Advisory Committee on Genetic Tests (SACGT). SACGT sent a letter to the Secretary recommending that HHS should assess the issue more fully. HHS agreed and tasked the NHGRI ELSI program with gathering data on the effects of DNA-based patents on access to and the cost and quality of genetic tests.

Dr. Leonard stated that the Task Force was generally supportive of the first 12 NAS recommendations, which address research issues and focus on ensuring that the public investment in genomics and proteomics is optimally benefiting society. However, the Task Force felt Recommendation 13 was untenable as written, because it is unrealistic to expect other laboratories to undertake the hardship, expense and work of validating a CLIA-certified test conducted by a sole provider.

The Task Force also felt that the NAS committee had thoroughly investigated the research and innovation issues, but that clinical practice and economic impact issues were not adequately addressed by the recommendations.

Based on this initial analysis, the Task Force recommended that SACGHS write a letter to the Secretary supporting the first 12 NAS recommendations, emphasizing those over which the Secretary has authority to have some effect (i.e., Recommendations 1, 2, 3, 4 and 11, with Recommendation 4 emphasized). In addition, SACGHS should urge the Secretary to educate researchers and clinicians on their rights and

responsibilities with regard to intellectual property, especially on the lack of a true research exemption for the use of patented information and materials.

Dr. Leonard stated that the second part of the charge to the Task Force was to determine whether there are areas that warrant further attention by SACGHS. The Task Force made three official recommendations on issues that SACGHS may wish to explore further: 1) licensing of genomic inventions and its impact on clinical practice; 2) the economic impact of patenting and licensing of genomic inventions; and 3) patent thicket (patent pooling) and related legislation.

Some areas of clinical impact on clinical practice identified in the NAS report overlap with the concerns previously raised by SACGHS. These include patient access to genetic and genomic technologies; competitive improvement of tests; IRB-approved clinical research in academic medical centers regardless of funding sources; professional education and training; independent validation of test results; and regulatory compliance.

Dr. Leonard summarized the goals for the Committee's discussion. First, the Committee was to reach consensus on whether to forward a letter to the Secretary supporting the first 12 recommendations, highlighting Recommendation 4, and encouraging educational efforts for researchers and clinicians on intellectual property issues. Second, the Committee was to determine whether SACGHS's research questions were sufficiently addressed by the NAS report. Given that the report does not address SACGHS's concerns related to clinical practice and economic impacts, Dr. Leonard suggested that this issue be addressed by SACGHS, noting that the Task Force had developed proposed steps to move forward on the issue if the full Committee decided to take action. Possible next steps included:

- Hearing from the NIH intellectual property (IP) working group established to address the NAS recommendations;
- Reviewing NHGRI ELSI program's research findings on the effects of DNA-based patents on access to and the cost and quality of genetic tests;
- Exploring the areas of clinical practice identified by the NAS report through a panel discussion with those who reported to NAS;
- Exploring the experiences and patent policies of other countries (e.g., Canada, European Union); and
- Monitoring the outcome of the Supreme Court patent case involving LabCorp and Metabolite Laboratories.

Full Committee Discussion

Dr. Collins provided an update on GAIN's IP policy. GAIN was described as a new public/private partnership that would provide resources to enable whole genome association studies of common diseases. Investigators with 1,000 cases and controls of a common disorder were being invited to file applications by May 9, 2006 indicating their desire to participate in this genotyping. Once genotypes are determined, all of the de-identified data, genotypes, and phenotypes will be entered in a database constructed by the National Center for Biotechnology Information, and accessible to anyone who signs a user certification agreement. Dr. Collins said there was an obvious concern about handling the IP rights. He reported that the strong sense in both academia and the private sector was for the data to be considered pre-competitive and not the subject of IP claims, although follow-on discoveries might have appropriate IP value. The GAIN IP policy document uses strong language to communicate these

expectations for users of the database.

In response to a question, Dr. Collins said there is not much that can be done about existing patents on genes already in this system, but hoped that the general philosophy might influence the USPTO in the future. Dr. Winn-Deen asked Dr. Collins what he thought should be the threshold for determining when a discovery would be considered patentable. Dr. Collins said that NIH has been attempting to make the case that public benefit should be the standard for determining whether something should be patented. He said NIH's philosophy is that the IP is in the platform, not necessarily in the discovery of the association. He stated that multiplex analysis of genetic variants will not be feasible if researchers are tangled in a thicket of patents owned by multiple individuals and the cost of dealing with this patent thicket is high.

