Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Eighth Meeting
October 19-20, 2005
Bethesda, Maryland

Committee Members Present

Cynthia Berry, J.D., Acting Chair
Sylvia Mann Au, M.S., CGC
Chira Chen
James P. Evans, M.D. Ph.D.
Kevin Fitzgerald, S.J., Ph.D., Ph.D.
Debra G.B. Leonard, M.D., Ph.D.
Julio Lucinio, M.D. (appointment pending)
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**

Francis D. Chesley, Jr., M.D. (HHS/Agency for Healthcare Research and Quality)
Gurvaneet Randhawa, M.D., M.P.H. (HHS/Agency for Healthcare Research and Quality)
Muin Khoury, M.D., Ph.D. (HHS/Centers for Disease Control and Prevention)
James Rollins, M.D. (HHS/Centers for Medicare & Medicaid Services)
Steven Gutman, M.D., M.B.A. (HHS/Food and Drug Administration)
Joseph Hackett, Ph.D. (HHS/Food and Drug Administration)
Sam Shekar, M.D., M.P.H. (HHS/Health Resources and Services Administration)
Suzanne Feetham, Ph.D., R.N., FAAN (HHS/Health Resources and Services Administration)
Francis S. Collins, M.D., Ph.D. (HHS/National Institutes of Health)
Alan E. Guttmacher, M.D. (HHS/National Institutes of Health)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Sheila Foran (HHS/Office for Civil Rights)
Michael Carome, M.D., (HHS/Office for Human Research Protections)
Steven Kaminsky, Ph.D. (Department of Defense)
Daniel Drell, Ph.D. (Department of Energy)
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

Wednesday, October 19, 2005

Welcome and Opening Remarks

Cynthia Berry, J.D.
Acting SACGHS Chair

Ms. Cynthia Berry served as Acting Chair in the absence of Dr. Reed Tuckson. Ms. Berry welcomed members and the public to the eighth meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). She noted that the public was made aware of the Committee's meeting through notices in the *Federal Register* and through announcements on the SACGHS website and listserv.

Large Population Studies Session

Session Overview and Report from the SACGHS Task Force on Large Population Studies
Huntington F. Willard, Ph.D.
Chair, SACGHS Task Force on Large Population Studies

Dr. Huntington Willard provided information on the activities of the Large Population Studies Task Force and updated the Committee on its progress since the last meeting.

The Committee's exploration of large population studies is one approach to learning more about the relationship among genes, environment, and common disease. The goals of these studies are to determine the mechanisms underlying common and complex disease, inform treatment and prevention strategies, and improve health.

In March 2005, the Committee heard a full day of presentations on the nature of large population studies and existing projects within and outside of the U.S. In June 2005, the Committee discussed a variety of relevant scientific, ethical, legal, and social issues. The Committee also decided to develop a report to the Secretary on the potential for a large population study in this country. The report would address broad policy and process issues but not the scientific issues that underlie a large population study. Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), endorsed this strategy.

Major action items for the Task Force arising from the June 2005 SACGHS meeting were to review the NIH work group report, *Design Considerations for a Potential United States Population-Based Cohort to Determine the Relationships Among Genes, Environment, and Health: Recommendations of an Expert Panel*, and to organize a session to gather input on large population studies from the scientific and ethics communities and the public at large. Upon further discussion after the June meeting, the Task Force decided it was not in their purview to seek in-depth public comment on the issue. Rather, they decided instead to provide the Secretary with advice on best practices in the area of public engagement.

In briefing the Committee on the NIH work group report, Dr. Willard explained that an NIH work group was established to examine scientific foundations and logistical concerns related to a hypothetical U.S. large population study. The work group report was assembled largely through the efforts of the National Human Genome Research Institute (NHGRI) with representation from a variety of experts in fields such

as genetics, genomics, epidemiology, and medicine.

The report stated that the goals of such a study would be to ascertain and quantify all of the major environmental and genetic causes of common illnesses in this country and to set the stage for a future of better preventive medicine and more effective therapy. The report indicated that approximately 500,000 and 1,000,000 participants would be needed for this prospective study. Participants ideally would be sampled from a number of different census tracts and would be recruited door-to-door over a 4-year period. The report stated that it would be necessary to oversample individuals from underrepresented minority groups to provide a level of power sufficient to detect significant trends in minority populations.

Data collection at entry would include a wide breadth of phenotypes and environmental factors to predict outcomes. The largest scientific issue would be deciding on the specific list of factors. These decisions would be balanced against the expected cost of the project and the potential burden on individual participants. The conclusion of the NIH work group was that a core group of baseline variables should be collected for all or nearly all of the participants. Disease outcomes over the course of the study would be assessed using inpatient and outpatient records and data sources such as Medicare claims.

The Task Force strongly emphasized the importance of several policy issues described in the NIH report, particularly public engagement. The Task Force felt that the success of a large population study would require a well-informed and fully supportive public. Another policy issue of note is the complexity of assembling a representative cohort in a society that is extremely heterogeneous. From a process standpoint, it also would be important to explore possible collaborations with ongoing U.S. and international projects. Protection of data always is a major research issue, but would be particularly complex for this large-scale study. Decisions on a policy for notifying participants of their results and providing genetic or genomic counseling also would require extensive thought. Other issues of concern included intellectual property, confidentiality and privacy, and informed consent. The Task Force asked what steps would be necessary to create a central Institutional Review Board (IRB) to manage the project. They highlighted the importance of electronic medical records for such a study, and noted that efforts to establish electronic medical records have been uneven in different parts of the country. Electronic capabilities would need to be improved significantly for optimal use of information obtained over a period of decades from as many as 1 million enrollees. Based on its analysis, the Task Force identified four categories of issues for SACGHS to consider:

Broad Social Issues. Are there data to support the inherent value of a large population study? Is a large cohort study the best way to obtain information about genetic and environmental influences on common disease? Given the nature of existing cohort studies already underway within the Department of Health and Human Services (HHS), are there other ways to approach this issue? How much would such a study cost and how does one balance this cost with other priorities within HHS or the biomedical research community? What tradeoffs would be necessary in terms of resource allocation? Would the benefits of such a study be distributed evenly to all groups in society? Would the study increase or decrease the stigmatization of individuals belonging to subgroups of the population on the basis of their genomes?

Engagement. How can public trust of science, specifically genetics, and of the Government be increased? How should preparation for such a study engage the public? How can input from the broader scientific community be gathered? Although the NIH work group engaged a significant number of individuals who contributed to the report, a much broader section of the scientific community must be

heard from.

Access and Health Care System Issues. Would the study reduce or exacerbate health care disparities? Would the results benefit people with limited access to care? How would such a project deal with the ethical dilemma created by diagnosing conditions that cannot be treated? What would be the cost burden to study participants? How would the cost burden affect access to study participation across different strata of the population? How should minority communities and the uninsured be reached?

Research Issues. How would a new large population study leverage the existing HHS cohorts that are already underway and are, at least in part, addressing many of the same questions? How would collected samples be secured, stored, and disposed of? To what extent would information be shared with family members and what processes would be in place to address that issue? What steps must be taken to ethically achieve a cohort of between 500,000 and 1,000,000 participants? What guidelines can be developed to govern the application of the research findings and anticipated technology developments? Special attention must be paid to avoiding discrimination and stigmatization as research findings come to light over time. What does the term "environment" encompass in this context, and how should environmental, socioeconomic, and behavioral variables be measured? How can protocols for recruitment, enrollment, and withdrawal be kept free of incentives that are coercive?

Dr. Willard noted the goal of the day's session was to obtain input on key policy and process issues from both the scientific and bioethics communities. Experts in the nature of public engagement also would speak on the variety of mechanisms that exist to engage the public. The information presented would help the Committee prepare a report for the Secretary.

Policy Perspectives: Scientific Community
Gerald R. Fink, Ph.D.
Professor of Genetics, Massachusetts Institute of Technology

Dr. Gerald Fink stated that he was responsible for managing a portion of the Human Genome Project, which was met with great skepticism on the part of the scientific media and the public at its inception. Dr. Fink described the early history of the Human Genome Project to demonstrate how this large science project eventually gained support and achieved success. He emphasized the importance of defined benchmarks, endpoints, and costs. The scientific community gained trust in the project as the benchmarks were met, the endpoints were reached, and when the actual costs were less than expected. As each tier was completed, basic scientists became the strongest supporters of the project because it added value to their endeavors.

Dr. Fink addressed areas in which skepticism about a large population study might be expected. For instance, a large population study would have to address policy issues concerning the kind of data obtained and how to maximize the identification of key genes involved in a multigenic disease. He recommended building on the experience of the Human Genome Project, stating that a pilot study would be equivalent to the early benchmarks used by the Human Genome Project. Choosing a heritable multigenic disease with defined benchmarks and endpoints and predictable costs would increase confidence that the researchers would obtain statistically significant data.

Dr. Fink posed several hypothetical questions: What would the Government do with information indicating that particular variant genes increase the risk of disease by several percent? Would the

Government collaborate with pharmaceutical companies? Would this effort take away from investigator-initiated research?

He expressed the opinion that a large population study would initially be viewed with some alarm because of the scientific issues involved and the risk to funding, just as the Human Genome Project had been. He said the community would be much more supportive if there were proof of principle. He also recommended a crisp definition of the question and said the current goal of the study as "an understanding of the relationships of genes, health, and common complex diseases" is too general for the scientific community. He believes that a large population study to identify risk factors for a specific disease would foster more trust. He also asked if NIH is the appropriate organization to host the study and said others have suggested the Centers for Disease Control and Prevention (CDC) or pharmaceutical companies. Dr. Fink closed by suggesting that a successful pilot study could reduce some of the ethical concerns with such a study.

Questions and Answers

Dr. Julio Lucinio asked whether there is hope of finding the information they are seeking on human disease. Dr. Fink replied affirmatively, but cautioned that the techniques used must be constantly refined and that statistical significance is essential. If there are large numbers of genes involved in a trait, each gene will have such a small effect that it will bring the value of the study into question. However, if small numbers of genes affect a trait, researchers will more easily be able to extract the data.

Dr. Emily Winn-Deen asked if it is necessary to initiate new pilot studies or whether a retrospective analysis of studies such as the Framingham Heart Study and the Women's Health Initiative would be sufficient. Dr. Fink acknowledged that he is not familiar with all the studies taking place, but stated that the Human Genome Project added a new dimension to research and some of the ongoing studies have not collected information in a way that would allow statistically significant differences to be detected. Many studies like these have been criticized because either the material or the family histories were not adequate.

Dr. Robinsue Frohboese asked Dr. Fink to share his insights on the ethical issues related to race, gender, and age. Dr. Fink said he is somewhat naive about ethical issues, but said that the media and the public can interpret many aspects of a study in unanticipated ways.

Dr. Francis Collins addressed Dr. Fink's proposal for a pilot project and discussed study design. He stated that the case/control study design, which is the type of pilot he believed Dr. Fink was suggesting, is now common, particularly with the HapMap making it possible to conduct whole-genome association studies. He said there are many pilot projects on case/control studies with good evidence of success. However, he said the population cohort study is not designed to discover variants that are involved in quantitative traits for diseases. Rather, it is designed to quantify exactly what variants contribute to risk. He stated that case/control studies are somewhat biased in that regard, especially when assessing gene/environment interactions, because often there is recall bias. He added that a U.S. population cohort study would take at least 1 to 2 years of planning and said sufficient pilot data would be in hand long before enrollment.

Dr. Muin Khoury asked Dr. Fink for suggestions on benchmarks or parameters of early success in a large population study. He noted that public health agencies collect data through birth defect surveillance

systems, cancer surveillance systems, and population surveys such as the National Health and Nutrition Examination Survey, but they are open-ended, i.e., they are not trying to test a scientific hypothesis. Dr. Fink said that spina bifida would be a good example if it turned out that there are people in the population who are particularly deficient in folic acid and could be helped by the study.

