Secretary's Advisory Committee on Genetics, Health, and Society
Summary of Seventh Meeting
June 15-16, 2005
Bethesda, Maryland

Committee Members Present:
Reed V. Tuckson, M.D., Chair
Sylvia Mann Au, M.S., CGC (appointment pending)
Cynthia E. Berry, J.D.
Chira Chen (appointment pending)
James P. Evans, M.D., Ph.D. (appointment pending)
Kevin FitzGerald, S.J., Ph.D., Ph.D. (appointment pending)
Barbara Willis Harrison, M.S.
Debra G.B. Leonard, M.D., Ph.D.
Julio Licinio, M.D. (appointment pending)
Agnes Masny, R.N., M.P.H., M.S.N.
Edward McCabe, M.D., Ph.D.
Joan Y. Reede, M.D., M.P.H., M.S.
Huntington F. Willard, Ph.D.
Emily S. Winn-Deen, Ph.D.

***Ex Officios*/Alternates Present:**

Martin Dannenfelser (HHS/Administration for Children and Families)
Francis D. Chesley, Jr., M.D. (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)
Joseph Hackett, Ph.D. (HHS/Food and Drug Administration)
Sam Shekar, M.D., M.P.H. (HHS/Health Resources and Services Administration)
Francis Collins, M.D. (HHS/National Institutes of Health)
Alan E. Guttmacher, M.D. (HHS/National Institutes of Health)
Tim Leshan (HHS/National Institutes of Health)
Robinsue Frohboese, J.D., Ph.D. (HHS/Office for Civil Rights)
Julia Gorey, J.D. (HHS/Office for Human Research Protections)
Sandra Howard (HHS/Office of Public Health and Science)
Ellyn Beary (Department of Commerce)
Colonel Martha Turner, USAF, NC, Ph.D. (Department of Defense)
Daniel Drell, Ph.D. (Department of Energy)
Amy Turner, J.D. (Department of Labor)
Sherrie Hans, M.D., Ph.D. (Department of Veterans Affairs)
Peter Gray, J.D. (Equal Employment Opportunity Commission)
Matthew Daynard, J.D. (Federal Trade Commission)

Executive Secretary

Sarah Carr (HHS/National Institutes of Health)

Wednesday, June 15, 2005

Welcome and Opening Remarks

Reed V. Tuckson, M.D.
SACGHS Chair

Dr. Reed Tuckson, Chair, welcomed members and the public to the seventh meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). He 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.

Dr. Tuckson thanked three departing members of the Committee - Dr. Edward McCabe, Ms. Barbara Harrison, and Dr. Joan Reede. He then welcomed four new SACGHS members - Ms. Sylvia Au, Ms. Chira Chen, Dr. Jim Evans, and Dr. Julio Licinio. Dr. Tuckson noted that these new members would serve in an ad hoc capacity until the processing of their appointment papers was complete.

Dr. Tuckson acknowledged Committee members' representation at several meetings. Dr. Reede presented the Committee's work on genetics education of health professionals at the National Coalition for Health Professional Education in Genetics (NCHPEG) meeting in January, and Cynthia Berry presented the Committee's work on genetic discrimination and coverage and reimbursement of genetic tests and services at a meeting of the America's Health Insurance Plans (AHIP) Chief Medical Officers Committee in June.

Dr. Tuckson then reviewed key points from a presentation made by Drs. Joe Boone and Stephen Groft at the February SACGHS meeting on efforts to improve access to quality genetic tests for rare diseases, many of which are considered genetic conditions. Genetic testing is essential to diagnosis and management of these conditions; however, the development of tests has not kept pace with research findings. At a 2004 conference, multidisciplinary experts developed recommendations designed to improve health outcomes for affected individuals and their families. A second conference is being planned for September 2005 to improve national awareness of the subject.

Turning to the tasks of the meeting at hand, Dr. Tuckson reviewed the 12 issues identified as priorities for the Committee in March 2004. He stated that the meeting would address two of these issues in depth: 1) coverage and reimbursement of genetic tests and services, and 2) pharmacogenomics. In addition, updates would be provided on three other topics of interest: 1) genetic discrimination, 2) direct-to-consumer (DTC) marketing, and 3) large population studies. Consideration of the issue of patents and access was deferred until publication of a report from the National Academy's Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions. A representative of that committee will be invited to brief SACGHS on its key findings and recommendations.

Dr. Tuckson concluded his introductory remarks by providing an overview of the agenda for the 2-day meeting.

Dr. Tuckson then turned the meeting over to Ms. Agnes Masny for an update from the SACGHS Genetic

Discrimination Task Force.

Genetic Discrimination Session

Update on SACGHS Efforts
Agnes Masny, R.N., M.P.H., M.S.N.
Chair, SACGHS Task Force on Genetic Discrimination

Ms. Masny provided an update on developments concerning Federal genetic nondiscrimination legislation. She stated that the Genetic Information Nondiscrimination Act of 2005 (H.R. 1227) was introduced in the House on March 10, 2005 and referred to three subcommittees. The bill is sponsored by Representative Judy Biggert and has more than 100 co-sponsors. The bill is very similar to the one passed by the Senate (S. 306), with the exception of some provisions that would amend the Internal Revenue Code. These provisions pertained only to church plans and were deleted from the House bill.

On May 4, 2005, the Committee's letter to Secretary Mike Leavitt on this issue was delivered, along with four enclosures. These included a compilation of public comments and articles on genetic discrimination, a DVD that highlighted the public testimony the Committee received on this issue at its October 2004 meeting, a copy of AHIP's February 2005 letter to Representative John Boehner, and a legal analysis of current gaps in genetic discrimination protections. The letter to the Secretary summarized the deep-seated fears expressed by the public. It also urged him to use his influence to encourage enactment of Federal genetic nondiscrimination legislation and recommended that he meet with key stakeholders who are interested in advancing consensus-building.

The Committee then viewed the DVD developed by the Task Force that highlights the public testimony received during the October 2004 SACGHS meeting on the fear of genetic discrimination. At the conclusion of the video, Ms. Masny stated that 150 copies had been generated for broad dissemination.

Ms. Masny turned to Mr. Peter Gray to summarize the legal analysis that was commissioned by SACGHS to determine the extent of Federal safeguards against genetic discrimination in health insurance and employment.

Overview of Legal Analysis
Peter Gray, J.D.
Equal Opportunity Employment Commission

Mr. Gray presented the findings of Mr. Robert Lanham, J.D., a consultant to the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA). He clarified that the presentation did not necessarily reflect the official views of the Equal Employment Opportunity Commission (EEOC). The scope of analysis performed by Mr. Lanham included Federal statutes governing health insurance, Federal protections for the privacy of medical information, State genetic nondiscrimination and privacy laws, Federal employment nondiscrimination statutes, Constitutional protections, and protections for Federal employees. EEOC, Department of Justice, Department of Labor, Centers for Medicare & Medicaid Services (CMS), and the Office of Civil Rights reviewed the resulting report for accuracy.

Mr. Gray stated that the report consisted of two sections, the first addressing health insurance and the second addressing employment. Speaking first on health insurance issues, Mr. Gray noted that approximately 60 percent of the U.S. population is covered by employment-based health insurance. Of these, most are covered by the Employee Retirement Income Security Act (ERISA) and the Health Insurance Portability and Accountability Act (HIPAA). HIPAA amends ERISA and other statutes to prohibit health plans and issuers from imposing a pre-existing condition exclusion on the basis of genetic information (unless there is an actual diagnosis of a condition) or establishing eligibility requirements for any individual based on genetic information. However, nothing bars the establishment of a group rate based on an individual's genetic information. HIPAA prohibits health insurance issuers in group and small group markets from refusing to renew a policy based on an enrollee's genetic information. It would not, however, restrict an issuer from taking genetic information into account when determining the overall premium. In fact, the report states that an insurer could require an individual to take a genetic test as a condition of coverage for the purpose of determining the premium for the entire group. In the individual market, HIPAA guarantees that certain individuals who have lost group coverage have the opportunity to purchase individual coverage without an exclusion based on genetic information. Again, however, the premium can be based on genetic information.

The report states that the scope and depth of HIPAA protections are incomplete, leaving significant gaps in coverage. A group health plan or issuer is not prohibited from: requesting, purchasing, or otherwise obtaining genetic information about an individual; requiring an individual to take a genetic test as a condition of coverage (not to deny coverage to the individual but to help determine premiums for the group); or charging all members of a group higher premiums on the basis of an individual's genetic information. Mr. Gray said that charging higher premiums could make health insurance too costly for small employers, and thus have the same effect as denying coverage. In addition, the pre-existing condition exclusion and nondiscrimination provisions do not apply to very small plans, retiree-only coverage, or self-insured non-Federal Government plans that elect to take advantage of a statutory exemption. HIPAA nondiscrimination provisions do not apply to individual health insurance policies (10 to 15 percent of covered individuals have such policies and the numbers are expected to increase). Despite the guaranteed renewability requirement, an issuer is not prohibited from adjusting a premium for an individual policy on the basis of genetic information.

Mr. Gray described the Social Security Act (SSA) and noted that Federal law sets national standards for Medicare supplemental (Medigap) policies. Medigap policies cover additional benefits not covered under Medicare and some Medicare deductibles and coinsurance payments. Although SSA contains provisions that prohibit discrimination in the pricing or issuance of Medigap policies on the basis of health status or medical conditions, it does not specifically prohibit discrimination on the basis of genetic information.

Title III of the Americans with Disabilities Act (ADA) states that no individual will be discriminated on the basis of disability, and all individuals, regardless of disability, will have access to the full enjoyment of goods, services, facilities, privileges, and advantages of any public accommodation. Although there are Federal court cases and comments by legal scholars arguing that Title III requires equal access not only to insurance offices but to the terms of insurance policies, the prevailing sense among most Federal appellate courts is that the ADA does not apply to the content of insurance policies. The report notes that even if Title III did apply to the content of insurance policies, a separate "safe harbor" provision in the

ADA limits its reach. The safe harbor provision means that Titles I through IV of the ADA are not to be interpreted to prohibit or restrict an insurer from underwriting, classifying, or administering risks that are consistent with State law. To date, the safe harbor provision has been broadly construed by the courts in favor of insurers.

Addressing the HIPAA Privacy Rule, Mr. Gray said it establishes the minimum national standard for protecting the privacy of identifiable health information. The definition of health information under this rule is quite broad, covering all identifiable information, including genetic information and family history. The report suggests, however, that there are gaps in the privacy rule, as it does not bar the use of medical information for activities such as underwriting and premium rating. It also does not limit employers' access to health and genetic information.

An analysis of State laws found that 47 States and the District of Columbia restrict or limit the use of genetic information in determining health insurance rates or eligibility in group or individual insurance plans. Twenty of these States have enacted privacy laws that are specific to genetic information, but they vary widely and are inconsistent in scope, terminology, and enforcement, resulting in different levels of protection. In addition, State-level protection against discrimination by health plans and issuers is limited, because self-insured employee benefit plans are generally exempt from State regulation under ERISA.

Mr. Gray then presented the report's findings on genetic discrimination in employment. As of August 2004, 32 States have restricted the use of genetic information in the workplace and 9 additional States were considering such legislation. Most of these laws establish greater protection for genetic information than for medical information generally, but they vary widely, with differing protections and terminology. Most do not encompass family medical history. The diversity of these laws can impose substantial burdens on companies operating across State lines.

No single Federal law directly prohibits or protects against genetic discrimination in employment. Title I of the ADA is the primary Federal law that addresses these issues. It prohibits discrimination in employment against individuals who have a physical or mental impairment that substantially limits them in a major life activity; who have a record of such impairment; or who are "regarded as" having such an impairment. An example of the latter is an individual who has a genetic predisposition for a disease but is asymptomatic, yet is not hired because of the disease risk.