The Committee agreed with the Task Force's conclusion that the clinical and economic access issues were not fully addressed. The Committee discussed whether to move from monitoring these issues to actively working on them. The Committee discussed at length whether to look at the impact of patents on access and cost. Dr. Korn recommended not attempting to change patent law because of the tremendous difficulties that would be involved in working with Congress. Rather, he suggested focusing on licensing practices and exploring an amendment to the statute that allows physicians and surgeons to practice medicine without fear of infringement. He gave the example that although a surgical incision can be patented, a surgeon cannot be prevented from using that incision in violation of a patent. He said this protection applies to physicians but explicitly excludes laboratory diagnostics and biotechnology patents. Dr. Leonard remarked that wording of the bill suggested by Dr. Korn was already available in a bill previously introduced by Representative Lynn Rivers.

The Committee agreed that they would have time to address new issues because other SACGHS projects were coming to a conclusion. Ms. Berry asked whether SACGHS was the appropriate group to assess and review the data on access and make an evaluation of the potential effect of this issue on clinical practice. She thought the Committee should examine whether another body was better suited to this work.

Dr. Tuckson summarized the discussion by suggesting that Dr. Leonard and the Task Force revisit the recommendations they presented and come back to the Committee in June with a plan for moving forward. Dr. Leonard pointed out that many of the members currently on SACGHS were not part of the original priority-setting process and may not have extensive knowledge of gene patent issues. She suggested that an informational session, arranged by the Task Force, be held at the June meeting. Dr. Tuckson agreed and said time would be allocated for this session on the next agenda.

Planning for June 2006 SACGHS Meeting and Concluding Remarks

Dr. Tuckson led the discussion of next steps and priorities for SACGHS. Regarding DTC marketing, the Committee decided that they would like to receive an update on the issue from FDA, FTC and possibly CDC in June. On the issue of oversight, the Committee agreed to ask CMS to provide an update on the status of the genetic testing specialty section of the CLIA regulations at the next SACGHS meeting. Dr. Tuckson asked if, in preparation for that presentation, staff could develop a chart that indicates where the authority lies for oversight of genetic tests. Dr. Sherrie Hans suggested that a timeline of CLIA's actions to date be developed. Dr. Tuckson agreed and also asked staff to identify FDA's plans in this area and remaining gaps.

Ms. Carr summarized the decisions of the Committee. Regarding the large population studies report, she

said that as a result of a discussion with the Large Population Studies Task Force during lunch, it was agreed that the timetable be revised slightly. Staff planned to revise the report in April to reflect the deliberations of the Committee and would put out a solicitation for comments through various mechanisms, including the Federal Register, SACGHS listserv, SACGHS website, and a targeted effort to reach the scientific community, general public and patient communities. Ms. Carr said they were waiting for clarification from Dr. Zerhouni on whether the Committee should write a letter to the Secretary prior to the next meeting or immediately after it providing an update on the status of the draft report, solicitation of public comments, policy issues identified, and importance of seeking broad scientific and public input.

Ms. Carr said the Pgx Task Force would further develop its recommendations and, with the assistance of ASPE and The Lewin Group, prepare a draft report for the Committee's consideration in June. Once the Committee accepts the draft report, it will go out for public comment.

Concerning genetic discrimination, the Committee had agreed to write a letter to the Secretary urging him to request a meeting with the Coalition for Genetic Fairness, Chamber of Commerce, and NAM to discuss unresolved concerns about the pending Federal legislation to prohibit genetic discrimination in employment and health insurance. The letter to the Secretary also would express SACGHS's concerns about the effects of fear of genetic discrimination on research, which is especially important given new research projects related to genes and the environment and potential for a large population study. In addition, it would ask the Secretary to send the compendium of public comments and the DVD to the House committee chairs. Ms. Carr said that in preparation for this letter, the Task Force would meet with the Coalition, the Chamber, and NAM.

Reporting on the Committee's decisions on patents, Ms. Carr stated that the Patents and Access Task Force would organize an informational session to be held at the June meeting.

Dr. Tuckson asked Lyla Hernandez to speak briefly on an Institute of Medicine (IOM) Roundtable on Translating Genomics-based Research for Health. Ms. Hernandez stated that the roundtable will be chaired by Wylie Burke and composed of representatives of public and private entities such as NIH, FDA, pharmaceutical companies, and genetic technology companies. Some of the planned topics for discussion include clinical utility, validation of clinical tests, provider education, workforce issues, and ELSI issues. The group was working closely with staff to make sure there was no duplication of effort with the Committee's work.

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