Policy Perspectives: Scientific Community
Sharon Kardia, Ph.D.
Associate Professor of Epidemiology, University of Michigan School of Public Health
Co-Director, Michigan Center for Genomics and Public Health

Dr. Kardia stated that a large population study of genetic and environmental factors has both advantages and disadvantages, and believes the disadvantages currently outweigh the advantages. She noted that a number of critical social and regulatory policy issues make the project premature. In her opinion, participating in such a study could be a liability for the public due to the lack of a Federal genetic anti-discrimination law. It would involve hundreds of investigators and clinicians, which could cause the public to question whether privacy and confidentiality can be maintained. She said there is already substantial fear concerning the actions of researchers, doctors, insurance companies, employers, and Government agencies who have access to biobank data and genetic information. She stated that many in public health practice are concerned that genetics research will increase health disparities and reduce access to care. There also are serious concerns about policies addressing the duty to warn research subjects and their families.

Dr. Kardia cited the current lack of genetic literacy among the public and health professionals, which make true informed consent problematic for this type of research. She said health education and health behavior research has demonstrated that the public struggles with genetic risk communication and genetic concepts. They often do not retain genetic concepts after a session and they misinterpret information. Many do not know where their genes are located or why a genetic test might be predictive. This basic lack of public understanding would present a major barrier to meaningful communication. Dr. Kardia stated that this lack of knowledge also is found among professionals, including policymakers. Since most genetics research is focused on identifying single causative factors and has not matured to complex models of genetic causation, scientists promote a naive biological, deterministic interpretation of complex disorders. This leads to further misinterpretation and misuse of genetic explanations in public policy, courts, health and life insurance policies, and medical practices.

Dr. Kardia does not believe there is an adequate infrastructure or scientific culture in which a large population study could be responsibly carried out. She stated that the genetic science of common complex diseases is not mature enough. Scientists do not understand why the real roots of the significant genetic factors in one study are not being replicated in another. She noted that this is especially relevant for a large population study, because some would use the power of the sample size to make definitive findings and statements. Yet these findings would represent only an overall result for the population and would not reflect the local heterogeneity of genetic/environmental factors, where actual clinical utility matters most.

Dr. Kardia stated that most geneticists are not sufficiently well versed in the social, behavioral, and environmental causes of disease. True interdisciplinary research that integrates knowledge from the influence of the genome to the influence of human ecology is just beginning. Geneticists and social behaviorists are currently pitted against one another at funding tables and in institutions. Representatives

of these fields are starting to learn each other's methodologies. Dr. Kardia stated that geneticists are appropriately criticized for simplistic genocentric analyses, a lack of key social-behavioral measurements, a lack of replicable results, and a lack of clear causative mechanisms. She said it is very difficult to move from a statistical genetic association to an understanding of the mechanism of action that would suggest new therapies and prevention and that would withstand evidence-based regulatory decision making. Genetic findings in complex disorders, especially gene/environment interactions, would therefore not help regulatory bodies create policies that protect people. Dr. Kardia stated that although there has been some progress in the field of gene/environment interactions, the results have revealed the immense complexity involved in integrating this type of knowledge into existing policy standards and methods.

Traditionally, public health policy has focused on population-level solutions. In contrast, genetic information is individually based, family-based, and ethnic group-based. Genetics will require intense research on the implications of specialized policies and regulations before vulnerable populations can be adequately protected. Dr. Kardia asked how regulatory agencies such as the Evironmental Protection Agency (EPA) and the Food and Drug Administration (FDA) would set standards and guidelines for businesses and products based on complex susceptible genetic subgroups. For every disease, there is likely to be a different combination of genetic factors involved. She stated that defining a vulnerable subgroup could be a "nightmare," especially when genetic definitions are overlaid with existing definitions of vulnerable populations. Dr. Kardia believes that the regulatory agencies do not have the resources to tackle this issue and they lack sufficient staff who understand genetics and genomics, although she said this is changing.

She noted that genetic testing companies can market directly to consumers and doctors without any regulations. These companies are not required to disclose the real utility or makeup of their products. Direct-to-the-public testing kits are freely available, even though there is not enough evidence to warrant their use.

Another factor affecting the timing for the study is that publicity surrounding the Human Genome Project has moved genetics into the public eye but the research findings tend to be overstated. This has led to a pattern of attributing simple genetic solutions to complex problems.

Dr. Kardia stated her belief that broader consultation with the scientific community to inform a decision about a U.S. population study would lead to a biased sample of very outspoken antagonists from the social epidemiology field who are worried about the geneticization of disease and the excessive use of resources by geneticists. She also believes it would lead to outspoken proponents who are primarily interested in accessing the project's funding.

She also noted that there is significant awareness by scientists of the potential for a U.S. large population study. However, many genetic epidemiologists she has talked to believe the mega-science model would fund only a few insiders, leaving little funding for the rest of the scientific community. There is fear that the model would not build on the years of experience of genetic epidemiologists who have already accrued data from numerous cohort studies. Their experience leads them to believe that the 500,000 or 1 million person cohort is unrealistically large and too broad to ensure quality. She said it takes tremendous effort to agree on what to measure, how to measure it, and how to package the results. She stated that science is not value-free and neutral. Scientists have a long way to go in terms of learning to collaborate and use existing resources. They are often competitive and have very strong, conflicting

opinions.

Dr. Kardia stated that although she believes such a project is too ambitious at the current time, the infrastructure might be in place within 5 to 10 years. She said many intermediate steps could be taken along the way, such as encouraging genetics researchers to work together to mine existing cohorts. Genetic researchers also can begin to learn how to work with social and behavioral epidemiologists and researchers. Dr. Kardia noted that genetics researchers have not typically utilized cancer registries, early death registries, and environmental health registries which contain data on key environmental factors that influence the public's health.

Dr. Kardia summarized by stating that given the right social and policy investments, she would be greatly enthusiastic about the project in the future.

Questions and Answers

Dr. Kevin FitzGerald asked Dr. Kardia whether her comments on a U.S. study would also apply to other countries conducting large population studies. Dr. Kardia replied that the situation is different in each country based on regulatory decisions and current standards.

Dr. Joseph Telfair asked for specifics on Dr. Kardia's education efforts. She said she starts with basic concepts, such as what genetics means in the family and the fact that there is a genome in every cell. She said health professionals are on the opposite end of the spectrum and want to know how they can use genetic information in their current practices. She said there is no connection in the middle, where doctors and patients can talk about genetics using a common language.

Dr. Collins challenged the idea that the project should wait 5 years because he felt that some of the current barriers are unlikely to improve without an impetus. He stated that regulatory systems rarely change unless they perceive a need. A public project with great visibility would serve as an impetus for action. He suggested that the project would provide an opportunity to educate the public, the media, public policymakers, and the scientific community. He said it would bring together the communities that are now unable to work together, just as the Human Genome Project did for those involved. Dr. Collins said that since the data would be publicly accessible, it would provide a stimulus for research and would not deprive researchers of funding. Dr. Kardia said her opinion was based on her experiences with researchers who are not able to work together because of disciplinary disconnects and turf wars. Concerning the regulatory agencies, she said there are no plans to use resources for the infrastructure needed.

Policy Perspectives: Scientific Community
Richard B. Marchase, Ph.D.
Vice President for Science Policy, FASEB

Dr. Marchase stated that the Federation of American Societies for Experimental Biology (FASEB) is a coalition of 23 member societies representing over 70,000 scientists in diverse areas of life science and medical research. In preparation for this talk, he said that discussions were held with FASEB's Clinical Research Subcommittee, the NIH Issues Subcommittee, and member societies, including the American Society of Human Genetics.

Dr. Marchase said that FASEB recognizes the potential of a large population study to improve health. However, he cited three key policy issues of concern to the scientific community he represents: 1) the prioritization of this study relative to other large-scale studies; 2) study goals and study design leading to useful data; and 3) the cost and possible effects on research grants, investigator-initiated studies, and other initiatives at NIH.

Concerning the prioritization of this study relative to other large-scale studies, FASEB would like an opportunity to put the large population study into perspective compared with other studies (e.g., the Children's Health Study and recent initiatives to increase NIH's presence in clinical and translational work). Dr. Marchase questioned whether other long-term studies have been mined sufficiently to set the stage for a large population study.

Dr. Marchase stated that more detailed consideration is needed regarding the following questions: How will the data be collected, stored, and made available? How will genetic and other personal information be protected? Does our current health care system have sufficient technology and infrastructure to support data collection and data sharing? Is there a way to restrict or focus the study more?

Dr. Marchase agreed that pilot studies need to be conducted first and emphasized that study outcomes need to be useful to the scientific community. He stated that the skepticism raised by Dr. Fink requires recognition of the project by the broader scientific community, not just geneticists and those who have biases against geneticists, but the range of scientists that FASEB represents.

The primary problem of concern to FASEB is that the study would be very expensive and is being proposed at a time when NIH funding is not increasing. An important question for their community is what would happen if these research funds were cut to fund a large population study. FASEB is concerned that the allocation of large funds to one project during a flat funding period would be detrimental to biological scientists. FASEB does not want to see the study funded in a manner that hurts the entry of scientists into the research field, while taking a high toll on scientists who are already working.

Dr. Marchase concluded by stating that FASEB recognizes the numerous potential benefits of such a study for public health. However, the fact remains that discretionary spending is very limited.

Questions and Answers

Dr. Khoury commented that in other countries they refer to work with biobanks and cohort studies as a "resource," because collecting information on a large number of people followed over time is not seen as an individual study. Rather, it is considered a resource that will lead to thousands of studies in the future. Dr. Marchase agreed that in the long-term, the large population study would be a very important resource available to the full spectrum of biomedical scientists. His concern was that in the short term, it might jeopardize scientists that are currently working. Dr. Marchase acknowledged that the estimated $350 billion for the study would remain within the science community, but was concerned that it would cause a shift in funding away from those who are non-geneticists. This could disenfranchise investigators from other disciplines.

Dr. Collins stated that NIH is deeply concerned about the R01 funding trends that support investigators. He agreed that losing 1,000 new grants to fund the project is not tenable. He stated, however, that there is

an opportunity for the biomedical research community to identify one or two compelling flagship initiatives that will benefit public health and that could generate enthusiasm and energy. He discouraged the impression that the project would use existing funds.
Dr. Debra Leonard commented that Dr. Kardia and Dr. Marchase seemed to be articulating a wish to hold onto the academic system as it currently exists. She said the NIH Roadmap Initiative, which values large collaborative efforts, is sparking a change to the academic system. She asked if the academic system should be re-evaluated. Dr. Marchase said he appreciates NIH's current direction, and recognizes that things are changing and that big science will become important in moving scientists forward. However, FASEB wants to ensure that the thinking of individual scientists is not disregarded while moving in the direction of big science. Dr. Kardia agreed that academia needs to change to an interdisciplinary approach, but asked where the funding is to accomplish that goal.

Dr. Steve Kaminsky asked Dr. Marchase if the clinical group articulated whether they thought the study would be better as a trans-NIH effort or should be placed in one Institute or Center, as the Human Genome Project was. Dr. Marchase said that issue was not addressed.

Dr. Sam Shekar cautioned Dr. Kardia about letting the perfect be the enemy of the good. He was concerned that she was making the assumption that there must be perfect societal and infrastructure development prior to this study. He asked Dr. Kardia what activities she recommends over the next 5 years to achieve the necessary level of support. Dr. Kardia explained that she is not a proponent of perfection, but that $2.4 million is not enough money for infrastructure building. She said genetics policy research also should take place on a large scale.

Dr. Khoury asked Dr. Kardia for her thoughts on a two-pronged approach: building big science while concurrently building infrastructure in smaller locales. Dr. Kardia said it is critical that people who representative of the population being served participate in research so that replication studies can be done to detect any population differences in allele frequencies, genetic factors, and environmental factors. Scientists tend to group unlike people, however. She recommended that researchers focus on big cities in which the largest public health burdens exist and work with local and State departments of health and local clinicians so that they can use the study data. She also said that a broad array of technologies should be used so that research findings can be translated into treatment and prevention options.