EEOC interprets the ADA as prohibiting genetic discrimination and settled its first court case on the issue in 2002. An employer was requiring employees to have a genetic test, and the Commission's position was that the test was not job-related or consistent with business necessity. Because the case was settled, no court has addressed the Commission's view on the matter.

Mr. Gray described the ADA's limitations. Its scope has been narrowed since 1995 by court cases that have limited the definition of disability. The report suggests that these cases make it unlikely that the Supreme Court would find that a genetic predisposition to disease or disorder constitutes a disability. In addition, the ADA does not prevent employers in all cases from asking for genetic information or requiring that individuals, including job applicants, take genetic tests. The law allows employers to use genetic information as the basis for refusing to hire an employee if hiring could be costly in terms of

attendance, productivity or insurance. Some of the traditional defenses employers use in ADA cases include maintaining that the individual lacked qualifications, that the disabled worker might pose a threat to self or others, or that employment decisions were based on factors other than those alleged.

Some Federal protections are provided through Title VII of the Civil Rights Act of 1964. This law prohibits employment discrimination on the basis of race, color, religion, sex, and national origin. The report states that it provides protection against discrimination on the basis of a person's genetic makeup when that discrimination disproportionately affects individuals belonging to a protected group. For example, a refusal to hire genetic carriers of the sickle cell disease trait or Tay-Sachs could constitute discrimination on the basis of race/ethnicity. If an employer selected a specific protected group (such as women) for genetic testing, this would also constitute a violation of Title VII.

Federal Constitutional protections have been addressed by the U.S. Court of Appeals (Ninth Circuit). The Court stated that an individual has the highest expectation of privacy in the area of genetic information. It also ruled that Fourth Amendment protection against unreasonable search and seizure applies both to the taking and the analysis of blood samples. These Federal Constitutional protections are limited; however, as they apply only to governmental action and, in specific instances, courts will weigh the infringement of individual rights against the public health or other interests.

Protections for Federal employees are provided under Executive Order 13145, which prohibits Federal government departments and agencies from using protected genetic information to discharge, not hire, or otherwise discriminate against any applicant or employee with respect to compensation or the terms, conditions, or privileges of employment. However, enforcement of the Executive Order is through the Rehabilitation Act, and therefore it must be shown in court that a violation of the Act occurred in order to enforce Executive Order 13145.

The report concludes that there are no Federal laws that directly and comprehensively address the issues raised by the use of genetic information. Although laws and court decisions address parts of these issues, they leave substantial gaps in coverage and offer inconsistent safeguards. The existing avenues for relief are both uncertain and likely to lead to costly litigation. Therefore, current law does not adequately protect against genetic discrimination based on genetic predisposition. A national, uniform standard is needed to fully protect the public and to allay concerns about the potential for discrimination.

Congressional Update
Jaimie Vickery
Legislative Assistant
Office of the Honorable Judy Biggert, U.S. House of Representatives

Dr. Tuckson introduced Ms. Jaimie Vickery, who updated the Committee on the pending genetic nondiscrimination legislation. Ms. Vickery works for Congresswoman Judy Biggert, who introduced H.R. 1227 in the House. Ms. Vickery commented on the legal analysis presented by Mr. Gray and agreed that current laws offer only a patchwork of protections against genetic discrimination. She stated that genetic privacy can only be protected by enacting legislation that specifically prohibits differential treatment on the basis of genetic information. H.R. 1227 would address this concern by prohibiting employers or health insurers from making employment or coverage decisions based solely on genetic

information. The bill is similar to one proposed by Louise Slaughter in the last Congress; however, it has some differences that make it more "business friendly." Ms. Vickery said these changes do not substantially alter the protections of the bill or its enforcement mechanisms.

The House bill has now been referred to three committees: Education and the Workforce, Energy and Commerce, and Ways and Means. Ms. Vickery noted that the Ways and Means Committee was expected to support the bill, while Education and Workforce held a hearing on genetic discrimination in July 2004 but nothing came of it. She explained that some in the business community are opposed to the bill because they fear administrative burdens or unwelcome restrictions on their business practices. Congresswoman Biggert is working with these groups, attempting to address their concerns without compromising the guarantees of genetic privacy. She is cautiously optimistic that these groups will adopt a neutral stance and will not actively work against H.R. 1227.

Ms. Vickery stated that one quarter of Congress is co-sponsoring the bill. However, most supporters are Democrats in a Republican-controlled Congress. Ms. Vickery emphasized that the bill's content is bipartisan and they are seeking more Republican co-sponsors. She said a version of this bill has been introduced every year since 1997 and that H.R. 1227 has made it further in the process than its predecessors. Ms. Vickery thanked the Committee for prioritizing and supporting this issue.

Committee Discussion

Dr. McCabe asked Ms. Vickery to describe the steps being taken to elicit support from business-friendly groups. Ms. Vickery discussed these strategies, which focus on in-depth negotiations with the organizations in question. They also are bringing to the attention of Congressional representatives the constituents who would be affected by the legislation. Ms. Vickery said the greater the support is for the bill, the harder it will be for these groups to oppose it, both politically and from a public relations standpoint. Ms. Masny commented that the districts of the individuals who testified before the Committee could be identified so the DVD could be sent to their representatives.

Dr. Francis Collins asked Ms. Vickery for her opinion on whether hearings are likely to occur, since the bill will not move forward without them. He also asked whether the bill would be more likely to pass if the employment protections were stripped out and it applied to health insurance only, although he said it would be unfortunate if that were to happen. Dr. Collins expressed his disappointment in seeing the continuing opposition of the business community, and he said that in States that have passed nondiscrimination legislation, there have been no frivolous lawsuits. In his opinion, the evidence for these lawsuits as a risk to business practices is not very compelling. Ms. Vickery replied that many genetic discrimination problems arise in the employment arena and the bill's sponsors would not be amenable to eliminating the employment title. She also stated that the House committees are more open to holding hearings on this issue than at any time in the past, although there are no guarantees.

Dr. Tuckson asked Ms. Vickery if there were ways to address the business community's fear of frivolous lawsuits directly in the bill. She explained that the current bill has provisions that can prevent a claim from being taken to court. In addition, there is a cap on the award amount that can be received based on the size of the company.

Dr. Emily Winn-Deen pointed out that the Committee has responded to two of the key objections to the legislation. The first objection often cited - that discrimination is not actually happening - is weakened by the public testimony and DVD. The second objection - that there is already adequate protection under the law - was called into question by the legal analysis commissioned by the Committee. She asked if there were other objections that could be specifically addressed by the Committee through the commissioning of additional reports or other actions. Dr. Vickery said the report on the legal analysis will be extremely helpful and she requested that a copy of the Committee's reports and DVD be sent to Congresswoman Biggert's office. She also stated that presenting this information in a concise format to staffers on the Hill would add to its benefit. Ms. Vickery commented that the Hill has been focused on the stem cell issue for some time, and now that they are moving away from that topic, the time is right to educate members on the importance of genetic nondiscrimination legislation.

In response to a question from Dr. Licinio, Ms. Amy Turner said the legal analysis supports the finding that once pre-existing conditions are diagnosed, they are covered by HIPAA protections. Ambiguity remains when there is genetic information but no diagnosis. The pending legislation is attempting to address such gaps.

Dr. McCabe requested that he go on the record stating that those who have written that there is no genetic discrimination should be ashamed of themselves.

Dr. Tuckson asked whether, in light of the fact that the Secretary has the materials developed by the Committee, there is further action to be taken. Ms. Masny asked if the Committee should extract some of the public comments from the professional and business organizations that voiced support for the legislation and send those to the Secretary as well. Dr. Tuckson said the idea was worth considering but he was concerned about adding more materials to the voluminous amount already delivered.

Direct-to-Consumer Marketing of Genetic Tests Session

Secretary Leavitt's Response to SACGHS Letter and Relevant Agency Activities
Dr. Tuckson

Dr. Tuckson recapped the Committee's work on direct-to-consumer (DTC) marketing of genetic tests and services, one of the Committee's priority issues. The Committee discussed the advertising and sale of dubious genetic tests and products over the Internet. At a previous meeting, Mr. Matthew Daynard presented on the role of the Federal Trade Commission (FTC) in regulating false and misleading advertisements and the commission's need for documentation of harm. Committee discussions addressed how spurious claims may drive consumers to waste precious health care resources or delay the introduction of valid therapies. Dr. Tuckson stated that consumers are vulnerable, in part because genetics can be confusing to the public, and that DTC marketing may add to the confusion. In December 2004, SACGHS sent a letter to the Secretary expressing concern about the potential for DTC marketing of genetic tests to harm consumers. The letter requested clarification of the role of the Food and Drug Administration (FDA) in monitoring DTC marketing and recommended that HHS collect data on the public health impact. It also asked that HHS collaborate with FTC on monitoring activities.

In March, the Committee received a response from the Secretary, and efforts have begun to address the

Committee's concerns. During an interagency teleconference in April, two working groups were established to respond to the recommendations. Mr. Daynard reported that DTC Advertising Work Group, composed of representatives from FDA, FTC and NIH, developed a compendium of genetic tests offered through the Internet and is examining the science behind the health and economic claims made by each product or service. The work group is trying to identify a company that makes a claim about its genetic test that is not supported by competent or reliable scientific evidence. He said the FTC needs a "slam dunk" case and that a lawsuit in this area would require an entirely new application of the FTC Act. Once good targets are identified, Mr. Daynard will take this information to the FTC Division of Advertising Practices and the Bureau of Consumer Protection. If they agree that a case is strong, they will take it to court or to an administrative law judge. Some of the claims under consideration include tests that are advertised as promoting long-term weight loss, determining susceptibility to cancer, or for guiding the prescription of nutritional diets that supposedly prevent disease. FDA is checking the science of these tests in terms of predictability.

Dr. Tuckson asked how the working group was deciding on a test case, as it seems there are many examples that could be used. Mr. Daynard described the complex process of examining the specific claim, the science supporting it, and the seriousness of the condition that the test purports to diagnose. They are looking at false claims for cancer cures, AIDS cures, and HIV test kits.

Dr. Muin Khoury then spoke about the DTC Data Work Group formed to address data collection on the public health impact of DTC marketing of consumer tests. He stated that they are focusing in two areas: genetic tests advertised directly to consumers but that are offered with the involvement of a health provider and those that are performed outside the health care delivery system. The ultimate goal is to determine whether people are being helped or harmed by direct-to-consumer marketing of genetic tests.

The work group discussed ways to proceed and initially considered partnering directly with private companies to seek data on those who use their services. However, there are business concerns and privacy issues that may not allow them to do this. In addition, they would need to communicate closely with the DTC Advertising Work Group to make sure they are not working with a company targeted by that group. The work group also considered pursuing information gathering through a health maintenance organization (HMO) research network, but acknowledged that this will miss out-of-pocket purchases and direct access. A third idea raised was to piggyback on existing, ongoing surveys conducted by the Centers for Disease Control and Prevention (CDC) and State health departments. Dr. Khoury mentioned CDC's Health Styles Survey and the State-based Behavioral Risk Factor Surveillance System as examples of existing data collection systems. The work group is exploring the possibilities of this approach.

FDA's Role in the Oversight of Direct-to-Consumer Marketing of Genetic Tests
Deborah Wolf, J.D.
Office of Compliance, Center for Devices and Radiological Health, FDA

Ms. Wolf stated that DTC marketing of genetic tests is taking place in the larger context of increased marketing of medical products and services in general. However, concerns raised about advertising genetic tests are different from concerns about drug and device advertisements. She said FDA's role in this new arena is uncertain. Using the example of *in vitro* diagnostics (IVD), Ms. Wolf said such

techniques provide information, not treatment. Therefore, FDA reviews their safety and efficacy differently than for drugs or devices used for treatment.

Ms. Wolf described the various aspects of promotion, labeling and advertising of medical devices examined by the FDA. Device labeling includes any sort of label, package insert, handout, glossy brochure, or material that's distributed with a device. Section 502(a) of the Act provides that a device is misbranded if its labeling is false or misleading. "Advertising" is not defined by the Act; however, the FDA Center for Drug Evaluation and Research (CDER) refers to, "...advertisements in published journals, magazines, other periodicals and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."

Ms. Wolf described additional regulations that pertain specifically to restricted devices. There are currently only three types of restricted devices: analyte-specific reagents, drug abuse test kits, and hearing aids. FDA can restrict the sale and distribution of these devices and may make the device available only on the written or oral authorization of a licensed practitioner. Section 502(q) of the Food, Drug, and Cosmetic Act provides that a restricted device is misbranded if the advertising is false or misleading, or if it is sold, distributed, or used in violation of any regulations prescribed under 520(e). Section 502(r) of the Act provides that a restricted device is misbranded if its advertising does not include a brief statement of the intended uses of the device and the relevant warnings, precautions, side effects, and contraindications.

Providing more detail on ASRs, Ms. Wolf said that labels and advertisements for Class I ASRs must make it clear that analytical and performance characteristics are not established. Labels and advertisements for Class II and III ASRs must state that analytical and performance characteristics are not established except as a component of a specific test. This prevents marketing claims from being made about the intended use of an ASR. 21 CFR 809.30(d) requires that advertising must include the identity of the reagent and the analyte.

Ordering of in-house tests developed using analyte-specific reagents is limited under 520(e) to physicians and other persons authorized by applicable State law to order such tests, unless they are sold to IVD manufacturers or organizations using reagents for purposes other than medical diagnosis. Their sale is restricted to IVD manufacturers, high-complexity clinical laboratories regulated under the Clinical Laboratory Improvement Amendments (CLIA) or Veterans Health Administration (VHA), and organizations that use reagents for other than medical diagnostic purposes (i.e., forensics, academic research, etc.).

Ms. Wolf explained that under the regulations, no one except physicians should have access to "home brew" tests that are developed in laboratories using analyte-specific reagents. However, in some States, the law allows physicians to write prescriptions for consumers who order the tests through websites. Currently, it is not clear how FDA can apply the law to restrict laboratories from accepting orders from someone other than a physician. The key question is whether laboratory-developed genetic tests can be considered a device. Ms. Wolf stated that limiting access to the tests would not prevent the laboratories from advertising them. FDA's jurisdiction over a product generally is initiated when a company claims a particular use for it. It is an open question whether advertisement of an ASR's specific use would be sufficient cause to require premarket approval.

FDA is currently focusing on risk-based reviews of genetic tests, in terms of both public health and resources. They are concerned about the validity of the tests and the impact of providing incorrect results, as important health care and employment decisions could be made based on false negative or false positive results. During these reviews, the agency considers the seriousness of the disease or condition being tested, the role of genetic counseling, and the burden genetic information may place on individuals. To date, FDA has cleared about 12 genetic test kits.

FDA and FTC have created a chart that identifies Internet companies that make claims about genetic testing on their websites. Claims include the ability to predict adverse drug reactions, tendencies toward obesity, and susceptibility to serious conditions such as cardiac disease, cancers, bone mineral density, osteoporosis, autoimmune disease, chronic disease, and a number of infectious diseases. The two agencies are working closely to coordinate the information collected to date.

Committee Discussion

Dr. Winn-Deen asked if the FDA has control over the laboratories that purchase ASRs from research supply houses rather than from certified manufacturers. She felt that certified manufacturers are not the Committee's primary concern. Dr. Debra Leonard expressed similar views. Dr. Joe Hackett replied that the agency is not looking specifically at the laboratories or companies that produce their own ASRs and perform in-house genetic tests. Companies come under FDA regulations only if they purchase the reagents elsewhere. He said the problem FDA is trying to address is whether the activities within the laboratory, as well as the ASR being sold to a laboratory, can be regulated by the agency. The other open question is whether home brew tests can be regulated. Ms. Wolf agreed to obtain more information on these issues from others at FDA.

Dr. Licinio stated his opinion that if the mainstream health care system does not make testing available, people will find other sources, regardless of any regulations.

Dr. McCabe asked if there was any action the Committee could take that would help FDA define Internet promotion as labeling or advertising. Ms. Wolf felt that SACGHS could probably not be very helpful in this regard.

Dr. Huntington Willard asked if anyone is looking at DTC marketing of genotyping or sequencing that uses swabs mailed by consumers. He expressed concern that the public is not prepared to interpret and act on the results they receive. Ms. Wolf asked for the name of these products and agreed to look into the companies marketing them.

Dr. Evans made the point that the Committee should try to find cases that are clearly not supported by science and that potentially could harm the public. Dr. Tuckson agreed that the Committee is primarily concerned about cases in which there is egregious behavior. He recommended that SACGHS write to the Secretary, acknowledging the importance of the two inter-agency work groups created to address this issue and offering the Committee's assistance in identifying appropriate cases for review.

Dr. Tuckson wondered if government scrutiny of the matter would help curtail some of these activities.

Mr. Daynard stated that this does have an effect, and for that reason, FTC is cautious about making statements that might negatively affect legitimate businesses. The agency issues consumer alerts when they are clearly warranted. Ms. Wolf commented that FDA's experience is that Government warnings work in some cases and not in others. Dr. Tuckson emphasized that the Committee does not want to hamper legitimate business, but he believes it is important to make it known that DTC marketing of genetic tests is being investigated. Mr. Daynard said he would speak to others at FTC about issuing an alert on this topic.

Ms. Wolf noted that FDA provides some educational information for the public on the agency's website. She suggested that the Committee consider this method for educating the public about genetic testing. Dr. Kevin Fitzgerald asked if Ms. Wolf could determine whether the consumer information on FDA's website appears in Web search results. He said there might be an opportunity to collaborate with various search engines. Ms. Wolf agreed to look into it.

Dr. Tuckson summarized the Committee's recommendations, which includes a follow-up letter to the Secretary expressing approval for the inter-agency work groups and urging them to find appropriate cases. In addition, the Committee will send information on relevant case examples as it becomes aware of them. The letter also will recommend increased public education on DTC marketing of genetic testing and make the Secretary aware of the lack of clarity concerning Internet promotion as a form of advertising.

Large Population Studies Session

Update on SACGHS's Work on Large Population Studies
Huntington Willard, Ph.D.
Chair, SACGHS Large Population Studies Task Force

Dr. Willard presented the history of the Committee's interest in the topic of large population studies on the influence of genomic or genetic variation and environmental factors on complex diseases and/or other traits. He stated that such large population studies involve a large and usually diverse cohort of subjects. A number of these studies are underway throughout the world. Planning has already started in the U.S. for a National Children's Study that will focus on the influence of environmental exposures on childhood disease, and the Veteran's Administration has been considering a project in clinical genomic medicine.

Dr. Willard reviewed the ongoing work of the Committee and Large Population Studies Task Force in this area. During its March 2005 meeting, the Committee held a session on the scientific, social, policy, and legal issues relating to large population studies. During this session, the Committee also received an update on several Federal programmatic activities under consideration or underway. After the March meeting, the Task Force held a conference call in which members agreed that numerous questions remained and that it would be premature to endorse a large population study. The Task Force decided that more information was needed from the broader scientific community and the public at large before such a recommendation could be considered.

More recently, the National Human Genome Research Institute (NHGRI), on behalf of NIH, posted a

report developed by a group of experts commissioned to examine the scientific foundations and study design issues related to a large population study in the U.S. Dr. Christopher Hook served as the Committee's liaison between SACGHS and the NIH Work Group. Dr. Willard said that the Committee may wish to address any significant remaining issues and asked Committee members to review the report in detail.

Some guidance on the Committee's role in this issue has been received from Dr. Elias Zerhouni, NIH Director. Dr. Zerhouni has indicated that the Committee should focus on key policy issues and the processes and pathways that might be used to address these issues, rather than on the scientific merits of a large population study. For example, who should be included in the decision-making process? What questions need to be addressed? Dr. Willard said the Committee could be helpful in providing guidance to NIH and HHS as the agencies make decisions about undertaking a study of this magnitude and complexity.

Committee Discussion

Dr. Collins said the NIH Work Group would welcome SACGHS's comments on the report. He stated that the Committee's help in gathering public input would be valuable. He noted that public support would be critical to success. Dr. Collins raised the idea of organizing a session at the October SACGHS meeting for the purpose of obtaining public input. Dr. Tuckson was in favor of the idea and suggested bringing in representatives from the scientific community as well. Ms. Masny agreed, and also suggested that the Committee invite experts with a background in ethics.

Dr. Winn-Deen said that the Committee should not be the only entity soliciting public opinion, although it can serve as one of many public forums. Dr. Collins stated that surveys, focus groups, and possibly town hall meetings would also be conducted in addition to the SACGHS session. Dr. Willard asked the group to consider the idea that NIH may not be the appropriate entity to conduct outreach to obtain public opinion because the agency could be seen as having a vested interest in the outcome. Dr. McCabe agreed and stated that NIH can have a role and SACGHS can serve as one public forum. Dr. Collins noted that CDC and the Environmental Protection Agency have also been involved in the planning process. He suggested that if NIH conducts substantial public outreach, the agency will likely contract with an outside organization to maintain some distance.

Dr. Tuckson asked Dr. Lana Skirboll from the NIH Office of the Director for her perspective on the October meeting session being discussed. Dr. Skirboll confirmed that the Committee was appropriate to call for public opinion. She also asked that the Committee recommend consultations both within and outside of the NIH community concerning the pathways and processes needed for a large population study.

Dr. Tuckson proposed that the Large Population Studies Task Force plan a session to coincide, if possible, with the October SACGHS meeting. This meeting would be used to solicit public comment and input from the scientific and ethics communities on issues to consider when proceeding with a large population study. SACGHS will serve as one source of input to inform the process but other Federal agencies also will be addressing the issue. The meeting will contribute to public education on large population studies as participants listen to and gain an understanding of public concerns. The Task Force

will decide the duration of the meeting and its location, as well as consider the specific methods for obtaining input. The Task Force also will consider any possible consultations that may be needed. The Committee unanimously approved this recommendation.

Public Comments

Greg Rabb
Independent Consultant representing the Advanced Medical Technology Association (AdvaMed)

Mr. Greg Rabb explained that AdvaMed is a technology association representing the medical device industry. AdvaMed has closely followed the Committee's work concerning coverage and reimbursement of genetic tests and services. AdvaMed members submitted comments addressing both the June 2004 and April 2005 versions of the draft report on this issue. Mr. Rabb stated that Advamed would be releasing a report on the value of *in vitro* diagnostic tests shortly. Developed by The Lewin Group, the report addresses factors associated with innovation, adoption, and diffusion of genetic tests. The report was commissioned to inform various audiences about the diagnostics industry and it identifies barriers that hinder innovation and patient access. Mr. Rabb said the current coverage and payment system is lacking and the report makes recommendations for reform. AdvaMed will provide copies of the report to SACGHS.