Dr. Lucinio expressed concerns about those in the proposed study who will not have health insurance. He does not want to see researchers watch people get sick over time, document their illnesses, and do nothing to help them. He recognized that it is not feasible to give health insurance to all those who are uninsured. However, he said there is a social responsibility and asked how the cost of the project can be justified in these circumstances. On the other hand, he noted that providing health care or health insurance to uninsured individuals enrolling in the study could be seen as being coercive. The ethics of enrolling people without offering adequate health care and the costs of the alternatives should be dealt with by ethicists and health economists before the project begins. He added that different approaches may be needed for young people, veterans, and people over 65. Dr. Collins noted that the obligation of research to provide medical benefits with being coercive is critical but not new. He suggested looking carefully at the large body of literature on the topic.

Dr. Jim Evans commented on the need to look critically at the potential outcomes before investing tremendous resources. He asked whether identifying polymorphisms that contribute 2 or 3 percent of the

genetic component of a disease would be considered a good return on investment. He suggested looking at the outcomes of case/control studies and large cohorts in other countries to see whether the return will be useful.

Dr. Telfair asked how the different points of view about the study could be bridged so that a consensus could be reached on whether to go forward. Dr. Marchase said that if the study can be done without disrupting the ongoing scientific community and without discouraging new investigators from entering the field, it should be initiated. Dr. Kardia suggested that 25 percent of the money allocated should be invested in infrastructure development in the public and in regulatory systems. She was skeptical that the integration of different fields would be sufficient because it takes years to develop the skills to become a quality investigator.

Dr. Khoury asked how investing 25 percent of study funds for public policy, public education, and infrastructure for health departments could be implemented. Dr. Kardia said a strategic plan could identify the greatest needs so that efforts could be prioritized. Dr. Khoury followed up with a question about what needs to be done to translate knowledge gained from the sequencing of the human genome and related technologies to population health. Dr. Kardia said regulatory bodies, health professionals, departments of health, and the public lack an understanding of genetics. Ms. Sylvia Au added that funding is needed for genetics professionals to deal with those in the public who will want services. She said there is no funding for training, which is very expensive. As a result, the field is losing geneticists and genetic counselors, and minority staff to work with minority populations is lacking. In addition, training is needed for genetics staff to work in public health departments. Currently, two-thirds of the States have State genetics coordinators who report having no formal training in genetics. She emphasized that primary care providers do not want to be educated in genetics; rather, they want a resource for their patients to contact to obtain these services.

Dr. Leonard was concerned about the exclusion of institutionalized persons who require long-term mental health or custodial care, which would exclude further study of the genetic underpinnings of mental illness. Dr. Collins said that consent issues were a greater concern but that the issue was open for further examination.

Dr. Willard asked Dr. Collins whether his colleagues at NIH have expressed interest or given positive feedback on the proposed study. Dr. Collins said all of the institute directors know about the project and that he has had numerous conversations with specific institutes that have large investments in this kind of research. He said there is great enthusiasm for such a study and its potential to generate useful knowledge. However, there also have been deep concerns about its cost given the current budget climate, especially if it did not receive new funding.

Public Comments

Kathleen Rand Reed, MAA
The Rand Reed Group

Ms. Kathleen Rand Reed's comments addressed the need for outreach to and genetic education of the 18- to 34-year-old hip-hop, rap and Hispanic urban generation. She also expressed a need for outreach to pre-migration communities, families, and relatives that incorporates transnationality within genetic educational models.

Ms. Reed also addressed the need to investigate the use and abuse of DNA samples contained in law enforcement databases when it identifies a family member and not the convicted offender (In Florida, DNA database operators are permitted to give investigators the names of convicted offenders who match a crime scene sample at 21 of 26 alleles. It has been estimated that two individuals that match on 21 alleles are usually siblings). In addition, a growing number of jurisdictions are collecting genetic information from arrestees, but they are not destroying samples of those who are found innocent. She urged the development of a policy that would require the destruction of physical samples used in DNA testing.

Ms. Reed also encouraged the establishment of a firewall that would protect against the use of health and disease-oriented genetic research data for law enforcement purposes. She said that reunification of Katrina families and children is hindered because there are no laws protecting samples collected for reunification purposes from being used for law enforcement purposes.

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

Dr. Joann Boughman stated that while there is widespread support for the concept of a large cohort study, there are diverse views on how the study should be implemented, what data should be collected, and the extent to which the data will influence treatment or prevention. She said the design of the study would be an immense challenge because the specific aims will be evolving over time. The data gathered must be broad enough so that undefined or currently unrecognized questions could still be answered. ASHG sees several questions and challenges that need to be addressed:

1. Can existing datasets provide some of the information sought by this study? If existing datasets do not have sufficient breadth and depth, are there ways that they can be further mined to reduce study costs?

2. Given the current fractious state of health care in the U.S., can a coherent cohort study be designed, data collected and analyzed, and benefit returned to the participants and others in the U.S. at a reasonable cost? Absent systematic electronic medical records and a realistic vision of uniform health care delivery system, the direct applicability of the results to the broader community must be questioned.

3. A cohort study demands identification of a population that has sufficient breadth and depth to allow analysis of a myriad of relevant questions, measurement and tabulation of numerous biological variables, and the creation of robust assessment and computational tools to define, measure and assess the effects of environmental changes over time. These requirements are far more complex than those associated with the Human Genome Project.

4. The substantial costs of the project must come from sources other than usual funding mechanisms. Otherwise, the effect on usual biomedical research funding could be highly deleterious or devastating.

5. The selection of individuals and populations to be sampled is extremely complex in such a highly heterogeneous society as the U.S. The need for the diversity and the manner in which that diversity is

handled must be carefully considered.

Remarks of the Acting Chair

Cynthia Berry, J.D.
Acting SACGHS Chair

Ms. Berry updated on relevant activities in genetic technologies by the *ex officio* agencies. Among the activities mentioned was the Surgeon General's Family Health Initiative, which was planning a second national event on Thanksgiving Day. Also noted was a recent meeting sponsored by the Agency for Healthcare Research and Quality (AHRQ) with the goal of identifying knowledge gaps and barriers concerning the clinical use of gene-based discoveries, developing strategies for overcoming the barriers, and improving coordination of Federal activities. Participants discussed potential opportunities for collaboration with various AHRQ programs and expressed interest in having methods workshops and conferences to discuss issues involved in linking laboratory and clinical databases.

Dr. Steve Groft, Director of the NIH Office of Rare Diseases, reported on the national conference on access to quality testing for rare diseases that was held in September. Conference participants stressed the need for an awareness campaign about genetic testing and genetic counseling services in the U.S. as well as the continued development of international quality assurance and quality control guidelines for genetic testing. Dr. Groft said another meeting is planned for 2006. In the meantime, the Office of Rare Diseases is hoping to broaden current molecular DNA-based test networks to also include biochemical and cytogenetic test procedures. He also hoped the Collaboration, Education, and Test Translation Program, which will stimulate the development of genetic tests for rare diseases, will be ready for implementation in January 2006.

Dr. Telfair, the SACGHS liaison to the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, provided a summary of its July meeting. Dr. Telfair said the Advisory Committee reviewed the public comments received on the American College of Medical Genetics (ACMG) report on newborn screening. The discussion focused on improving access to services by underserved and vulnerable populations, ensuring services of high quality, and looking closely at issues related to culturally competent care, including health literacy. The Advisory Committee plans to send a letter to Secretary Leavitt conveying the ACMG recommendations in the newborn screening report. The Advisory Committee also were updated on the status of newborn screening in the U.S. and the activities of three subcommittees on education and training, follow-up and treatment, and laboratory standards and procedures.

Dr. Leonard, liaison to the CDC Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, reported on the group's recent meeting. She stated that the Steering Committee has developed a process for selecting the genetic applications to evaluate. The first evidence-based review selected will look at cytochrome P450 testing for patients with depression either prior to or while receiving treatment with selective serotonin reuptake inhibitors. A review center has been selected and has been given a 9-month timeline. The second review will examine HNPCC testing for patients with newly diagnosed colon cancer. A Request for Task Order (RFTO) is scheduled go out shortly and there will be a 13-month time frame for review. Requests for Task Orders (RFTOs) also will be going out to evidence-based review centers asking them to review additional topics selected by the working group. The working group will then make recommendations based on the reviews. In addition to

these reviews, Dr. Leonard said the working group is considering whether and how to do fast-track evaluations when a narrower evidence-based review is desired or when literature is limited. The working group also is analyzing medical benefits, diagnosis/prognosis/treatment options, patient benefits, family benefits, societal benefits, and public health benefits.

Dr. Winn-Deen and Mr. Stuart Hogarth reported on a policy research project in the U.K. on the evaluation of clinical genetic testing for complex conditions. The 3-year project involves talking to stakeholders who have an interest in the evaluation of clinical genetic testing, including Government agencies, health technology assessors, regulators, clinicians, patient groups, and industry. The project team conducted focus groups with a number of U.S. experts to gather perspectives on how genetic tests can be evaluated before entering routine clinical practice and how regulatory and health care systems can ensure the availability of valid clinical information for the interpretation of genetic test results. Among the topics raised by the focus groups were the need for translational research, the lack of support for moving basic research findings into clinical practice, and the need for a more coordinated infrastructure.

Ms. Berry closed the morning session by stating that Suzanne Goodwin gave a presentation on the SACGHS coverage and reimbursement report at the Western States Regional Genetic Summit, which was organized by Ms. Au and colleagues at the Hawaii Department of Health.

Large Population Studies Session (continued)

Exploring Mechanisms for Public Engagement
Joan A. Scott, M.S., CGC
Deputy Director, Genetics and Public Policy Center, Johns Hopkins University

Ms. Joan Scott described the spectrum of public engagement. A consultative approach to public engagement assumes that the public brings valuable experiences and values that will inform an issue. There are many different levels at which the public can be engaged, including surveys, focus groups, workshops, and scenario development. With the deliberative democracy approach, participants are provided with an opportunity to hear from experts with different points of view and then deliberate about the issues. Participants are asked to reach consensus about the best option. A more collaborative approach to public engagement invites the community to participate early in the process with issue identification and prioritizing. They help set the agenda for the engagements and devise outreach strategies. At the farthest end of the spectrum, participants are not only empowered to make a decision, but the decision they arrive at is abided by. In the case of a large population study, engagement may be aimed toward the communities from which participants will be recruited, or may require a more national or regional conversation.

Ms. Scott said one of the criticisms of public engagement is that people are sometimes asked to comment about technologies with which they may have little personal experience. The deliberative approach provides participants with in-depth background information about the topic. Ms. Scott stated that a credible deliberative process requires four things: broad, representative participation; balanced and accurate information; an environment with ample opportunity for deliberation; and involvement of policymakers from the outset.

Ms. Scott described the Public Policy Center's approach to the genetic town hall meetings on reproductive genetic technologies that were held in six cities around the United States during Summer

2004, in concurrence with 15 discussion groups held online. The Center did extensive background work using surveys, focus groups, and interviews prior to the town halls. It also prepared a DVD that provided an overview of reproductive genetic testing and comments from experts conveying different perspectives. The Center strived to ensure that the content was consistent and balanced. Additionally, the Center partnered with the Public Forum Institute. It recruited town hall participants through local coordinators with contacts in the communities. They used a variety of outreach strategies, including notices in libraries, hospitals, clinics, grocery stores, and community centers and targeting community organizations and leaders. The center used the media by placing editorials and advertisements in newspapers, working with local reporters, and talking on local radio shows. They asked people to register so they could monitor recruitment. The town halls lasted 3½ hours, during which content was presented and participants took part in small and large group discussions. People were asked 36 questions, eight of which were repeated at the end of the session to see if there was a shift in attitudes.

The online group met for three 1-hour sessions over the course of 3 weeks. Participants were recruited through Knowledge Networks' web-enabled panel, which is representative of the general population. Participants took an 80-item survey and signed up for one of the 15 time slots available. They were mailed headsets and instructions ahead of time and the sessions were moderated by genetic counselors. Most of the engagement was through audio, but there was also a box for text messaging. About 1 week after the last session, 76 of the questions were repeated to document changes in knowledge and attitudes. A control group of 400 individuals took the pre- and post-test but did not participate in the discussions.