Sharon Terry
Genetic Alliance and the Coalition for Genetic Fairness

Ms. Sharon Terry stated that the Genetic Alliance has over 600 organizational members, most of which are genetic disease advocacy groups and underserved community-based organizations. The Coalition for Genetic Fairness is composed of the Genetic Alliance and more than 100 additional groups and companies dedicated to the enactment of substantial genetic discrimination legislation. Ms. Terry offered the assistance of these alliances to the Committee. She acknowledged that the major arguments for genetic nondiscrimination legislation had been addressed earlier in the meeting and asked the Committee to continue to encourage the Secretary to articulate the urgency of this issue. Ms. Terry said their coalition has been working with Congresswoman Biggert to move H.R. 1227 forward. They do face opposition from some in the business community, but she believes this barrier will not deter the passage of legislation. She stated that research is being impacted as individuals shy away from clinical research out of fear of being discriminated. She said the coalition is working hard to gain the support of Republicans in all States through mobilization of their 14 million grassroots members.

Dr. McCabe asked if the coalition is affiliated with the Chamber of Commerce or small businesses affected by genetic discrimination. Ms. Terry replied in the affirmative but said these members are less inclined to comment. They claim they would be more vocal if the Chamber would lessen its resistance to the legislation. The Chamber says they would be more vocal if these groups would come forward more overtly. Ms. Terry said the coalition has been trying to appeal to biotech companies and PhRMA.

Coverage and Reimbursement Session

Dr. Tuckson described the efforts of the Coverage and Reimbursement Task Force in soliciting

comments from the public on the draft report on this issue, which has been in development since March 2004. He explained the extensive review process that had taken place and asked the Committee to weigh the public comments carefully before making additional changes. He then turned the floor over to Ms. Cindy Berry for an update on the public feedback received on this document.

Overview of Public Comments on SACGHS Draft Report on Coverage and Reimbursement of Genetic Tests and Services
Ms. Cynthia Berry, J.D.
Chair, SACGHS Coverage and Reimbursement Task Force

Ms. Berry stated that the purpose of the report is to describe the current state of the problems associated with coverage and reimbursement of genetic tests and services and to offer recommendations to the Secretary for removing unnecessary barriers to coverage. The report's ultimate objective is to improve access and appropriate utilization of genetic tests and services throughout the health care system.

Recently, the Committee issued a request for public comments on the draft report and recommendations. The public comment process took place from April 4 to May 6, 2005. Four outreach mechanisms were used: the SACGHS website; a notice in the Federal Register; the SACGHS distribution list, which reaches almost 1,000 individuals; and a targeted mailing to 34 individuals and organizations with relevant expertise. A total of 86 separate comments were received, including 61 individuals and 25 organizations. The comments represented health providers, health plans, academia, patients/consumers, and students.

Ms. Berry stated that those who commented were generally positive about the recommendations. Different approaches were offered for refining the recommendations. Others provided information to help clarify technical points in the body of the report. Several commenters shared anecdotes illustrating the link between inadequate coverage and access problems. Additional barriers were described in the area of inadequate billing and reimbursement mechanisms for non-physician genetic counselors. Numerous comments encouraged SACGHS to specifically recognize the American Board of Genetic Counseling (ABGC) and the Genetic Nursing Credentialing Commission (GNCC) in the recommendation concerning direct billing. Several comments discussed the potential impact of the recommendations on health care resources and the health care system's long-term capacity to handle the costs of genetic testing.

Ms. Berry said all the comments have been reviewed by the Task Force. The Task Force has proposed several changes to the recommendations based on the public comments received. Committee members were provided with marked-up versions of the report's text in their table folders so they could compare the previous version with the revised version.

Committee Discussion

The Committee then spent considerable time reviewing and editing the wording of each recommendation in detail. The following paragraphs describe these edits and the full Committee's reaction to them.

Recommendation 1 addresses evidence-based coverage decision making for genetic tests and services. A

sentence that was considered redundant was deleted and several minor changes were made that clarified meaning.

Recommendation 2 addresses Medicare's influence on the private insurance market. The word "pediatric" was deleted and the recommendation modified to place emphasis on the benefits of prevention and screening components.

Recommendation 3 addresses the Medicare coverage decision-making process. This recommendation was revised to add language urging CMS to consider a mechanism that would automatically initiate a national coverage review process for any test or service that is approved for coverage by more than a defined number of local carriers.

Recommendation 4 addresses the Medicare screening exclusion. Ms. Berry conveyed information received from CMS representatives through personal communication, specifically that CMS would not be able to act on the Committee's recommendation as currently worded in the absence of statutory authority. Rather, CMS suggested that the recommendation be directed to Congress rather than CMS. Ms. Berry had not been able to obtain a formal legal opinion from CMS to conclusively determine whether this is true. Dr. Tuckson suggested that the Committee ask the Secretary to study the issue. The Committee decided that in order to move forward on the recommendation, the Secretary would have to explore the facts as a next step. The Committee agreed that the wording of the recommendation did not need to be changed.

Recommendation 5 addresses Medicaid coverage of genetic tests and services. The Committee agreed to refer to Recommendation 1 in parentheses, as the two recommendations are related.

Recommendation 6 addresses the Medicare clinical laboratory fee schedule. Dr. Leonard asked if CMS has rules that govern how inherent reasonableness evaluations will be conducted, in order for CMS to act on this recommendation. The Committee discussed whether to add wording to the recommendation directing CMS to establish a mechanism for conducting these evaluations. They also discussed whether to add language indicating that the Committee would like CMS to take action as soon as possible. The Committee decided to leave the Task Force's wording as written, with the addition of the words "expeditious implementation."

Recommendation 7 addresses billing and reimbursement for genetic counseling services and consists of five sub-recommendations. She said the first point was more complex than the others because it addressed the mechanism by which direct billing decisions for genetic counseling services should be made. Some public comments requested that the Committee reword the recommendation to recognize ABGC- and GNCC-certified health professionals as qualified providers of genetic counseling services allowed to bill independently, and thereby exempt from the proposed review mechanism. The Task Force's opinion was that it was not appropriate for the Committee to determine which genetic counseling providers are qualified to bill directly or to endorse specific organizations above others. Instead, they encouraged these types of determinations to be left to the Secretary but added a footnote stating that more information about these professional societies and their credentialing standards could be found in an appendix to the report.

As discussion of the recommendation began, Dr. Tuckson asked if there was any new information or additional clarity that might empower the Committee to make a specific determination. Ms. Berry replied that no new information had been received by the Committee or Task Force. Ms. Barbara Harrison said she disagreed that there was not enough information to support listing ABGC and GNCC specifically in the report. Ms. Berry stated that the Committee had not received enough information on these issues for SACGHS to make an informed determination on who should be allowed to bill directly. Dr. McCabe believed the footnote and reference to the appendix supplemented the recommendation in a balanced way. Ms. Au was concerned that the footnote might be overlooked or separated from the body of the recommendations. She felt strongly that it should be moved up into the actual recommendation and urge examination of the credentialing procedures of genetics counseling organizations such as ABGC and GNCC. The Committee agreed that this approach represented a fair compromise.

Dr. Tuckson clarified that because the Federal Government cannot create the mechanism described in the first bullet, the Committee is recommending that the Government, through the Secretary of HHS, use its convening authority as a catalyst for action. He emphasized that no inappropriate authority is being ceded to the Government.

Ms. Berry called the Committee's attention to a flowchart in the table folder that depicted a decision tree for direct billing determinations. The flowchart asked such questions as whether qualified genetic counselors are able to provide services without physician supervision and whether they can bill Medicare directly. The logic of the flowchart on direct billing determinations was put into sentence structure and added to the recommendation. Several other minor changes were made to eliminate redundancy and clarify meaning.

The Committee moved to the second and third bullets of Recommendation 7, which stated that government programs should reimburse for prolonged service codes when reasonable and necessary and that HHS should assess the adequacy of existing CPT E&M codes with respect to genetic counseling. No changes were made other than to reverse the order of the two bullets. The next bullet in Recommendation 7 related to non-physician health providers' eligibility for a National Provider Identifier. The Committee accepted the proposed wording with a few modifications.

Recommendation 8 addresses education and training of health providers. The concept of integrating genetics into all areas of health care was added to the introductory statement of the recommendation. Ms. Berry stated that a sentence was added by the Task Force to respond to a comment that the Secretary should support studies that link education and training tools to improved health outcomes. The Committee suggested breaking this addition into two sentences and changing the wording to emphasize that providers should meet established genetic competencies. The Committee made a few additional editorial changes.

Recommendation 9 addresses public education on genetic technologies. The Task Force was recommending that language be added on gathering and utilizing family history. The Committee also made several editorial changes that eliminated redundancy and clarified meaning.

Ms. Berry described several other changes made by the Task Force in the body of the report. These changes included rewording the objective in the introduction to the report and reframing the section,

"What are genetic/genomic tests and technologies?" to "A Discussion of Genetic/Genomic Tests and Technologies" to indicate that the text is meant to provide a description, not a definition. The Committee unanimously accepted these revisions.

In closing the session, Ms. Berry described the time frame for moving forward with the report. OBA staff members planned to continue incorporating minor editorial comments into the body of the report and to develop an Executive Summary. Once this process was completed, the Committee would receive the final version of the report for review via email. She hoped the Committee the final draft would be completed by the October meeting.

Presentation of Certificates

Dr. Raynard Kington, NIH Deputy Director, came by to thank the departing SACGHS members for their service and present them with engraved plaques. He also welcomed four new members: Dr. Sylvia Au, Ms. Chira Chen, Dr. Jim Evans, and Dr. Julio Licinio.

As Day 1 came to a close, Dr. Tuckson announced that he was unable to attend on the second day of the meeting and that Dr. Willard would be filling in as Chair.

Thursday, June 16, 2005

Opening Remarks

Huntington Willard, Ph.D.
Acting SACGHS Chair

Dr. Willard stated that throughout the day, the Committee would hear various perspectives on the current state of the field of pharmacogenomics and related policy issues.

Pharmacogenomics Session

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

Dr. Winn-Deen stated that pharmacogenomics has the potential to significantly impact health care by being able to identify a patient's genetic variants or biomarkers through an individualized approach. This information can help doctors select appropriate pharmaceutical interventions based on individual genetic variation. In this way, pharmacogenomics serves to further integrate and transfer knowledge resulting from the Human Genome Project into the practice of medicine.

Last year SACGHS identified pharmacogenomics as an issue warranting in-depth examination. When setting priorities to guide the Committee's work in this area, the Pharmacogenomics Task Force focused on physicians' need for relevant and practical advice on the clinical application of pharmacogenomic data. They created a framework consisting of four areas: 1) the state of the field of pharmacogenomics; 2) the status of translational efforts in pharmacogenomics; 3) the ethical, legal, and social issues (ELSI) that might be raised by pharmacogenomics; and 4) the roles of Government agencies.

The Task Force also sent a request to the agencies asking them, "What does your agency see as the most important policy issues, concerns, or voids in the field of pharmacogenomics?" and, "From your agency's standpoint, what are the specific questions that SACGHS should address?" The HHS agencies identified the following issues: integrating pharmacogenomics knowledge into the drug development process (NIH); assessing clinical validity, analytical validity, and clinical utility (CDC, CMS, Health Resources and Services Administration (HRSA), and NIH); and integration of pharmacogenomics into clinical and public health practice (CDC, FDA, HRSA, and NIH). In the public health arena, CDC, NIH, and HRSA identified the following important issues: the role of ethnic and racial variation in data analysis of pharmacogenetic research and ensuring inclusion of diverse populations in such research, the potential for pharmacogenomics to be used for screening purposes, and the need to monitor the impact of pharmacogenomics. The poor and uninsured populations' access to clinical applications of pharmacogenomics (HRSA) and cost (CDC, HRSA and NIH) also were cited as important concerns.

Additional issues were identified through outreach efforts, including conference calls with individuals in the private sector. Specifically, the Task Force consulted with Bill Clarke, Chief Technology Officer and Chief Medical Officer for GE Healthcare, and Mara Aspinall, President of Genzyme Genetics, and her

colleagues at Genzyme. These individuals identified the following additional barriers in pharmacogenomics: the lack of uniform reporting standards for pharmacogenomic assays, the need for an approach to evaluate the value of pharmacogenomic testing, a lack of robust, reasonably priced technology, and the need for clarification on whether FDA approval will be required for reimbursement of pharmacogenomic tests. Genzyme felt it was important for the Committee to address laboratory-developed tests, as well as FDA-approved tests since most of the work in the field is being done with laboratory-developed tests. They also identified a need for a catalytic event that will move pharmacogenomics out of academia and into clinical practice. Although there is substantial data on the correlation of genetic variation with different drugs, the body of data is not sufficient to develop sound dosing guidelines for many of these drugs. Ms. Aspinall and colleagues noted that pharmacogenomics represents a paradigm shift and that all key constituencies within the health care system must understand its role.

Dr. Winn-Deen said the purpose of the pharmacogenomics session was to provide a common understanding of the fundamentals of pharmacogenomics and the current state of the field, to identify policy issues that will be critical to address as the field moves forward, and to determine whether the Committee can play a role in facilitating the translation of this new knowledge into the practice of medicine. She reminded the Committee that their goal is specifically to advise HHS and that they would not be able to solve all the problems raised. However, as a number of agencies within HHS are working in pharmacogenomics, the Committee can assess whether they are adequately responding to the identified issues or whether there are recommendations that could be made to move the field forward more actively or more cooperatively.

She then outlined the agenda for the day, which included presentations on the fundamentals of pharmacogenetics and pharmacogenomics, the public health and practice of medicine perspectives, and input from both the diagnostics and pharmaceutical industries. Also, CDC, FDA and NIH were scheduled to present on their efforts and future directions, followed by a talk on ELSI considerations and full Committee discussion. During the discussion, Dr. Winn-Deen said the Task Force would be seeking guidance from the Committee concerning further actions needed prior to the October 2005 SACGHS meeting.

Fundamentals of Pharmacogenetics: Origins, Definitions, and Concepts
Richard M. Weinshilboum, M.D.
Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine
Mayo Clinic College of Medicine

Dr. Weinshilboum provided an overview of pharmacogenetics, which he defined as the study of the role of inheritance in individual variation in response to any xenobiotic, including prescription drugs. He stated that pharmacogenetics represents a confluence of two revolutions: the therapeutic revolution and the genomic revolution. The therapeutic revolution has been a dramatic, yet quiet change in the number of therapeutic agents that have become available. In parallel, the genomic revolution has been accelerated by technology that arose from the Human Genome Project. He said his definition of pharmacogenomics is the convergence of the advances in pharmacogenetics that have been made over decades combined with the striking progress made in human genomics.

The scientific goal of pharmacogenomics is to correlate variation in DNA sequence and/or structure with variation in drug response, the so-called "genotype/phenotype correlation." The clinical goals of pharmacogenomics include avoiding adverse drug reactions, maximizing therapeutic efficacy, and selecting patients who respond best to specific drugs. Dr. Weinshilboum said all doctors who write prescriptions understand that the role of genetics is only one of many factors affecting individual variation in drug response. The patient's age, gender, underlying diseases, and drug interactions also play a role. Yet genetic information, because it is objective, can be helpful to the physician. Dr. Weinshilboum said that assisting practicing physicians as they integrate genetic information into the therapeutic encounter presents an interesting challenge.

Dr. Weinshilboum described thiopurine methyltransferase (TPMT), CYP2D6, CYP2D9 and VKORC1 as examples of biomarkers that have been validated and extensively studied. He also described pharmacokinetic factors that influence the final drug concentration at its target, predominantly drug metabolizing enzymes and pharmacodynamic factors that influence the response of the target itself and all the downstream signaling that comes from the target.

Questions and Answers

Dr. Licinio asked why established tests, such as the one for CYP2D6, are not generally available through mainstream clinical practice. Dr. Weinshilboum replied that part of the difficulty is at the level of the practicing physician, who may not understand the language of genetic testing. He also stated that patients are beginning to drive the process, as they access to information on genetic testing via the Internet. They may have the test performed on their own or request it through their doctors.

Dr. McCabe asked whether FDA discussions concerning labeling of TPMT included pharmacogenetics. Dr. Weinshilboum said he attended the two public hearings that were held and his impression was that the labeling was changed to make information about the existence of the genetic polymorphism and the availability of testing known to physicians.

Pharmacogenomics: The Public Health Perspective
Robert Davis, M.D., Ph.D.
Professor, Department of Epidemiology
University of Washington School of Public Health

Dr. Davis began by noting there is a significant step between understanding how testing works on the clinical level and understanding how this knowledge can be applied at the public health level. He explained that the public health goal for pharmacogenomics is the same as that of practicing clinicians: to prescribe the right drug for the right person at the right time. Public health professionals are trying to determine the real-world effectiveness of pharmacogenomics and are monitoring its applications. Dr. Davis said that the U.S. needs a system that guides scientists in producing evidence, integrating that evidence, and understanding its long-term implications.

Dr. Davis described the increasing evidence on beta-adrenergic agonists, the most commonly used medications for asthma treatment. The basic science approach addresses the evidence concerning how albuterol and genes work together to affect lung function. The public health approach asks whether our

knowledge of this polymorphism affects measurable clinical outcomes and leads to increased morbidity and mortality among treated asthmatics, and whether the polymorphism leads to increased health care costs or decreased quality of life among treated asthmatics. The public health approach is the clinical application of this bench research. For example, what happens when the effect is studied with the co-use of prednisone or fluticasone? What happens when it is used by the elderly, who may already suffer from diminished lung function? What happens in children, in which asthma is a somewhat different disease than asthma in adults? What happens in various ethnic groups, who carry other genes that may modify the effect of the adrenergic receptor?

Dr. Davis then described the types of studies that can be used to collect information on measurable clinical outcomes concerning morbidity and mortality in a diverse population set, including the elderly, children, and different ethnicities. He said there are three primary study options: observational studies, randomized clinical trials, and large practical trials, each having varying strengths and weaknesses.

In order to obtain the kind of effectiveness evidence that is needed to address pharmacogenomics issues in the United States, a network is necessary that consists of clinical researchers, epidemiologists, biostatisticians, and trialists. A large study would require full-time staff dedicated to looking at pharmacogenomics and pharmacogenomic tests. Dr. Davis said relationships also must be developed with large organizations and systems, such as managed care organizations, VHA, CMS, and state Medicaid programs to facilitate discussions on networking researchers together to conduct large, practical clinical trials and large observational and randomized clinical trials. Data standards also must be developed for such studies.

Dr. Davis said that published medical evidence should be part of a systematic analysis of drug and test effectiveness. This would be done primarily through systematic reviews and formal meta-analyses, and would incorporate evidence from randomized clinical trials, large practical trials, and observational studies. He said such efforts are already underway, referring to CDC's Evaluation of Genomics Applications in Public Practice (EGAPP) project.

Dr. Davis stated that unlike the United Kingdom, which has the Cochrane Collaboration, the U.S. research enterprise has failed to sufficiently integrate evidence into clinical practice. The Agency for Healthcare Research and Quality (AHRQ) launched the Translating Research into Practice project, but Dr. Davis said that the U.S. is still far behind in systematically integrating evidence into practice. The traditional way to move this evidence into practice in the U.S. has been to educate doctors. However, he made the point that doctors who are educated in a specific area do not always apply the evidence. Dr. Davis stated that educating patients yields some results in terms of better knowledge, but unless doctors change their practice, there is little effect. He concluded that none of the current approaches have been very effective in moving evidence into practice.

Dr. Davis described a new movement to perform randomized clinical trials or quasi-experimental trials as a means of testing ways to integrate evidence into care. He stated that this kind of study does not require an epidemiologist, but would use health services researchers instead. It also would require substantial software development to design and support an electronic medical record (EMR) system.

Dr. Davis stated that the ideas he was presenting assumed the availability of EMR data. Researchers

could collect evidence, conduct trials that integrate evidence into health care, and provide information that guides and monitors clinical care through an electronic system. He described electronic pop-up alerts for prescribing medication, collecting family history, or indicating high-risk conditions. Dr. Davis said that none of this technology currently exists, but there is a tremendous need to develop electronic health records. Most electronic health records that do exist are part of home grown systems, including those developed by large players in the clinical arena. Research is imperative in several areas: collecting and processing information, structuring data in files so they can be extracted for research purposes, and implementing security measures and methods for data transmission.

He then addressed surveillance, which is a standard part of the public health approach. The three types of surveillance he described included quality measures, ethics, and safety. Quality measures would provide standards that could be compared against data received in a national system. The ethics aspects of surveillance would identify genetic discrimination, decreased access to service, loss of insurance, and incorrect use of tests, and other unintended outcomes. Addressing safety, Dr. Davis described the vaccine and pharmaceutical models which have a passive reporting system for unintended effects and adverse events. This type of surveillance system for pharmacogenomics will require safety, health services, and ethics researchers who are specially trained to grapple with these issues.

He stressed that a systematic approach is needed to create automated files, electronic medical records, and networks of providers and researchers who can collect effectiveness evidence, study the integration of evidence into clinical care, and conduct surveillance. Dr. Davis said this system will require extensive work and substantial funding, but it is not yet clear who will lead this effort. He said that funding could come from AHRQ, CDC, FDA, NIH, PhRMA, and insurers. He concluded by stating that there also is a role for some of these agencies in standards development.

Questions and Answers

Dr. McCabe noted that the establishment of an electronic infrastructure as well as diagnostics development and use might be driven by litigation. Since the latter is likely to happen more rapidly, he asked Dr. Davis how he would formulate a rapid response to the medical/legal industry. He expressed concern that a new lawsuit trend in this area might arise for which the field is not prepared. Dr. Davis acknowledged that there is no network in place, but the capability of setting up such networks has been demonstrated. The reason it has not been done for pharmacogenomics is a lack of funding, and he said a substantial allocation of new resources will be required.

Dr. Winn-Deen asked Dr. Davis whether the health care system could handle the costs of large clinical trials to address the many pharmacogenomic questions that might be posed. She asked for his thoughts on prioritizing the questions that need to be addressed. Dr. Davis said that genetic testing and pharmacogenomics have the ability to either bankrupt the system or dramatically reduce health care. He said that the costs of large clinical trials may not be as high as one might think. However, significant costs will need to be invested to set up an infrastructure. Dr. Davis explained that most patients in large clinical trials are already being seen and receiving medication, and the technology to run their gene chips and collect information already exists. He said it is a matter of putting the pieces together and funding a network. The next step will be to empower a group of people with the right experience to set the priorities. Priorities are usually driven by morbidity and mortality or cost. The patients considered at

greatest need are usually middle-aged to elderly people who are at risk of death because of congestive heart failure, stroke, or heart attacks. Dr. Davis thinks the priority setting process also should consider gender-specific effects, pediatrics, and the very elderly.

Dr. Winn-Deen asked Dr. Davis if he had an opinion about which Government agency should take the lead in developing an overarching plan. He said there is no single agency that has public health as its mantle. However, he sees clear roles for AHRQ, CDC and FDA, although such work would expand the CDC's mandate. He also mentioned that NIH could play a strong role.

Since one of the expenses involved is sequencing, Dr. McCabe asked about the anticipated time frame to achieve the "thousand-dollar genome." Mr. Tim Leshan said NIH is hoping to reach that level within the next 10 years, depending on how well the technology develops. He noted the need to break barriers within the academic and physician communities so that the public will want to invest and participate in these advances.