The demographics indicated that people who were willing to take 3½ hours out of their schedules to come to an engagement were more likely to be stakeholders who already had a specific perspective. The Center was able to document clear shifts in opinion before and after the engagement. Many shifted toward disapproval over the course of the engagement, while the control group did not shift their opinions. The Center staff heard numerous concerns about the use of genetic testing and equal access to the benefits of advances in genetics. Despite these concerns, the public was optimistic about advances in genetics and the potential for health benefits. Ms. Scott said that both engagement methods allowed for reflective conversations about genetic technologies.

She said the approach for a large population study would need to use different methodologies appropriate for the entire engagement strategy. She suggested televised town halls and increased media involvement to reach a wider audience and have a broader ripple effect. Ms. Scott stated that tracking over time is important for monitoring effects.

Partnership for Public Engagement
E. Yvonne Lewis
Executive Director, Faith Access to Community Economic Development
and Toby Citrin, J.D.
Director, Michigan Center for Genomics and Public Health
University of Michigan School of Public Health

Ms. Yvonne Lewis and Mr. Toby Citrin spoke about three engagement projects they conducted that have relevance for the proposed large population study. The Communities of Color and Genetics Policy Project engaged African-American and Latino communities on genetics issues at the grassroots level to formulate policy recommendations that would enhance benefits and minimize harms to these populations. The University of Michigan, Michigan State University and Tuskegee University partnered

with 12 community-based organizations in Michigan and Alabama. Each of the community organizations sponsored a series of five dialogue sessions lasting about 2 hours each. The sessions started with a basic educational module on genetics research, followed by discussion. Approximately 20 members of their communities attended each session. The community organizations worked closely with the academic team in developing and implementing the process and in crafting the summaries and ultimate recommendations. Both the community organizations and the academic partners met with policymakers in Michigan and Alabama to share their recommendations. In a 2-day visit to Washington, they met with community partners, members of Congress, Congressional staffers, and the President's genetics advisors to share the recommendations that resulted.

The Genetics Education Needs Evaluation (GENE) project involved two communities in New York and Michigan. Building on previous relationships, they reached out to several community-based organizations, including churches, social organizations, Greek organizations, and a school system. To help determine educational needs, they provided community members with basic education about genetics and asked them how that education might be facilitated. The information that was gained was reported back to the community in a town hall meeting. This collaborative process led to a statewide initiative that looked at improving cancer outcomes for African Americans in Michigan. They worked with the Department of Community Health and a number of community leaders from five cities in Michigan to raise the level of awareness, reduce myths, and engage people in screening programs.

Ms. Lewis said that distrust stems from a history of research in which the benefits were not translated to the community. She said that to build trust, an honest and frank discussion must take place, and individuals must believe they are an integral part of the project and understand the purpose of the project, how it is designed, and who will benefit from it. She stated that recognition of the relevance of the project to the community results in engagement, and engagement raises the community's expectations. Ms. Lewis warned that not fulfilling these expectations will lead to mistrust and opposition.

Mr. Citrin stated that the proposed large population study poses a major risk of generating distrust among communities of color. He remarked that the key lesson they learned from their projects is that a successful project must be a true partnership between the researchers and those who are researched, which in turn builds trust and ensures engagement. The avoidance of that distrust and the achievement of support depend on the concept of co-ownership across the communities that are most at risk from the study. If a sense of co-ownership can be achieved, powerful advocates will support the infrastructure-building that is necessary. Ms. Lewis said that decision making and planning must engage the community from the outset. The study process must be explicit in addressing the issues of race and racism, and individual representatives of racial and ethnic groups must be meaningfully involved in developing plans and methods. Mr. Citrin also noted that it is important to pay attention to how the media is utilized to ensure that lack of trust and fear do not become predominant messages.

Mr. Citrin disagreed that an infrastructure must be in place prior to the project. If the project engages the community and is fully participatory, it can be a vehicle for community education as it moves forward. Ms. Lewis and Mr. Citrin said that to achieve full engagement, the community must be involved in all stages of the project, including study design, development of the instruments and materials, and reporting to the public. Ms. Lewis added that the process for partnership building must be evaluated continuously, leading to a common language, understanding and goals.

Mr. Citrin noted several national organizations that could help to foster dialogues with scientists,

professionals, practitioners, public health representatives, and grassroots community members. Ms. Lewis added that community-based organizations (CBOs) are valuable intermediaries who can maintain synergistic and consistent engagement and expand the level of involvement. These CBO connections can be made at local, State, and national levels. Ms. Lewis said that there is a National Community Committee that represents community-based individuals.

Ms. Lewis summarized by stating that subjects should be referred to as individual "study partners" and should be kept informed through ongoing communication. The success of a large population study may depend on whether it is perceived as a project carried out *by* the public or conducted *on* the public.

Thoughts on Engaging Public Interest, Participation, and Support
Mary Woolley, M.A.
President, Research!America

Ms. Mary Woolley described the key considerations of a possible large population study. She stated that broad support from the scientific community and the public is critical. She noted that the proposed study would compete with many other public agenda items and that the high overall costs of the study would affect public perception. Ms. Woolley also said that to help address current mistrust of Government, the new program must be framed to underscore the fact that researchers work for the public.

Another key consideration is the importance of identifying an urgent, compelling goal. People want to participate in an endeavor that is exciting and that they can understand immediately. Ms. Woolley explained that individuals and decision makers want to feel that they are part of history.

Public involvement is another consideration. She described the difference between public engagement and public relations, which is a different area of expertise that comes later in the process. Ms. Woolley also noted the importance of terminology used in engaging the public. Ms. Woolley stated that the fewer words used, the better. She said researchers need to be trained on how talk about their work in three sentences or less. Also, an authentic messenger makes a great deal of difference. Ms. Woolley remarked that it is also important not to try to engage the public before they are ready.

For her final point, Ms. Woolley said that funding was the least significant of the considerations. If value and need have been established and a project has the confidence of key people in the public and the scientific community, the money will follow.

Roundtable Discussion

Ms. Leonard asked Dr. Collins if it would be possible to proscribe that the research be funded proportionately to benefit the ethnicities reflected in the database. Dr. Collins replied that the initial idea was that anyone who had IRB approval would have access to the data to empower those with good ideas. However, he asked for the panel's reaction. Mr. Citrin acknowledged that the issue is very difficult to address at the basic research phase, but he thought it would be useful to think about how data gathered from diverse communities would be used. The possibility of reducing health disparities would foster community engagement and public support. Dr. Telfair suggested thinking of a broader way to define who should be involved and not limit the discussion to particular racial and ethnic groups. He said that those at risk or vulnerable cuts across ethnic and racial boundaries.

Dr. Lucinio spoke about his work in community engagement in genetics with the Mexican-American community in Los Angeles. Some of the issues that arose were: Who speaks for a diffuse community? How do researchers handle differences of opinion in the community once the community is engaged? Mr. Citrin stated that he did not advocate a model of community approval with voting or balloting; rather, he encouraged stakeholders representative of the community to be consulted. He said that although not everyone will support the project, stakeholder representation lends credence to it. Also, describing the project as an effort to determine the mechanisms underlying common complex diseases would make it clear that it is a project for everyone, leading to buy-in by the community as well as policymakers.

Dr. Khoury spoke about the history of the Human Genome Project and said the next initiative could lead to the translation of the first phase of gene sequencing to actual improvements in public health. He asked how, if the next project were to be considered a translational population-based effort to take genes from the "bench to the trench," should money be spent for the contextual elements that would allow the initiative to move forward? Mr. Citrin recommended that a substantial amount of money be spent on engagement and education and stated that a number of existing networks can play a role in this effort. Ms. Scott emphasized that starting early in the process is critical. Mr. Citrin suggested using the media to stimulate national attention, engage the public, and facilitate dialogue between scientists and stakeholders. Ms. Scott noted that it is not important that the public understands every scientific detail of the project, but how it applies to them. She said the public is capable of understanding complex technical, social, and ethical issues and putting them into the context of what they already know about (i.e., complex diseases). Ms. Lewis observed that the science community needs to understand the language of those who are not in the science community.

Dr. Willard asked the group to suggest concrete steps for engaging the public. Ms. Woolley suggested surveying public opinion. Ms. Scott suggested first clearly identifying the communities they wish to engage and going to them to obtain a sense of their concerns, then focusing on the long-term engagement process. Mr. Citrin recommended convening a group that would engage in a dialogue at the national level. It would have representatives from the science community, public health leadership, and stakeholders with national prominence who have credibility with communities interested in reducing and eliminating health disparities. Even if it were an informal meeting, participants could engage in a dialogue on how they might further the project and maximize community engagement of their constituencies. Ms. Lewis added that representatives should be identified up front from the communities of concern so they can be at the first meeting. Resources should be allocated to ensure their long-term participation. Dr. Willard said that the partnership being discussed would require that everyone who comes to the table would be willing to listen to others' perspectives and that differing opinions would be respected.

Policy Perspectives: Bioethics Community
Henry T. Greely, J.D.
Deane F. and Kate Edelman Johnson Professor of Law
Stanford Law School

Mr. Henry Greely recommended that SACGHS undertake a careful study of large-scale projects conducted previously, such as the Human Genome Project, to help identify the "land mines" experienced and the solutions developed to resolve those problems. He spoke on several ethical issues concerning a large population resource, including access to and control of materials and data, return of information to

participants, and confidentiality.

Mr. Greely stated that research participants must have the ability to control how data and personal biological materials are used. Mr. Greely stated that people have sensitivities concerning how their data will be used. They may not want information about themselves or their family members to be used for certain types of research. Not respecting this right can lead to loss of trust. This concern is particularly complex with the creation of libraries and databanks. It is impractical to obtain informed consent for the numerous possible uses of this dataset over time. Even if resources were available to obtain consent for each use, people would not want to have to do so. Mr. Greely stated that use of the term "informed consent" for such studies is a misnomer, because no one knows what specific research will be conducted or what diseases, genes or environmental effects will be examined. The very purpose of the resource is to make it available for scientists to do everything that seems useful over time. Mr. Greely said consent in these circumstances is not truly informed.

He said that none of the possible solutions to this problem are perfect, but some can mitigate it. At the beginning of the process, he recommended asking the research participant whether there are specific research areas for which he/she does not want his or her material or data to be used. He said that a short, targeted opt-out list of the most sensitive areas might be helpful for the participant to review. Another alternative used in a Veterans Department project is to have continual monitoring of the research topics, both by an IRB and by a group drawn from the research participants. They could discuss the new protocols proposed, decide whether a significant number of subjects might object, and determine whether individual reconsent is necessary. Mr. Greely noted that problematic issues are most likely to arise in the area of behavioral genetics. This monitoring approach would rule out the alternative mentioned by Dr. Collins, in which the material is open to anyone who has IRB approval. Mr. Greely stated that if that goal is a high priority, the informed consent must warn people up front, in plain English, that they have no control over the ways in which their data and materials will be used.

Concerning confidentiality, Mr. Greely said that Americans value health privacy, but increasing networking of and access to data undercuts the possibility of complete confidentiality. In most research situations, participants have a high degree of confidentiality, but there is still the possibility of abuse. It is hard to protect privacy in a longitudinal project like the large population study because of the comprehensive of the data it contains and repeated access to it. This will become a bigger problem as more data are placed online. On the other hand, de-identifying data will result in an unquantifiable loss of potential scientific value. The solution he recommended was complete and total honesty, but he said that will be expensive in terms of recruitment. Some research subjects will refuse to participate if absolute confidentiality cannot be guaranteed. The alternative is that they will feel betrayed when they discover that full confidentiality is not possible. Mr. Greely closed by stating that treating research subjects well is ethically important for science and for scientists; research subjects who feel betrayed and mistreated are unlikely to lobby for, vote for, or support biomedical research.

Policy Perspectives: Bioethics Community
Pilar Ossorio, Ph.D., J.D.
Associate Professor of Law and Medical Ethics
Associate Director, Center for the Study of Race and Ethnicity in Medicine
University of Wisconsin Law School

Dr. Pilar Ossorio discussed returning results back to participants. Dr. Ossorio made the distinction

between building a resource and conducting follow-on studies, saying that there are different ethical and pragmatic differences between them involving the proximity of the researchers to participants in both space and time. In addition, follow-on studies may be more likely to generate information that is not yet validated and may be subject to regulatory requirements in slightly different ways, which could affect the level of difficulty in reporting information back to participants.