Dr. McCabe asked Dr. Sherrie Hans if there has been any discussion of starting a pilot study using the VA population. Dr. Hans agreed that at the conceptual level, the VA has the necessary patient population, information technology infrastructure, research infrastructure, and delivery system to undertake such a study. She said the limiting factor would be the additional costs of running such a large-scale research program under the current budget. Dr. Davis said he has been encouraged by the interest expressed by the staff at CMS, the VA, America's Health Insurance Plans, and managed care organizations. He said that, unfortunately, there are no coordinated discussions taking place among these entities at this time to generate momentum.

Dr. Licinio asked who would fund the large studies needed to validate this effort. He said natural experiments in settings such as health care organizations would not work because patients often are taking multiple drugs. He stated that research studies typically look at the effect of only one drug. Ideally, in Dr. Davis's proposal, the studies would look at established drugs, not new drugs that are just entering the market. However, the drug companies are usually not willing to invest in this kind of study for a drug that is selling well and possibly is at the end of its patent. He thought the NIH institutes (with the exception on NIGMS) understandably would be reluctant to conduct this type of large study for pharmacogenomics because of the high cost and because they may not think the effort and cost involved in sample collection are worth the investment. Dr. Davis agreed and said there are many reasons why people might not want to participate. He said the work will have to done by those who already are paying the costs (e.g., CMS and other insurers). Dr. Francis Chesley said that cost would be less of a barrier when a strong business case can be made for conducting such studies. He said cost-effectiveness and efficacy research is needed that demonstrates to payers that it makes sound business sense to participate in effectiveness studies. He believes that all players - both Federal and non-Federal - would come together at that point. Dr. Davis predicted that cost-effectiveness studies will show that there is a tremendous amount of waste in the health care system, and that such findings will form a basis for the business case.

Pharmacogenomics in the Practice of Medicine
Richard M. Weinshilboum, M.D.
Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine

Mayo Clinic College of Medicine

Dr. Weinshilboum addressed the challenges and opportunities associated with the translation of pharmacogenomic information into the practice of medicine. Dr. Weinshilboum stated that those in academia tend to think their funding agencies will influence pharmacogenomic changes. He described this approach as shortsighted, because drug development in the United States since the Second World War has focused on the pharmaceutical biotechnology industry. Rather, the focus should be on the regulatory agencies, particularly FDA. He emphasized that improvements in information exchange between NIH and FDA will be very important to the advancement of pharmacogenomics.

Dr. Weinshilboum stated that knowledge of the sequence and structure differences in DNA continually changes, which has practical implications for translation to practice. The kinds of assays needed also change continually, and this is an area in which basic scientists help the team stay current. At Mayo Clinic, they found that the involvement of basic scientists is critical to the work of their teams, which include molecular epidemiologists, population scientists, and clinical investigators. The participation of basic scientists ensures that the latest developments in health care are incorporated into the team's research. Research scientists will interact with clinicians who have patients with the DNA needed to test the hypotheses. Dr. Weinshilboum said barriers must be broken down between basic science and clinical science. He said the field will be able to move forward with the right organizational structure and tempered egos.

Dr. Weinshilboum said the involvement of pharmacogenomics in the drug development process has been taking place in some form since the 1930s, despite a lack of pharmaceutical industry incentives to develop medications that will work for only a small subset of patients. Although there is some resistance to thinking about market segmentation related to pharmacogenomic knowledge, the pharmaceutical industry's interest in pharmacogenomics has increased with FDA's growing attention to the field. He predicted that eventually a great deal of pharmacogenomics will be included in the drug development process. This will create significant regulatory and economic implications.

Speaking on the challenges and opportunities of pharmacogenomics, Dr. Weinshilboum made the point that clinical trials should collect DNA as well as blood samples, so that researchers can prospectively or retrospectively ask the questions raised by Dr. Davis in his presentation. He noted the challenges of public/private partnerships, which create significant issues related to intellectual property and proprietary interests.

Dr. Weinshilboum addressed the third topic of his presentation: ethical, legal, and social issues. He remarked that, as in all other areas of DNA testing, confidentiality is important. He also noted the importance of educating health care professionals. Although some clinicians have not embraced pharmacogenomics, he said that gastroenterologists with whom he has worked have come to see the value of testing for TPMT. He said the field must recognize that there are sociological differences in the way physicians view this issue within different medical subspecialties.

Dr. Weinshilboum ended his presentation by reiterating that all doctors want to maximize the efficacy of drugs. He stated that treatment would be much more cost-effective if doctors could select responsive patients at the front end.

Questions and Answers

Dr. Leonard asked why the FDA does not require TPMT testing before mercaptopurine can be used for a specific patient. She asked if that kind of labeling requirement is within the purview of FDA. Dr. Felix Frueh said it was his understanding that FDA's advisory committee decided not to require a test, in part because there was no commercial test available. Instead, they provided the necessary scientific information in the label. Dr. Weinshilboum said he was present at both of the FDA public hearings and believed the committee approached the issue in a measured and judicious fashion. He said the concerns expressed were primarily those of the hematology and oncology communities, who felt the net outcome might be reduced doses of thiopurine and increased mortality.

Dr. Leonard remarked that because it has been demonstrated that physicians do not understand genetics, FDA's approach doesn't seem to be effective. Dr. Frueh said the agency must make sure that information can be applied in the clinical setting. He said at this point in time, the best approach is to provide information and allow physicians and patients to make educated decisions about treatment. He did not think the field has sufficient information to determine what actual treatment should look like.

Dr. Winn-Deen asked Dr. Weinshilboum if clinical practice guidelines have been developed by hematologists for the oncology community on the use of TPMT testing, including adjusting dosing based on results. Dr. Weinshilboum said such guidelines are being developed or are in discussion. He noted that the FDA advisory committee had expressed concerns about the lack of clearly defined guidelines and systematic clinical trials that might guide the practicing physician. The development of practical information for physicians has proven to be a barrier, even for some of the most well developed examples.

Dr. Leonard asked about Mayo Clinic's TPMT testing guidelines. Dr. Weinshilboum said that the Mayo Clinic uses the test, that homozygous-low individuals are either not treated with thiopurines or are treated with one-tenth to one-fifteenth the standard dose, and that patients monitored over time. He said the larger, more controversial challenge is the 10 percent of the European population that is heterozygous and has intermediate activity. There is no consensus with regard to the appropriate algorithm for dosing those patients.

Dr. Licinio asked if it is realistic to think that clinicians who are "in the trenches" practicing medicine can adjust their therapeutic decisions, or whether changes will have to wait for the next generation. Dr. Weinshilboum said he believes practicing physicians are educable and stated that there is no choice but to train the current generation of health care professionals.

Dr. McCabe asked if any geneticists are present on the FDA review panels when pharmacogenetics is under discussion. Dr. Frueh replied in the affirmative and said he is heading a group in the Office of Clinical Pharmacology and Biopharmaceutics that is dedicated to genomics. However, he acknowledged that there is a lack of expertise in this area and the agency is taking steps to rectify it.

Dr. James Evans asked if any lawsuits in this area had been filed by patients, and he expressed the opinion that one lawsuit would propel pharmacogenomic information into the mainstream. Dr.

Weinshilboum and Dr. Frueh said they had not heard of any lawsuits to date.

Dr. Khoury asked about the "value added" of pharmacogenomics in practice. Dr. Khoury asked if it would be effective to monitor the levels of the drug and its toxicities, rather than using an expensive pharmacogenetic test to screen the whole population, especially if the prevalence of the genotype is rare. Dr. Weinshilboum said that the costs of not screening must be considered over the long term. He said it makes more sense to screen first, rather than administer the drug and then see whether the patient develops problems. He advocated that physicians learn to prevent the adverse effects of the drugs.

Dr. Willard pointed out that the examples given were for pharmacogenetics, not pharmacogenomics. He asked, since there are so many challenges and difficulties demonstrating clinical efficacy for a single gene when scientists know exactly what to look for, it would be much more difficult when there are hundreds of variants around the genome that are not well understood, even though there is solid evidence of their interrelationship and combination and the effect they would have on drug response.

Dr. Weinshilboum agreed with Dr. Willard that researchers will find many haplotypes scattered across the genome, and eventually they will identify 20 or 30 genes that affect the use and dosing of many drugs. He said he has great confidence that this information will eventually reduce morbidity and mortality and be made cost effective because of ongoing advances in technology. He believes the data will be validated and become a standard part of medical practice. He said that demonstration projects underway are useful to stimulate discussion of these issues.

Perspectives from Industry
Eric Lai, Ph.D.
Vice President, Discovery and Pipeline Genetics
GlaxoSmithKline

Dr. Lai described the current drug development process and how it affects pharmacogenetics. He emphasized that most drugs are effective for a majority of patients but not for everyone, and stated that all drugs have side effects. Dr. Lai said that, unfortunately, there is not any drug that is effective for everyone and that would not have any side effects.

Approximately 90 to 95 percent of the molecules GSK researches have no efficacy whatsoever, or they have some efficacy but the major adverse reactions are so high that Phase IIb and Phase III studies are not conducted. Dr. Lai said that pharmacogenetic studies are not necessary for drugs that are effective in the majority of patients with a very low percentage of major adverse reactions. Many over-the-counter drugs fall into this group. Dr. Lai then described a patient-drug combination for which efficacy pharmacogenetics research is extremely important. In this subset, the drug is very effective and the side effects are low enough for the general population. Many cancer drugs, such as Herceptin, fit into this group. The last group of drugs he described is effective in a majority of the population, but has a high percentage of adverse reactions and is a good candidate for adverse reaction pharmacogenetic studies.

He noted that there are basically two groups of pharmacogenetic studies: those that examine efficacy and those that examine adverse reactions. Pharmacogenetic studies are used to increase the risk/benefit ratio, so that the benefit to patients is higher and the risk lower. Findings will allow doctors to target the group

of individuals most likely to benefit from a drug without experiencing adverse reactions. This type of research will lead to more accurate, clinically relevant information about the safety and efficacy profiles of medicines and result in a more efficient approach to drug development.

He said the existing barriers in the field are the factors that affect the application of pharmacogenetics to medicine. Using the example of cytochrome P450, he discussed some reasons why testing has not been widely adopted in clinical practice. First, P450 is a complicated gene family and the assays are difficult. He also said doctors have limited awareness of the test. However, he said the most significant reasons are a lack of access to the test and the need for comprehensive interpretation on the part of doctors when making prescription decisions.

In summarizing, Dr. Lai said that over the next 10 years, there will be an increased application of genetic information prior to the prescription of some medications. The integration of pharmacogenetics into medicine will help identify those who respond better to some medications and those who could have serious adverse reactions. He emphasized that pharmacogenetics warrants consideration by policymakers as they attempt to improve health care.

Dr. Lai recommended several areas for SACGHS focus. First, public education is needed to change misconceptions. He reiterated that no medication is totally safe and effective, yet drugs have been taken off the market because as few as three or four individuals have had adverse reactions. Next, he acknowledged that the public needs protection from and assurance against genetic discrimination. Finally, he said support from the research and health care environments is necessary for the use of genetic information. Stakeholders should include patients, providers, regulators, payers, Government, PhRMA, the diagnostics and biotech industry, and bioethics and policy organizations.

Walter Koch, PhD.
Vice President and Head of Research
Roche Molecular Systems

Dr. Koch focused his comments on policy challenges in the field. He said the first of those challenges is developing pharmacogenetic tests for drugs that are already on the market. Warfarin and azathiaprine are well known examples of marketed drugs that exhibit wide variation in drug response due to genetic factors. However, Dr. Koch pointed out, once drugs are on the market, manufacturers typically do not sponsor studies on pharmacogenetic tests. The burden of clinical validity and utility therefore falls on the diagnostics developer. Dr. Koch said FDA has expressed strong interest in specific pharmacogenetic examples, such as TPMT and warfarin.