Dr. Ossorio said that a number of policy committees have studied these issues and made recommendations, but have not achieved consensus. At one end of the spectrum is the option not to return any individualized results. Most genetic studies have not returned individual results, partially because many of the data were not validated or viewed as clinically useful. Current views about the permissibility of not returning individual results are changing. Dr. Ossorio noted that the large population initiative would produce clinically relevant information.

She said there are good reasons not to return individual results, including lack of clinical validation. The costs of sharing results when they are ambiguous are high. By not returning results, the researcher also increases confidentiality and privacy protections. The relationship between the researcher and the participant is a factor because there may have been no direct personal contact, which lessens the feeling of mutual obligation. If time has passed, the information may be outdated. Finally, not returning results helps maintain the cognitive and legal distinction between research and the provision of medical care. A middle view is to provide a very limited set of clinically relevant results.

Dr. Ossorio said the project under consideration would almost certainly require the return of at least some results. The following questions will therefore arise: Which results, to whom, how, what is the process of returning them, and when should it be done? She said there is wide agreement that researchers should not return results unless there is some analytic and clinical validity. The reasons in favor of returning results also are stronger when they have serious medical implications for the participant, would change medical management, are unlikely to be discovered through routine medical care, or when there is a robust relationship with the researcher so that the expectation of reciprocity is greater. Although little research has been done on whether participants want results back, the data so far indicate that participants have a fairly high degree of interest in obtaining results and that there is a small risk of harm.

Dr. Ossorio discussed findings that are the focus of the research, those that are incidental but foreseeable, and those that are unforeseeable. She said these are different categories to which different degrees of permissibility or obligation to report might be attached. In Category I, the researcher is obligated to report results. Very few circumstances fall into this category. In these cases, it would not matter what the focus of the research was or who was doing it. Category II is very broad and includes information that is permissible to report back at the researcher's discretion. This type of information and its reporting requirements should be delineated in the protocol, approved by the IRB, and included in the consent form. Category III includes information that is not permissible to report back.

The method for reporting depends on the category. For all categories, if data will be reported back, it must be approved by an IRB, included in the consent, and reported by a person with relevant expertise. Depending on the type of information uncovered, determining the type of expertise needed by the person reporting back may be difficult. Genetic information should be validated in a CLIA-approved lab. For Category I, the initial contact might be made by phone or letter to invite the individual to an in-person discussion about a clinically relevant finding. In Category II, a data safety monitoring board may be needed to help researchers decide which results are significant enough to be report back. The question of

when to report involves addressing issues regarding data that exists for years without being analyzed and new implications for existing data.

Participants should be given options on how data are reported back, i.e., either not getting information back or getting it back from a specific individual. Dr. Ossonio concluded by stating that there are trade-offs concerning what is permissible versus what is obligatory, in part because reporting back adds cost to the study. She stated that community engagements could help the researchers formulate the bounds of permissible reporting back.

Almost all ethics guidelines say there is a right not to know, but many clinical researchers disagree. She said the dividing line is clear for clinicians who are conducting a clinical exam in the course of their research and feel an obligation to disclose findings because their duties as physician overlap with their researcher role.

Policy Perspectives: Bioethics Community
Troy Duster, Ph.D.
Professor of Sociology
New York University

Dr. Troy Duster stated that it is important that a large research project accurately represents the population. In a large population study, people are likely to raise the question of whether race is being used as a taxonomic system, even though scientists know that race as a category is fluid biologically, socially, anthropologically, politically, and culturally.

Dr. Duster asked what it means to have a population study that is representative of the U.S. population. Most would assume the inclusion of whites, blacks, and Asians. Dr. Duster asked rhetorically if there could be a study that represents those who live near toxic waste dumps and those who do not, given that cancer rates in this country are highest near toxic waste sites. His concern was that by framing the study as genes and environment, it assumes an interaction that is more or less equal. Empirically, there are good data indicating that the environment plays a dominant role in many diseases. However, he said it seems that the imprimatur of science is on the genetic side. The assumption is that if an ethnic group has a higher rate of some disease, it must be because of their ethnic or racial category. However, some epidemiological studies suggest that the differences disappear when cross-cultural studies are conducted. For example, hypertension is high in the black communities of this country, but a study of eight countries on three continents indicates no differences between blacks and whites. To arrive at the conclusion that the different hypertension rates in the U.S. are a function of differences in genetic structure is a leap, unless functional genomics back it up. If racial categories are used, the method for reporting the results becomes vital.

Roundtable Discussion

Dr. Fitzgerald asked Dr. Duster about the advantages and disadvantages of addressing the composition of the study cohort using the community engagement model. Dr. Duster replied that community engagement is a good start to a probe into the relevance of the research but is not the complete answer. He emphasized the importance of educating people on issues in genetics. Mr. Greely said there is an important role for community consultation in the creation of appropriate informed consent protocols and methods for preliminary discussions with communities and research participants.

Dr. Lucinio asked Dr. Ossorio under what circumstances is it appropriate to tell a research participant about the risk of disease, including in both high- and low-risk situations and in cases where treatment is available and not available. Dr. Ossorio said that situations in which there is a 5 percent probability for a common complex disease would not fall into the category of information that is obligatory to report back.
She said community engagement could help decide how to prioritize information that is reported back. In addition, participants can be given a range of choices.

Dr. Licinio also asked whether study data should be used for purposes of apprehending criminals or relatives of study participants who are suspected of committing a crime. Dr. Ossorio replied that the data access policy for non-medical uses of the database must be delineated up front. However, law enforcement could, in some cases, obtain a court order to obtain access to the data. She said the Federal Bureau of Investigation is very interested in obtaining genetic information. Some State laws would protect a research database against uses for other purposes. Mr. Greely said the consent form should state that although the data is anonymous, the records could be obtained by court order.

Dr. Khoury described the methods used by public health researchers to obtain stratified random samples and enrich the sampling scheme by race and ethnicity. He asked Dr. Duster to identify other important variables and environmental factors that should be used to create representative samples. Dr. Duster said that a national study reduces the capacity to tease out the issue of genes versus environment. The points in his presentation were more relevant to studies across countries or continents. Dr. Ossorio suggested that perhaps stratification should be done by a particular medical focus, such as looking first at cancers or heart disease. She also suggested learning more about the environmental datasets already in existence, because they might help guide the sampling schemes.

Dr. Evans asked Mr. Greely for his opinion on informing participants in the aggregate about ongoing research projects and providing them with the opportunity to opt out as a way of attaining better informed consent. Mr. Greely first suggested that the initial interaction of the research participant should be called permission rather than consent to distinguish it from the concept of informed consent in the context of a multi-use, multi-decade resource. He agreed in principle with maintaining communication and informing participants about what is being done with their data. However, he said it would be problematic to maintain a high degree of contact and repeatedly ask for reconsent.

Ms. Berry asked Dr. Duster if the danger is actually in the interpretation of the data once it is collected, not in the collection of data from different racial groups. Dr. Duster replied that both create problems. Initially framing the study in terms of race tends to make people believe that the patterns seen are caused by racial differences. Dr. Ossorio said it is important to have broad representation with respect to race and gender, not necessarily to achieve a particular scientific goal but because the project would cost millions of Federal dollars and those categories are politically important. Full participation by all racial and ethnic groups is a way of saying to people that their needs matter, especially given that health disparities that map onto racial and ethic categories.

Dr. Michael Carome from the Office for Human Research Protections (OHRP) asked for reactions to the OHRP guidance involving the use of coded private information or specimens, which states that coding can be done so that the recipients of the data and specimens cannot readily ascertain the identity of the individuals. He noted that research using coded data does not involve human subjects and, therefore, it

doe not need further IRB review, informed consent, or an exchange of information with the subjects. Mr. Greely stated that he found it problematic because of the limitations on confidentiality and anonymity that he spoke about.

Committee Discussion

The Committee noted that the idea of a large population study is not being promoted by NHGRI alone; many Federal agencies have contributed extensively to the conversation. The work, if it proceeded, would not necessarily be conducted out of NHGRI's offices.

The Committee agreed that it would be appropriate to draw upon the expertise of panelists and other experts in drafting a report to the Secretary. Dr. Willard asked each of the Committee members to express their opinions on the feasibility of the study and to identify key issues or recommendations for consideration. The Committee consensus was one of support for the project, balanced with recognition of its complexity. It was agreed that the community consultation process should serve as a starting point. Some of the issues suggested for discussion in the report were:

- The critical importance of public engagement and the question of how early these efforts should begin;
- The possibility of developing a new paradigm for the way research is conducted using community engagement;
- The difficulties of conducting the project in the context of the current U.S. health care system;
- The need to integrate knowledge from similar studies taking place in the U.S. and around the world;
- The importance of the project as a means of maximizing the impact of the Human Genome Project;
- The need to define key elements of the study and commit to timelines for their completion;
- The importance of broad Government agency and private sector participation;
- The potential for non-health-related outcomes as well as individual and public health benefits;
- The need for an environmental taxonomy, which is not currently described for this study;
- The need for new funding;
- The need for protections against discrimination; and
- The need for smaller studies to lay the groundwork for the project as it moves forward.

It was agreed that staff would develop an outline and draft a report to the Secretary for the Committee to review at the March 2006 meeting. The Task Force would be expected to review the report during development, and other experts would be asked to assist as needed.

The SACGHS meeting adjourned for the day.

Thursday, October 20, 2005

Introductory Remarks

Cynthia Berry, J.D.
Acting SACGHS Chair

Ms. Berry began the morning by asking the Committee to vote on the edited version of the Coverage and Reimbursement Report. The Committee approved the edited version of the recommendations with a few modifications.

Genetic Discrimination Session

Ms. Berry introduced the session on genetic discrimination, stating that the Committee has been closely monitoring Federal legislative activities on the issue. In May, SACGHS sent Secretary Leavitt a compilation of public comments, a DVD of testimony highlighting public perspectives on the issue, and a legal analysis of the adequacy of current law. These materials also were disseminated to the public through the Committee's website.

Update on the Status of the Genetic Information Nondiscrimination Act of 2005 (S. 306/H.R. 1227)
Frank Swain, J.D.
Counsel
Coalition for Genetic Fairness

Mr. Frank Swain provided an update on the legislation introduced in the House of Representatives, H.R. 1227. The bill would prohibit the negative use of predictive genetic information about an individual for employment and health insurance purposes. The employment title has been assigned to the committee that has jurisdiction over labor matters, and the health insurance title is assigned to the committee that has jurisdiction over insurance matters. Additionally, some parts of the bill must be reviewed by the Ways and Means Committee because it indirectly affects Medicare. The House bill has 150 cosponsors. The primary sponsor is Congresswoman Judy Biggert from Chicago, who has been aggressively encouraging many of her fellow Republicans to sign on.

Although this bill is identical to one passed by the U.S. Senate in February by a vote of 97-0, it has been more controversial in the House. Mr. Swain addressed the barriers facing passage in the House, including significant apprehension among the business community that the bill will make it easy to challenge routine workplace decisions under the guise of genetic nondiscrimination. The Coalition is working to make sure the bill is clearly written so it can only be used as intended. Some worry that the bill would somehow inevitably lead to national health care. Another issue is the significant number of individuals who buy health insurance in the individual market, where there is medical underwriting. Although medical underwriting often uses family history, the Coalition believes it would not be considered genetic information.

Mr. Swain said they are involved in informal discussions with the U.S. Chamber of Commerce, the National Association of Manufacturers, and other groups that have some concerns about the legislation. He stated that it is a positive sign that these groups have agreed to try to work on areas of disagreement.

Mr. Swain pointed out the importance of the Committee's recommendations to the Secretary on this matter and said that active advocacy is needed at every level within the administration, the scientific community, and the business community. He said the biotechnology and pharmaceutical communities have not stepped up to the plate on this legislation.

Mr. Swain closed by stating that this Federal law is needed because only 33 States have laws on the rights and responsibilities of employers, employees, and insurance companies concerning genetic discrimination.

Public Attitudes toward Advances in Genetics, Genetic Privacy, and the Potential Misuse of Genetic Information
Christy White
Principal
Cogent Research Corporation

Ms. Christy White explained that Cogent is a market research firm that works with both industry and the government. They see genetic discrimination as an important issue to track on behalf of both sectors. They conduct research to provide a comprehensive and actionable assessment of American views to help inform industry strategy and policy development.

Using a web-based tool, the most recent study asked 1,000 consumers 205 questions on four main areas: 1) awareness of and interest in genomics; 2) catalysts and barriers to adoption and use; 3) preferences for delivery; and 4) messaging and communication. The study targeted U.S. adults representative of the population on the variables of ethnicity, region, and gender. Consumers were asked if they were aware of issues concerning the use of individual genetic information to understand and optimize health. Three-quarters of Americans have heard something about this issue but do not have a very sophisticated understanding of it. Most do not know how genetic information could potentially alter or improve their health.

General attitudes of the public were shown to be highly favorable. Many people see promise in genomics. Fifty-eight percent said they are in favor of using their individual genetic information to make informed choices about prescription drugs. The study also asked questions related to efficacy, safety, and preventative or proactive uses of prescription medication. The conclusion reached was that consumers are ready for this knowledge and can easily be brought around to understand how they can use it. The public is most interested in information they can apply, such as reducing their risk of specific diseases, and not as much in information they cannot do anything about.

Ms. White said the three areas critical to long-term acceptance of genomics are ethical issues, emotional consequences, and privacy concerns. Thirty-three percent of people agreed with the statement, "Meddling with our genes and DNA is trying to play God. Scientists, researchers, and doctors should stay out of it altogether." Fifteen percent agreed with the statement, "Genetic testing should be stopped because it will ultimately lead to cloning or altering human genes." These types of moral concerns could prevent genomics from being used altogether.

The emotional costs relate to the idea that knowing one's genetic profile is a great responsibility that impacts the whole family. Close to one-fourth of Americans were in agreement with that statement. Slightly more said it would be depressing to know they were going to get a disease, particularly if there

was nothing that could be done about it.

On the issue of privacy, 68 percent of Americans are concerned about how their personal genetic information would be stored and who would have access to the information. One-third said that concern would prevent them from having a genetic test. Half are worried that their DNA sample may be used for tests other than the ones authorized. Sixty-eight percent of Americans agreed with that statement, "Insurance companies will do everything possible to use my genetic information to deny health coverage."

However, sixty-four percent said that their interest would be higher if they were assured by law that no one could access their DNA information without consent. Seventy-one percent agreed that, "The government should establish specific laws and regulations to protect the privacy of genetic information." Only 24 percent agreed that the Government should create a national database of DNA information for the future health of all Americans.

Ms. White concluded with key findings. She stated that there must be an effort to deepen Americans' understanding of genomics, particularly on how individuals can use it in their own lives. The focus should be on diseases for which solutions exist, because telling people about diseases they are likely to get that have no treatment will unnecessarily upset them. Privacy protections also are important. Lastly, moral concerns should be addressed by framing the issues so that people can understand how this research can benefit them in the long term.

Ms. White stated that in the future, Cogent will be looking more closely at workplace discrimination and awareness and opinions on proposed legislation and existing protections.

Roundtable Discussion

Dr. Lucinio asked whether, if nondiscrimination legislation passes, there would be fine print in medical forms that might result in people waiving their rights. Mr. Swain said that individuals have broad authority to waive protections. Health insurance companies can demand to know details about why reimbursement is being sought, and he was not aware of anything in the legislation that would alter that. Health insurance companies will still be allowed to access health information, and it would not constitute misuse. However, an increase in premiums because of genetic information would be considered misuse under the bill.

Dr. Fitzgerald asked Mr. Swain about the difference between family history versus genetic information and how the two terms are differentiated in the law. Mr. Swain said that the legislation is intended to lessen apprehension about receiving or undergoing genetic testing; it does not specifically address family history.

Dr. Lucinio asked Mr. Swain if the largest issue preventing passage of the legislation is the business community's fear of litigation related to someone's employment. Mr. Swain said that was correct. Dr. Lucinio asked Mr. Swain to explain the logic behind those fears. Mr. Swain gave an example in which an employer might not hire an individual with a genetic marker for breast cancer out of concern that the person will cost the employer's insurance plan a large amount of money if they become ill.

Ms. Berry asked Mr. Swain about the impact of IBM's announcement that it will not use genetic

information against its employees. Mr. Swain said he considered it a leadership move and hopes that other U.S. employers will adopt similar policies.

Ms. Au asked Ms. White about the range of demographics for the Internet-based study. Ms. White responded that the study's sample was derived from a panel of more than 7 million Americans. Because specific populations are underrepresented on the Web, including people over the age of 75, Hispanics, and people with less than a high school education, Cogent oversamples those populations.

Dr. Fitzgerald asked Ms. White what would happen to their numbers if they substituted the word "nanotechnology" for genetics. Ms. White said they would never use the term nanotechnology because the term is not well understood. She said the surveys are designed at a 6th grade reading level. The researchers also talk to the participants beforehand and pretest the survey instruments.

Dr. Suzanne Feetham asked Ms. White about trends in the data. Ms. White replied that they did examine data trends but did not see significant changes in awareness over the past year. A literature search also indicated that there was no increase in the number of stories on the issue.

Ms. Masny asked Ms. White if the Committee could include a summary of the survey data as an addendum to the materials sent to the Secretary, as it adds to the momentum for passage of the legislation. Ms. White agreed.

Dr. Telfair requested that Ms. White's next survey ask whether the public is willing to work with the Government on issues of privacy, i.e., participate in public engagement. Dr. Sherrie Hans asked Ms. White to share with the Committee data on the delivery system. She felt it was pertinent to the deliberations concerning the return of information. Ms. White agreed and also said that Cogent is launching the first physician-based study that will look at awareness as well as catalysts and barriers to adoption of genetic information.

Pharmacogenomics Session

Session Overview and Goals
Emily S. Winn-Deen, Ph.D.
Chair
SACGHS Pharmacogenomics Task Force

Dr. Winn-Deen explained that the pharmacogenomics session was designed to continue fact-finding on some of the issues identified at the June meeting so that the Committee could proceed with development of recommendations. She listed the key issues of concern to the Committee in the area of research and development as: drug diagnostic co-development, collecting evidence on effectiveness and safety, funding sources, and orphan disease or orphan drug status. In the infrastructure area, she said the Committee would hear from FDA on their attempts to create data standards, followed by progress on regulation and information on surveillance. Key issues concerning integration into clinical practice include access, education, the need for evidence and guidelines, and liability. Ethical, legal and social issues include allocation of resources, health disparities, informed consent, privacy and confidentiality, discrimination, race, unintended psychosocial harms, intellectual property, and genetic exceptionalism.

Since the last SACGHS meeting, the Pharmacogenomics Task Force developed an outline for a

comprehensive report based on discussions during the most recent meetings. Also, HHS agencies provided feedback on the policy priorities they thought SACGHS should address.

Update from FDA
Steven I. Gutman, M.D., M.B.A.
Director, Office of In Vitro Diagnostics, FDA
and
Allen Rudman, Ph.D.
Center for Drug Evaluation and Research, FDA

Dr. Gutman spoke about the diagnostic side of the pharmacogenomics pipeline. He stated that FDA approved two pharmacogenomic tests to during the last year: the Roche AmpliChip and a UGT 1A1. The products were considered Class 2 medical devices and reviewed under a new *de novo* process. This mechanism provides FDA with increased flexibility when it encounters a new test that lacks a clear predicate and is of low risk or has some ability to mitigate risk.

Dr. Gutman also described a concept paper on the co-development of diagnostics as they relate to drugs. The paper lays out in a preliminary manner the scientific issues associated with the analytical and clinical validation of these types of tests and elucidation of their clinical utility. It states that when a diagnostic is used to select a drug, the two become inextricably intertwined, i.e., the diagnostic may drive the performance of the drug, or the drug might drive the performance of the diagnostic. After review of the comments received, the concept paper will be converted into a draft guidance, which is expected to be ready by the end of 2005. Additional comments will be sought on the guidance before it is finalized.

Dr. Gutman stated that guidance on pharmacogenetic tests is in the final stages of review and is expected to be completed in 2005.

There is interest in possibly revisiting the issue of whether incremental changes can be made to either the ASR exemption or regulation of genetic tests provided as laboratory services. Dr. Gutman said AdvaMed submitted a frequently asked questions document to FDA that attempted to clarify analyte specific reagents (ASRs). As part of this effort, AdvaMed reached out to the laboratory community for input. FDA may use it as the basis for a draft guidance.

Dr. Gutman described an ad hoc group working to identify misuses of direct-to-consumer (DTC) testing. Given that FDA regulations on home brews and cleared and approved devices were not strong enough, the group used FTC's criteria to evaluate websites, which requires advertisements to be "outrageous" and potentially harmful, and planned to use FTC's enforcement mechanisms. The task turned out to be more challenging than they were expecting. Over time, the sites being reviewed changed the tone of their advertisements in ways that made them more elusive. Dr. Gutman asked the Committee to let the group know if they become aware of any sites that meet the criteria he described.

In closing, Dr. Gutman said that efforts are underway to establish a working group that brings together the pharmaceutical and diagnostics communities to explore opportunities for industry and FDA to address the unique challenges they are facing with diagnostics.

Dr. Allen Rudman stated that FDA's mission is to protect and advance public health by helping to speed innovations that make medicines and food more effective, safer, and more affordable. This mission is

reflected in the Critical Path initiative, which lists opportunities to find paths to new medical procedures. A white paper entitled, *Innovation, Stagnation: Challenges and Opportunity on the Critical Path to New Medical Products*, describes how emerging pharmacogenomic and proteomic techniques show great promise for increasing drug effectiveness. In addition, the National Cancer Institute and FDA announced a joint program to streamline cancer drug development, which include developing biomarkers for evaluating new cancer medicines as one of its goals.

Dr. Rudman said that in March 2005, FDA finalized guidance on voluntary genomic data submissions (VGDS) from industry. The goal is for companies to voluntarily submit genomic data so that FDA can track them and meet with the companies. The process included conferences and workshops with industry, the public and NIH so that the knowledge gained could inform policy. Dr. Rudman displayed an overview of the use of biomarkers in drug development and the strategic use of VGDS. It depicted the process from basic research to FDA approval and all the steps in between. Ultimately, the key questions that arise at the end of the process are: What does the test's analytical validation process consist of? How should validation be done? What criteria should be used to assess its validity? What are the test's preclinical feasibility, clinical validity, and clinical utility? Dr. Rudman noted that the fact that there is a test does not necessarily mean it will be useful for public health purposes.

Internal (within FDA) and external education on pharmacogenomics also has been an important goal. An Interdisciplinary Pharmacogenomic Research Group (IPRG), which has representatives from across FDA, has been established to help achieve this goal. Located in the Office of Clinical Pharmacology and Biopharmaceutics, the IPRG conducts numerous activities, including the review of genomic data submissions. Research efforts include a cooperative research and development agreement on biomarker validation, development of information on designing clinical trial protocols, and analysis of labeling information relating to pharmacogenomics. Information technology efforts include the development of new software and databases.

To date, 24 VGDSs have been received, and 12 have either scheduled or held meetings. Dr. Rudman stated that companies are now providing follow-up information and coming back with many different types of submissions. Genomic information has been received in therapeutic areas such as cancer, Alzheimer's, hypertension, hyperglycemia, depression, obesity, and rheumatoid arthritis. Scientific information has been received on biomarker development, genotyping devices, microarray analysis, analysis software, databases, metabolic pathways, biostatistics, and enrichment design.