He then spoke about the development of genetic tests and said he uses the term pharmacogenomics to describe both genetic and gene expression-based tests. Dr. Koch said multiple duplications, deletions, and other genetic variations pose challenges to test development. Novel microarray-based technologies are opening doors for multiplex assays that had not previously been contemplated. Dr. Koch that said as more variants are discovered, updates will be made to the tests.

Another challenge relates to intellectual property. As an example, Dr. Koch stated that he could not report on a specific allelic variant because he was not able obtain a license for it. He noted that

analytical validation is difficult for uncommon allelic variants. Although Roche researchers worked with many investigators around the world to find genomic DNA samples they could use to validate performance, in some cases they could not find them. Instead, they made the variants by site-directed mutagenesis and pooled them back into real genomic DNA to prove they could be detected.

Dr. Koch said researchers are increasingly considering biomarkers during drug development. Clinical drug trials will ultimately require prospective clinical trials sponsored through public/private/academic partnerships. Dr. Koch said the trials' results will be used to make differential drug or dose decisions and to demonstrate outcome differences.

Dr. Koch stated that FDA has expended considerable effort to provide guidance on the co-development of drugs and diagnostics, including topics such as the analytical properties of multiplex tests and pharmacogenomic data submission by the pharmaceutical industry. Dr. Koch said an important point in the guidance documents is that an analytically validated test could be made in the preclinical phase. However, researchers frequently do not know which marker predicts efficacy or adverse reactions until later-stage Phase II studies. Therefore, a fully validated IVD test that demonstrates clinical utility in the pivotal Phase III trial is unlikely. He said investigators therefore are asking whether a well-validated prototype test that demonstrates clinical utility in Phase III can be used to cross-validate the IVD so that the drug and diagnostic efforts can merge and launch at the same time. Absent such an approach, it would be very difficult for the drug and diagnostic development to take place in parallel without one substantially delaying the other. In addition, there are risks on the diagnostic side because many drugs do not survive Phase III and tests developed for these drugs would never be used. Dr. Koch said that the alternative—two independent Phase III trials—would be very expensive for routine practice and would hamper pharmacogenomics efforts.

Dr. Koch said that because humans are so genetically rich, people with different geographic origins have different genetic variations in their DNA. Therefore, biomarkers discovered and validated in one population may not be predictive in a population with different ancestry. He said tests need to be broad so that they are useful in a country as diverse as the U.S. AmpliChip was made with these considerations in mind.

Dr. Koch highlighted several statements made by CDC endorsing large clinical and epidemiological studies to assess pharmacogenomic issues. At NIH, the Pharmacogenetics Research Network provides some support for translational clinical research to determine the utility of pharmacogenetic tests. Dr. Koch said he hoped more support would be forthcoming.

Concerning pharmacogenetic education needs, Dr. Koch pointed out that package inserts have extensive information for physicians but they often are not read. He suggested that this information be made more user-friendly.

Dr. Koch also addressed the antiquated reimbursement system for pharmacogenomics diagnostics. He said that it is based on the Medicare system, which is fraught with inconsistencies, is not value-based, is in need of a new coding structure, and is subject to continual budget cuts. He also said that reimbursement models for preventive actions do not exist.

In closing, he recommended partnerships among academia, Government and the private sector so that pharmacogenomics can reach the clinic and provide patients with better health care.

Questions and Answers

Dr. Fitzgerald asked both speakers about the size of the subgroup needed to determine whether the market is sufficient to encourage product development. Dr. Lai said that as a scientist with limited financial knowledge, he is not aware of a hard cutoff percentage. Dr. Koch said that many of the early examples of use of this technology are based on the science, not necessarily the market size. For example, there are not large numbers of patients who use Gleevac, but the drug is doing well and has diagnostics available. He stated that when there is a real medical need and benefit for both therapy and diagnostics, the science will drive it.

Dr. Leonard asked if FDA expects to see diagnostic-therapeutic combinations coming into the agency requesting approval at the same time. Dr. Hackett replied that they are assuming some will come in together, but FDA does not know what to expect in terms of frequency. Dr. Koch added that although it would be ideal, there often is no way to have an IVD final product ready for the pivotal Phase III trial and it is difficult to align the two processes so that they come together at the end.

Dr. Leonard asked if FDA takes lab-developed tests and ASRs into account when determining the ability to bring drugs to market. Dr. Hackett said the agency is looking at that issue, with a focus on early communication with industry so that problems can be resolved as they arise.

Mr. Leshan asked for more background on reimbursement for AmpliChip. Dr. Koch said that typically the CPT codes used are for DNA extraction and amplification. He thinks it is a mistake to use technical steps to assess the value of a test. His view is that the relevance of the clinical information being provided should drive reimbursement. Two tests might follow the same procedures, but the value of their predictive information may be very different.

Ms. Harrison asked if diverse populations should be studied before guidelines are developed. Dr. Weinshilboum replied in the affirmative and said that in the Pharmacogenetics Research Network, using samples from African Americans, Caucasian Americans, Hmong Chinese Americans, and Mexican Americans are a standard part of their resequencing studies. They find striking differences in allele frequencies and types in different populations.

In response to a question from Dr. Khoury, Dr. Lai said the Committee and FDA should consider developing an evidence-based decision analysis model to determine which drugs should be integrated into clinical practice, especially those for which the decision is not clear-cut. The model would need to consider the size of the target audience, the target audience's responsiveness to the drug, the severity and frequency of side effects, and the long-term medical costs associated with the inability to predict an adverse reaction. Pharmacoeconomic models for adverse reactions have been developed in Europe.

Dr. Khoury also asked about the high percentage of failed drugs (90 to 95 percent) and asked if there is a way to save some of them. Dr. Lai responded that many drugs fail because they are directed at the wrong target, have high toxicity, and for other reasons. Pharmacogenetic studies allow researchers to

determine why the drugs failed.

Dr. Leonard asked Dr. Weinshilboum to provide more information on the Pharmacogenetic Research Network (PGRN). Dr. Weinshilboum explained that it is a network supported by multiple NIH institutes, with the National Institute of General Medical Science (NIGMS) taking the lead. It has approximately a dozen research centers and one knowledge/data base at Stanford University. The research centers perform both basic and translational studies, including laboratory-based studies, discovery of new polymorphisms and haplotypes, functional characterizations, and testing for enhanced efficacy and decreased toxicity. Funded studies focus on a range of diseases, including cancer, cardiovascular disease, asthma, and psychiatric illness. Research teams include molecular epidemiologists, statistical geneticists, and laboratory-based investigators. The goal of PGRN is for the core facilities to provide analysis broadly across many research programs and interface with various ongoing clinical trials. Dr. Weinshilboum noted that PGRN has proposed a regional translational research center to raise pharmacogenomics' profile throughout biomedical science.

Public Comment

JoAnne Glisson
American Clinical Laboratory Association (ACLA)

Ms. JoAnne Glisson spoke on behalf of ACLA, an association of independent national, regional, and local clinical laboratories. She told the Committee that ACLA looks forward to working with them as they continue to consider pharmacogenomics issues.

Dr. Winn-Deen noted that there was no intent to slight the reference laboratories that are doing laboratory-based tests. Rather, there was not enough time to hear from all constituencies in one day. She stated that the Committee recognizes the valuable role they are playing and indicated that they may ask ACLA to present at a future meeting.

Robert Yocher
Genzyme, Vice President of Regulatory Affairs

Mr. Robert Yocher spoke on behalf of Genzyme, a biotechnology company that is a laboratory service provider of genetic tests and clinical pathology results. He stated that pharmacogenomics is in its earliest stages. While there have been a handful of notable successes, most of the fruits of the drug companies' efforts will not be realized for another 7 to 10 years. In the meantime, an agreement on the systems and requirements necessary for pharmacogenomic testing must be put in place. Genzyme recommends several strategies so that the full potential of pharmacogenomics can be realized. The company believes there must be a broad, coordinated effort among key constituencies within the health care system, all of whom need to understand the role of pharmacogenomics. Physicians, other providers, payers, and patients need to be educated about pharmacogenomics as a concept and as a benefit to patients. Education and coordination of agencies must take place throughout HHS, including FDA for drug and test development, CDC and CMS for laboratory services, CMS for adequate payment, CDC for education, and NIH for experimental design and statistical approaches. He said that efforts between the agencies must be coordinated as new rules and recommendations are created. For example, biomarkers

deemed valid by FDA also should be accepted by CMS.

Mr. Yocher said there must be a shift in thinking about targeted populations and cohort outcomes. The classic drug approach traditionally has focused on large populations; however, there is now a need for new statistical methodologies to look at outliers. He stated that agreement should be reached across organizations on standard terminology.

Genzyme believes the Government should pay to encourage innovation, as it is critical to move the health care system forward. Mr. Yocher said laboratory-developed tests are considered the state-of-the-art in diagnostic tests and are often the means by which innovation occurs. In many cases, however, manufacturers do not seek FDA approval for these products or devices through 510(k)s or PMAs because these routes are not economically viable due to the products' small target populations. In addition, the technology is changing so rapidly and the pipeline is so long that by the time a test is approved, the technology has moved on. Mr. Yocher said drug manufacturers need Government incentives, such as label extensions or exclusivity for drugs associated with new pharmacogenomic tests, to justify additional costs and timelines. Furthermore, drug manufacturers must understand and recognize the benefit of pharmacogenomics in establishing a drug's efficacy and safety. He said the current multiple approaches to diagnostic access should be supported, especially the inclusion of laboratory-developed tests, which are not discussed in the FDA models. In closing, Mr. Yocher said that Genzyme stands ready to assist the Committee as efforts move forward.

Pharmacogenomics Session (continued)

HHS Efforts and Future Directions in Pharmacogenomics
Rochelle Long, Ph.D.
Chief, Pharmacological and Physiological Sciences Branch
National Institute of General Medical Sciences, NIH

Dr. Rochelle Long reviewed a portfolio of pharmacogenetics work supported by the NIH Institutes, specifically the extramural grants, and described PGRN. Through a search of the Computer Retrieval of Information on Scientific Projects (CRISP), Dr. Long found over 400 NIH awards that have as their key phrases pharmacogenetics or pharmacogenomics. Approximately 70 awards are for training programs and 70 are cooperative agreements. The latter include some large, multi-million dollar awards through PGRN as well as clinical trials that plan to conduct pharmacogenetic/genomic studies. There is support for 40 large centers and programs concentrated at a single institution, as well as awards to two facilities and centers. Dr. Long found that nearly 200 individual research grants, 15 small business awards, and 8 conference grants are supported by NIH.

Dr. Long noted that many of the NIH Institutes are conducting large-scale clinical trials to identify the genetic contributions to complex diseases and banking DNA samples for subsequent analysis. She provided examples of the ongoing work at NIH with a pharmacogenomics component. At the National Institute of Mental Health, the STAR*D (Sequence Treatment Alternatives to Relieve Depression) trial is analyzing biological samples for genetic predictors to determine which individuals might respond to specific drugs used to treat depression. The National Institute of Child Health and Human Development supports the Pediatric Pharmacology Research Units Network, which includes limited pharmacogenetic

studies. The National Heart, Lung and Blood Institute (NHLBI) sponsors Programs in Genomic Applications (PGAs), which support tools for researchers' use, both nationally and internationally. The National Institute of Diabetes, Digestive, and Kidney Disorders has a drug-induced liver injury network (DILIN) comprised of researchers who set protocols to collect materials from individuals with severe drug-induced liver injuries. The National Human Genome Research Institute (NHGRI) supports the HapMap Project, which uses SNP blocks as a tool to look at how genetic variation influences drug responses. The National Institute of Drug Abuse has studied drug-metabolizing enzyme systems that are common to many different classes of drugs. The National Institute of Aging supports clinical trials for Apo-E alleles and Alzheimer's correlations.