Dr. Rudman described the steps being taken toward harmonization. He stated that because most of the large pharmaceutical companies are global, it is increasingly important for there to be consistency across Europe and the U.S. On May 17th, the first joint FDA-European Medicines Evaluation Agency (EMEA) meeting was held via videoconference. Interaction before the meeting included in-depth scientific evaluation of sponsors' questions and pre-meeting dialogue between FDA and EMEA, since they operate under different regulatory environments. FDA and EMEA issued joint minutes on the voluntary genomic submissions and shared them with the sponsor. The evaluations by the two agencies had only minor differences. Three more joint meetings are scheduled. The information resulting from this process is informing guidances, concept papers, and several workshops.

In his concluding remarks, Dr. Rudman stated that FDA's VGDS and pharmacogenomics programs have been very successful. The VGDS submissions have provided FDA with a wealth of significant genomic data and therapeutic, scientific, and technical information that would otherwise be unavailable. He said

that to expedite the approval of new drugs and indications and to get them to the public, pharmacogenomic research must be seen in the context of biomarker development and validation as well as disease management. Dr. Rudman said SACGHS could help by recommending the formation of a task force to develop national standards for pharmacogenomic assays.

Questions and Answers

Dr. Lucinio asked for advice on a starting point for national standards for testing and where the authority for this effort lies (e.g., FDA or CDC). Dr. Rudman stated that there are numerous questions that first must be identified, and responsibilities could then be assigned accordingly. Dr. Gutman added that for the diagnostic industry, the Clinical Laboratory Standards Institute (CLSI) is the premier group for crafting standards and is also the Executive Secretariat for the international standards group working in the area of labs, ISO CT212. Although they are focused largely on diagnostic issues, they could become more inclusive.

Dr. Evans asked about the purview of FDA in the reporting of results and whether information will be made more understandable to clinicians. Dr. Gutman said FDA does not regulate the reporting system itself. Dr. Khoury noted that the Secretary's Advisory Committee on Genetic Testing developed recommendations relating to the oversight of genetic testing and the transition from research to practice; however, there are many gaps in the process that are being uncovered by pharmacogenomics. SACGHS might consider taking on these issues.

Ms. Masny addressed previous speakers' concerns about large population studies due to a lack of genetic literacy among the public, Federal agencies, and health professionals. She asked Dr. Rudman to elaborate on the education initiatives he mentioned. Dr. Rudman stated that there is a series of internal FDA seminars and training sessions in genomics and internal websites. Externally, the two mechanisms used are workshops and a website. There also have been preliminary discussions with universities and the American Association of Clinical Science about moving forward with education programs.

Public Comments

Jean Jenkins, Ph.D., R.N., FAAN
International Society of Nurses in Genetics

Jean Jenkins said health care options will increasingly rely on genetic and genomic information. The clinical application of this knowledge has major implications for the nursing profession at both basic and advanced practice levels. Nurses must be able to integrate genetic and genomic knowledge and understand their implications for health care delivery.

Ms. Jenkins said that several Federal agencies, including NHGRI, CDC, HRSA, and the American Nurses Association and the International Society of Nurses in Genetics (ISONG), met in September 2005 to reach consensus on a document that defines essential genetic and genomic competencies for all registered nurses, with the intent that the genetic and genomic perspective will be incorporated into all aspects of nursing practice and education.

Pharmacogenomics Session (continued)

Feasibility of Integrating Pharmacogenomics into Drug Development from an Economic Perspective

Thomas A. Metcalfe
Head of Biomarker Program
F. Hoffman-Roche Ltd.

Mr. Thomas Metcalfe defined biomarkers as an objective measure or evaluation of normal biological or pathogenic processes or pharmacologic responses to therapeutic, preventive or other health care interventions. They can increase understanding of drug metabolism, drug action, efficacy, and safety; facilitate prediction of therapy response; expand the molecular definition of disease; and provide information about the course of disease progression. This broad definition includes all diagnostic tests, imaging technologies, and other subjective measures of a person's health status.

Mr. Metcalfe described new developments, including the fact that genetics, genomics, proteomics, and modern imaging techniques allow scientists to measure many more markers than previously. There also is an improved understanding of the targets of pharmaceutical interventions, signaling pathways, metabolism, and mechanisms of toxicity, which helps researchers to understand biomarker data. Biostatistics and bioinformatics allow researchers to collect, store and interpret these data more effectively.

These new marker data help with decisions in late research and early development about which projects should move forward. However, there are currently few validated surrogate markers that allow for considerably shorter trials, and there are very few highly informative response markers that allow for smaller trials enriched for potential responders.

The biomarker utilities in drug development are pharmacodynamic markers that confirm biological activity and optimize dosing and scheduling, prognostic markers that correlate with disease outcome, disease-specific markers that correlate well with the presence or absence of a disease, and predictive markers such as HER2 overexpression in breast cancer that correlate strongly with the activity of drugs. Mr. Metcalfe stated that, in many cases, disease biomarkers lack the specificity to be used as predictive pharmacodiagnostics.

He then focused on predictive pharmacodiagnostics in relation to its impact on the economics of drug development. He stated that pharmacodynamic and prognostic tests tend to increase value, principally because the size of the market is not really affected. As a result, revenues do not decrease and in fact may increase because of improved dosing and their ability to improve decisionmaking, trial design, and reduced attrition, which offsets the cost of marker research and development. On the other hand, the value impact of predictive markers is less clear. They may reduce the size of the market, but this reduction may be offset by improvements in market penetration, increased average duration of therapy, and pricing.

To include response markers in a drug development program, it is important first to have a reliable understanding of the biology of the marker and the test for that marker. Considerable time is spent in early drug development and biomarker discovery, then in biomarker test development and validation, and as the drug is introduced, collecting and storing samples. The most informative time in early development is Phase II. After a test has been developed, it is possible to conduct a retrospective analysis of the biomarkers on samples collected during Phase II and correlate these with response and possibly safety.

One could prospectively recruit patients for Phase III trials using biomarkers found to be useful at the end of Phase II, but only if they were very informative and reliable biomarkers. An alternative might be to balance the various arms of a trial to make sure that both are equally populated with patients who have a good chance of response using the marker. This would require tracking of more information but would not change the trial protocols for drug development.

Mr. Metcalfe spoke about the acceptable response rate for a novel drug and when to apply stratification with a response marker. He said that when there is a very low response rate, the drug might not be viable. A response marker might make sense, however, when the response rate is above 10 percent. Mr. Metcalfe said a response rate above 50 percent is excellent for a novel drug. Mr. Metcalfe discussed the issues related to the definition of "response." At the end of Phase II, researchers try to correlate markers with responders. If they do not have a clear idea about who is a responder and what is the response phenotype, problems can arise.

Another set of questions relates to the response rate and safety markers. The balance between increasing efficacy and increasing safety should tilt toward increasing safety because of the practical issues concerning the ability to predict adverse events (AEs). He said AEs might be infrequent with a useful drug. The researcher also must take into account the balance between efficacy and risk as they relate to the specific indication being looked at. If there is a great medical need, one may be willing to take on more safety issues because of the potential benefits.

There are many different pharmacodiagnostic test requirements. Many are analytical, but some are practical. Ideally, the test should not be particularly invasive and the results should be returned within a short time. Availability and reliability of the test, high predictive value, and ease of administration also are important.

Some of the challenges in coordinating drug and diagnostic development include identifying the right biomarker early enough, developing the within drug development timelines, and ensuring collection of enough samples and storing them effectively. Mr. Metcalfe said there must be incentives for pharmaceutical companies because the work is expensive and the companies must balance investments in biomarker work with investments in new medicines.

When discussing the economic rationale for personalized medicine, Mr. Metcalfe emphasized that capturing value of an innovative medicine depends on pricing and reimbursement conditions, intellectual property protection, competition, and timing, as well as scientific and clinical considerations. His opinion is that it would be wise to encourage value-based, flexible pricing and reimbursement systems to provide a level playing field that rewards diagnostic and therapeutic innovation. Current reimbursement schemes for diagnostics do not reward value creation. So there are insufficient incentives, in many cases, for diagnostic companies to invest in such research, particularly taking into account that only 3 percent of drugs in the development pipeline ever reach market. Mr. Metcalfe stated that value also is measured by the amount informed patients are willing to pay for life years gained, improvements in quality of life, reduction of morbidity, and reduction in uncertainty. Targeting adoption by good responders leads to strong net benefits. Good responders also may have improved compliance, which benefits companies who offer long-term therapies for chronic conditions. Inability to set price is a disincentive for manufacturers to conduct this type of research. Mr. Metcalfe said the price for novel drugs is nearly always set early in the drug's life, immediately after registration. Manufacturers want to reduce the uncertainty concerning the number of responders, as this affects the setting of price.

The Economic Challenges of Integrating Pharmacogenomics into Clinical Practice
Kathryn Phillips, Ph.D.
Professor of Health Economics and Health Services Research
University of California, San Francisco

Dr. Kathryn Phillips explained some of the economic challenges associated with integrating pharmacogenomics into clinical care.

Dr. Phillips stated that economics can be reduced to the concepts of incentives and value. She explained that the first step in maximizing the value of pharmacogenomics is understanding the importance of economic and non-economic incentives. Adoption of pharmacogenomics will occur only if there are properly structured, aligned, and built-in incentives. These incentives vary based on the characteristics of the intervention, including:

- Whether the condition that the intervention targets is life-threatening or chronic;
- If there is strong advocacy group or industry interest;
- If there is coverage and high reimbursement rates;
- If pharmacogenomics is used early in the pipeline rather than later;
- If it is used for immediate versus future treatment decisions;
- If it is used for focused, narrow treatment decisions;
- If it can be used for off-label indications;
- If it is used for ongoing monitoring versus one-time use;
- If it targets an acquired versus an inherited mutation;
- When it dictates the type of treatment that will be used as opposed to suggesting the treatment or dosage; and
- When it is not considered pharmacogenomics but rather personalized medicine, targeted therapy, or smart drugs. People find it easier to understand and support the concept of personalized medicine than genetic testing.

Dr. Phillips spoke about the case study of Herceptin. It had a very fast and successful adoption, which proved that targeting small populations can be feasible and profitable for industry. One economic analysis concluded that Herceptin cost $125,000 per quality-adjusted life year gained. Dr. Phillips noted that usually, any cost over $50,000 raises questions about the overall benefits of a drug. She then described Iressa is an example of a fast but unsuccessful adoption. FDA accelerated approval of the drug, but it has essentially been withdrawn from the market because post-approval clinical trials showed no significant survival benefit. Iressa illustrates how failed adoption has the potential to create large, societal losses. Third, CYP450 testing illustrates slow adoption. There have been many implementation challenges, including the multifactorial nature of drug response, a lack of data linking mutations and clinical outcomes, and variability across and within drug classes.

Dr. Phillips said that for Herceptin and Iressa, it will be challenging to develop and determine the most appropriate diagnostic. Several tests were approved for Herceptin but there is still debate over which test to use. CYP450 testing illustrates that it will be challenging to adopt pharmacogenomics when the product is relevant to multiple diseases, because P450 testing takes place only once in a lifetime but the results are relevant to multiple diseases, drugs, and clinical specialties. It is unclear who will advocate for P450 testing. In addition, Medicare covers diagnostic tests, but not screening tests. It is unclear which of

those CYP450 really is.

She noted that there is very little documentation of the value of pharmacogenomics. There have been only 11 cost-effectiveness analyses of pharmacogenomic interventions under a very limited range of conditions, and the results were mixed. Data linking pharmacogenetics to outcomes and data on comparative effectiveness on therapeutics and the products themselves also helps determine value.

There are few incentives to assess economic value from a societal perspective. Advocates, industry, FDA, CMS, and insurers do not usually evaluate pharmacogenomics from the societal perspective. Another challenge is the fact that pharmacogenomics often prevents harm (e.g., the prevention of adverse effects), which is hard to measure.

Dr. Phillips suggested using innovative approaches to evaluate diagnostics, co-developed diagnostics and drugs that will require cooperation between historically divided industries and regulatory mechanisms and early consideration of diagnostics. She said that three key barriers in the diagnostic pipeline are money for initial investment, reimbursement, availability of data and samples, and the fact that the clinical utility of tests is often not evaluated, making it difficult to demonstrate the value of diagnostics.

Dr. Phillips closed by emphasizing the importance of developing an evidence base. She cited the database being developed by the Pharmacogenomics Research Network and EGAPP as examples. She believes there will be an inevitable push towards pharmacogenomics because it is part of a larger trend toward personalized medicine. Dr. Phillips stated that the government has a critical role in facilitating pharmacogenomics' appropriate use.

Roundtable Discussion

Dr. Khoury commented on drugs that are effective for many people but have side effects for a small percentage and are therefore withdrawn from the market. He asked why the drugs are pulled instead of studying why a small number of people have side effects. Mr. Metcalfe said it is difficult to reliably predict who is likely to suffer an adverse event when the percentage of cases is very small. Very large studies would be required. If there is an alternative drug on the market, there is less incentive to invest in the drug with side effects.

Dr. Fitzgerald asked about the possibility of rehabilitating drug products that failed if the groups who could benefit from them had not been previously identified. Mr. Metcalfe stated that as long as there is sufficient patent protection, there are many incentives to use such drugs for new indications. He also commented that there are no incentives for the diagnostic industry to invest speculatively because it is not reimbursed based on the value of the test.

Dr. Evans wondered about the lack of lawsuits against physicians who do not test for TPMT. He noted that liability can serve as an incentive. Mr. Metcalfe said that when there is a clear standard of care that is not adhered to, there is a much higher risk of litigation. Dr. Evans also asked whether insurers would try to deny coverage for individuals if there is evidence that they may not respond well to a drug. Mr. Metcalfe said this would definitely happen if there is clear evidence that a patient is highly unlikely to derive benefit. He said the less clear-cut cases have not been sufficiently debated. Dr. Phillips added that patient advocacy has a role in determining which pharmacogenomics interventions move forward. In the case of Herceptin, the manufacturer was reluctant to move forward but patients demanded the drug.

Dr. Winn-Deen asked the panelists if there were specific steps that should be taken at the HHS level that would benefit the industry. Dr. Phillips suggested more funding of economics research. Mr. Metcalfe recommended development of a clear regulatory framework and set of standards, more funding for translational research, and incentives for profit-oriented companies.

Ethical and Social Issues Associated With Using Race and Genetics in the Study of Differential Drug Response

Wylie Burke, M.D., Ph.D.
Professor and Chair, Department of Medical History and Ethics
University of Washington

Dr. Burke stated that "race" is a term that is generally used to identify groups with shared ancestry. In the U.S., it is assumed that race is closely related to genetics. However, she stated that the definition of racial groups has changed over time and that the term "race" can take on a variety of different meanings.

Dr. Burke said there is an indirect relationship between race and pharmacogenomics. Self-reported race is correlated only in a rough way with genetic measures of geographic ancestry. Researchers have developed marker panels for the five major racial groups: African, European, Asian, Native American, and Oceanic. Dr. Burke stated that categorizing people by race in this way indicates the prevalence of many gene variants, some associated with drug response. As an example, she said the prevalence of CYP2C9 variants is associated with a reduction in dose for warfarin and is believed to apply to Asians in particular. But she noted that that the preponderance of studies on warfarin have been conducted in North America with people of European descent. Dr. Burke stated that the evidence base that Asian patients require lower doses of warfarin is not strong, yet is widely believed based on clinical observation.

A study of a different gene provides evidence of a possible genetic contributor to the apparent Asian requirement for a lower dose of warfarin. This study looked at the association between warfarin dose and two VKORC1 variant haplotypes (Group A and Group B). Group A was associated low dose requirements; Group B was associated with high dose requirements. There was a difference in prevalence among racial groups related to these two haplotypes. The Asian sample had a very high proportion of the VKORC1 haplotype associated with low dose. Dr. Burke said this indicates a genetic explanation for the clinical observation. She said there are other undetermined factors as well, which may be genetic or non-genetic. Non-genetic factors include diet, age, multiple interacting drugs, and other health conditions. Dr. Burke stated that, granting that both genetic and non-genetic factors contribute to drug response, there is great complexity on the genetic side. There are many genes involved in the metabolic processes by which the body responds to ingested warfarin, most of which have not been studied.

Based on a study of the prevalence of APOe 4 allele in populations around the world, Dr. Burke stated that racial groups are highly heterogeneous, which is another reason to be cautious about generalizations. The only populations for which a broad distribution was not seen in this study were three populations of Oceanic origin. Dr. Burke said this part of the study indicated that sampling individuals with four grandparents of similar geographic ancestry does not necessarily mean the researchers are sampling the same geographic ancestry.
She noted that broad sampling is very important because race and geographic ancestry are related but not congruent. Estimates from genetic testing indicate that the West African contribution to individual African American ancestry averages 80 percent but ranges from 20 percent to 100 percent.

Approximately 30 percent of self-identified European Americans have less than 90 percent European ancestry. The mixture is even higher and more variable among people who self-identify as Hispanic.

Dr. Burke addressed whether race is clinically important in drug treatment. She said that although race captures many potential group differences, such as diet, housing, occupation, and environmental exposure, it is uncertain whether race has sufficient predictive value to assist in drug treatment. To identify all the variants relevant to a particular drug response, diverse populations must be studied in large numbers. Therefore, any one observation must be examined for its place within that mix, and gene/gene and gene/environment interactions are likely.

Orphan genotypes are a significant consideration from the standpoint of ethics and policy. Dr. Burke explained that rare genotypes that predict drug response are likely to be less studied and could be neglected in drug development. In the U.S., genotypes common in minority populations but not in the population overall could become orphan genotypes. Dr. Burke cited the example of loss of lactase, leading to a condition called lactose intolerance. A group of researchers wrote an article in 1999 in the *Journal of the National Medical Association* claiming racial bias in Federal nutrition policy. The policy recommends milk products as an important source of calcium. However, an inability to digest lactose, an enzyme in milk products, is very high in virtually all racial groups except Europeans. One could argue that policy has been made based on the needs of a dominant group in the population that happens to have a genetic predisposition that is quite unusual worldwide.

Dr. Burke stated that the data suggests there is more mistrust about the misuse of genetic information among minority populations. For example, in a survey of minority pre-medical students, 74 percent strongly agreed that genetic testing might lead to discrimination. She said it is critical to develop partnerships that incorporate minority communities in research.

Dr. Burke described the significant risks that derive from the use of race and genetics and the study of differential drug response. She stated that there is too much research in the U.S. and Europe and not enough in other parts of the world, where the populations that are minority in this country are not in the minority. Attention also must be paid to the size and sampling methods used for populations. She said there also is inadequate attention given to multiracial groups even though we live in an increasingly multiracial society. There is a need to recognize that even when genetic predictors are found that help identify those with a higher or lower likelihood of adverse effects or effective responses to a drug, that is only one of many contributors, and it should not be inflated beyond what the findings indicate. As pharmacogenetics moves forward, Dr. Burke stated that the field must avoid the error of misrepresenting race as a genetic entity. Researchers need to recognize that there are many social causes of racial group differences and much genetic variation within racial groups.

Dr. Burke emphasized the need for outcome data. There is a need to move beyond hypotheses about benefit to actual proof that drug outcomes are improved by genetic testing. Her final point highlighted the fundamental concern about equal access to quality health care.

Questions and Answers

Dr. Lucinio said that in some countries in which many residents are of mixed ancestry, the concept of race is almost non-existent. Dr. Burke stated that this point speaks to the importance of making sure research occurs in populations other than the U.S., where there is less clarity about racial categories. She

said that movement should be in a direction away from racial categories, as they will have increasingly less utility. Good population sampling should look for relevant variants or other non-genetic factors.

Dr. Khoury asked Dr. Burke to suggest possible recommendations for HHS. Dr. Burke said the agency should carefully consider inclusionary approaches and make sure there is a broad selection of populations. She encouraged studies outside the U.S. and advocated for approaching communities that have not been involved in research and that may have some mistrust. From the clinical integration side, she raised the following questions: How can outcome studies be funded and how can post-market studies be conducted? She also noted an HHS imperative to consider access issues. She said that genetics should be integrated into the public school curriculum and that models should be developed for educating health care providers. Dr. Burke stated that the public needs assurances that research will be conducted in respectful and appropriate ways.

Committee Discussion

Dr. Winn-Deen asked participants to examine the list of key issues in pharmacogenomics discussed at the last SACGHS meeting and to review the outline for a potential SACGHS report on the topic. Dr. Winn-Deen asked whether the Committee wanted to develop a report on pharmacogenomics issues and the activities underway by various agencies. It was agreed that such a document would provide a useful status report and should include specific recommendations to the Secretary.

The Committee discussed the draft outline and suggested additions, including information on outcomes as they relate to financial issues, a discussion of community engagement. Dr. Telfair advocated for more attention to be paid to the way populations are selected. He stated that the heterogeneity within those groups is not adequately taken into consideration, and recommended that criteria be developed that require researchers to look more closely at the population than just representation of the five major racial groups. The Committee discussed the possibility of requesting changes in the way FDA guides companies to ensure diversity in clinical trials. Dr. Fitzgerald recommended beginning public engagement on this issue right away.

Dr. Gutman wondered if a mechanism could be devised for better coordinating and integrating HHS activities in pharmacogenomics. He raised the idea of the Department appointing the equivalent of a "drug czar" at the level of Secretary Leavitt's deputies. This individual could map out a direction for the Department in pharmacogenomics.

Dr. Gurvaneet Randhawa recommended, in addition to identifying more useful outcomes, distinguishing efficacy outcomes from effectiveness outcomes. He also hoped the report would distinguish near-term initiatives from long-term initiatives. Dr. Khoury suggested adding recommendations on the surveillance and outcomes research infrastructure needed.

Planning for March 2006 SACGHS Meeting and Concluding Remarks

Cynthia Berry, J.D.
Acting SACGHS Chair

Ms. Berry led the Committee in summarizing the deliberations of the previous two days.

Despite the considerable challenges identified, Committee members were enthusiastic about the concept of mounting a large population research initiative on genes, environment, and common disease in the U.S. because of its potential to generate significant health benefits. Support for the concept would serve as the context for a report to the Secretary. The Committee was impressed with the range of policy issues and mechanisms identified by the scientific, public engagement and bioethics panels and agreed that sufficient information had been gathered to move forward with the report. The report will include the Committee's recommendations concerning the mechanisms that might work best to address the policy issues. The Committee reaffirmed the belief that the public must be involved in all stages of the development, planning, and conduct of any large population research initiative. The Large Population Studies Task Force will be augmented to include additional ad hoc members who will guide staff in the development of the report, including the gathering of additional information as needed. The Task Force was scheduled to complete a draft report with proposed recommendations in time for discussion at the March 2006 meeting.

Dr. Collins requested the Committee's viewpoint on whether it should proceed immediately with efforts to engage the public concerning views on the concept of a large population research initiative, including how it should be carried out. The Committee noted that its role is to advise the Secretary, but given how crucial public engagement is, the Committee did not wish to inhibit NIH from moving forward immediately.

Ms. Berry reminded the Committee of the upcoming National Academy of Sciences (NAS) report on intellectual property rights on genomic- and protein-related inventions. An NAS Committee member would be invited to the next meeting to present on the NAS report. Drs. Leonard, Evans and Winn-Deen agreed to review the NAS report and identify areas that may warrant the Committee's attention.

During the meeting, the Committee also reviewed and agreed to the proposed edits to the language of the Coverage and Reimbursement Report recommendations.

Next steps on genetic nondiscrimination efforts would include transmitting to the Secretary relevant data from Cogent Research's presentation on public attitudes toward genomics and genetics; suggesting relevant questions for Cogent's next survey(s) of the public and providers; and following up with Cogent Research to obtain additional relevant information, if available.

Next steps concerning pharmacogenomics include continuing to develop the report and drafting proposed recommendations for the Committee's consideration at the March or June 2006 meeting.

Ms. Berry closed the meeting by stating that the next SACGHS meeting will be held on March 27-28, 2006.

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.

Cynthia Berry, J.D.
SACGHS Acting Chair

Sarah Carr
SACGHS Executive Secretary

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