Dr. Long said that PGRN was started by NIGMS in 2001, with nine institutes and offices now contributing to the effort. Each of the groups involved was charged with putting together an interdisciplinary team with pharmacological, genetics/genomics, and statistics backgrounds, along with clinical researchers. Dr. Long said that the groups are studying such areas as metabolism and transporters, breast and colorectal cancer, leukemia in children, cardiovascular and pulmonary diseases, and research on the implications of pharmacogenetic/genomic studies for minority populations.

The Network is united by PharmGKB, which is used to determine the functional and clinical implications and medical decisionmaking points for predicting responses to drugs. It allows researchers to browse through genes, look at primary data, enter simple queries, and pull up data. At present, PGRN is primarily focused on cutting-edge research. Researchers are establishing the knowledge base in PharmGKB and actively depositing data sets for genotypes and phenotypes and correlations between the two. Dr. Long emphasized that PharmGKB was conceived of, and still is, a research tool. A great deal of research must be done before genetic contributions to drug responses can be accurately predicted. At this time, practicing physicians cannot access the system to determine which drug to prescribe for a patient.

Policies were developed to address informed consent and intellectual property concerns. The strategy used was to encourage provisional patent applications so that important and meaningful results can be commercialized while also being shared with others. The Network is developing principles for clinical study designs, statistical analysis, and methods for more efficient experiments. Dr. Long said that Network participants are encouraged to share their work with the research community. The Network has generated sample sets from individuals in Hmong Chinese communities and others from Mexican Americans in greater Los Angeles. Extensive community consultation was conducted prior to these efforts and a concerted effort was made to inform people that their samples were to be used for research purposes.

The Network is currently authoring a series of four white papers. The first will provide an overview of cutting-edge issues, barriers, and recommendations for pharmacogenetic studies. The second paper examines pharmacogenetic testing for research purposes, including processes, considerations, and ethical and regulatory frameworks. The third will deal with guidelines for educating medical professionals in this area. The fourth white paper is tentatively planned to address association studies in pharmacogenetics/genomics. Each paper will ultimately be targeted to a journal that will reach and stimulate discussion among the appropriate audiences.

Felix Freuh, Ph.D.
Associate Director for Genomics
Office of Clinical Pharmacology and Biopharmaceutics
Center for Drug Evaluation and Research (CDER), FDA

Dr. Frueh said that pharmacogenomics was identified through the FDA Critical Path Initiative as one of the key opportunities that can lead to new medical products. To be successful, regulation efforts must address the combination of drug therapy with diagnostics. FDA has developed a series of guidance documents that illustrate the current thinking in the field.

The guidance document for pharmacogenomic data submissions was published in March 2005. It explains how FDA will review genomic data submissions. It also is a guide to drug development, empowering FDA to make the review process more efficient and describing several news ways for industry to interact with the agency. It introduces a classification of genomic biomarkers and clarifies the type of genomic data that must be submitted to FDA. It also describes a new voluntary submission pathway that encourages industry to submit exploratory genomic data, and a new agency-wide review body, the Interdisciplinary Pharmacogenomics Review Group. Dr. Freuh said the most important point for industry to understand is that the guidance does not create new processes for the review of data submissions; it places genomic data within the existing framework.

The voluntary genomic data submission (VGDS) pathway was developed for exploratory data, whether part of an active investigational new drug application or a new drug application. The pathway is intended to build expertise and a foundation for developing scientifically sound regulatory policies. VGDS creates a forum for scientific discussions with FDA outside the regular review process. Dr. Freuh explained that the data discussed in the voluntary forum is not used for regulatory decisions. It therefore allows for more interaction between FDA scientists and industry scientists. The first voluntary submission was received in March 2004, and another dozen submissions since then. FDA is evaluating the complex raw data received and having ongoing dialogues with investigators.

Dr. Freuh then described the guidance document on the instrumentation for clinical multiplex test systems. He stated that these devices are intended to measure and sort multiple signals generated by an assay from a clinical sample. They are used with a specific assay to measure multiple, similar analytes that establish a single indicator to aid in diagnosis. The guidance explains that these devices are intended for testing DNA to identify the presence or absence of human genotypic markers encoding a drug-metabolizing enzyme. The devices aid in determining treatment choices and in individualizing dosages. Dr. Freuh said that because these devices are highly complex, the agency must look at them in combination.

Dr. Freuh acknowledged the difficulties that companies have in trying to develop the tests and drugs simultaneously. Labeling is a critical component and can be crucial in determining whether the product reaches the market. FDA developed a strategy to combine the devices and drug development processes, and in April 2005, published a drug/test co-development concept paper. The concept paper describes key steps during concurrent drug and test development. He emphasized that during this process, interaction between CDER, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research is critical. Dr. Frueh said the comment period for the paper is still open and the agency is

planning to issue the draft guidance late in 2005.

He stated that there are several obvious benefits to drug/diagnostic co-development. Co-development has the potential to prevent drugs from being withdrawn, and can rescue candidate drugs that otherwise would be stopped in the drug development process. It also can be used for patient stratification and to enrich clinical trials, which affects both safety and efficacy.

Muin Khoury, M.D., Ph.D.
Director
Office of Genomics and Disease Prevention, CDC

Dr. Khoury described key CDC efforts in genetic testing over the last 10 years. In 1999, in response to an NIH/Department of Defense task force report, several interagency HHS working groups were formed to analyze the data needed to transition genetic tests from research to practice. They also considered ways to monitor the impact of genetic tests. After the SACGT oversight report in 2000, CDC started the ACCE project. It laid the foundation for the kinds of questions that could be asked about all genetic tests, from analytic performance in the lab to ethical issues.

In 2004, the EGAPP initiative began as a 3-year model project to establish and evaluate a sustainable, systematic evidence-based process for assessing genetic tests and other applications of genomic technologies in transition from research to practice. The goal is to move genomic applications into practice at a faster pace. The EGAPP planning objectives are to integrate previous recommendations for action with the knowledge gained from the ACCE model project, existing processes for evaluation and appraisal, and international experience coming out of the U.K., Canada, and other groups.

Dr. Khoury said the basic infrastructure is the EGAPP Working Group, a multidisciplinary, independent working group that interacts with various stakeholders, including health care providers, consumers, professional organizations, policymakers, public health officials, regulatory groups, industry, labs, and payers and purchasers. The Working Group will request evidence-based reviews to be conducted by Evidence-based Practice Centers (EPCs) to identify gaps in knowledge about genetic tests. Based on the information received from the EPCs, the Working Group plan to develop and disseminate information to health providers, consumers, policymakers, payers, and purchasers. EGAPP may refer a small number of tests for more direct appraisal to the U.S. Preventive Services Task Force and the Community Preventive Services Task Force housed at AHRQ and CDC, respectively.

In January 2005, EGAPP held an expert meeting on evidence-based reviews of genomic applications, with 21 participants representing evidence-based medicine, health care, genomics, epidemiology, ethics, and health economics. The group considered existing and potential methods for systematic evaluation of genetic tests and other genomic applications. The EGAPP Working Group was formed in March 2005. Its first meeting was held in May 2005, with a second meeting scheduled for July 2005. Three subcommittees have been formed. The first is deciding on potential topics for evidence-based reviews, focusing first on applications recognized as common and important, such as screening tests and tests used in clinical situations to guide interventions. The second subcommittee is finalizing the analytical framework that was formulated at the January meeting. The third subcommittee is looking at health outcomes and patient and family-related outcomes.

Dr. Khoury said that products forthcoming from the Working Group include their published methods, the criteria and prioritized list of topics, the approved evidence-based reviews, conclusions and recommendations, and lessons learned.

Questions and Answers

Dr. Fitzgerald asked if there is a specific definition or threshold of clinical benefit that will help avoid controversy as pharmacogenomics moves forward. Dr. Frueh replied that there is no generally applicable definition; it is looked at on a case-by-case basis.

Dr. Licinio asked Dr. Long if PGRN efforts will be coordinated with NIH's General Clinical Research Centers (GCRCs) that are addressing pharmacogenetics. Dr. Long said they are trying to identify the groups working in this area and coordinate with them.

Ethical, Legal, and Social Implications of Pharmacogenomics
Patricia Deverka, M.D., M.S., M.B.E.
Fellow, Center for Genome Sciences and Policy
Duke University

Dr. Patricia Deverka stated that a novel framework is needed to deal with the ethical, legal and policy issues that are arising because pharmacogenomics is bringing together three controversial areas: genetic testing, managed care, and the pharmaceutical industry.

Dr. Deverka said the history of eugenics and beliefs in genetic determinism in the United States have contributed to the sensitivity surrounding genetic testing. In addition, pharmacogenomics challenges the traditional approach to genetic testing for disease susceptibility, which has predominantly focused on rare disorders. Since genetic testing has been misused in the past when only a handful of experts were using it, society is concerned that wide use of pharmacogenomic testing in primary care settings may result in more widespread mishandling.

She said that managed care is a significant actor in this area. Because of the Medicare prescription drug benefit, Dr. Deverka said that managed care organizations will play a large role in the field of personalized prescribing. Because these companies are perceived to be primarily focused on cost containment, individuals and agencies, such as CMS, are reluctant to trust them. Furthermore, their approaches to cost containment as well as use of restricted formularies and therapeutic substitution run counter to the concept of personalized prescribing. Some are concerned that these practices may hinder market entry of pharmacogenomic products.

The pharmaceutical industry also has a poor public image. People tend to mistrust these companies because they have not always been transparent about safety issues with some drugs. In addition, they have not fully published all of their clinical trials and charge high prices for their products. There are concerns that they cannot be trusted to use pharmacogenomics appropriately, i.e., they might "cherry pick" to address pipeline and profitability problems.

Dr. Deverka then addressed pharmacogenomic concerns relating to clinical research, beginning with the issue of informed consent for DNA banking. Because informed consent is the primary mechanism by which human subjects are protected in the research setting, some have argued that the framework for informed consent needs modification to take into account the large biorepositories that may be created. She stated that with clinical research, privacy and confidentiality concerns vary depending on whether the data are identifiable or coded, and said procedures are needed to limit unauthorized disclosures. Breaches in confidentiality could result in genetic discrimination, based on fears that medical coverage will be more expensive for some patients than for others. In addition, a failure to guard privacy could harm individuals, families, and groups, because test results may reveal susceptibility in several disease areas. Furthermore, she said the idea of stratifying individuals based on pharmacogenetic tests has caused concerns that new orphan drugs will be created.

Dr. Deverka explained that one of the benefits of pharmacogenomics is that clinical trials can move drugs into the market more rapidly if subjects are selected for trials on the basis of their pharmacogenetic profiles. However, some have argued that this might result in the less safety data supporting their safety and efficacy at the time the product goes to market. Doctors who do not follow the labeling instructions when prescribing can exacerbate safety problems. Dr. Deverka touched briefly on the issue of the incentive structure in clinical research, stating that intellectual property issues are critical. Patent bottlenecks can result when several different entities hold patents on various genetic markers, which drive up costs because multiple licenses must be obtained to develop one test.

Dr. Deverka stated that the pharmaceutical industry focuses predominantly on the development of new drugs, not on researching drugs already on the market. She said many of these companies have few resources to conduct pharmacogenetic studies on marketed drugs, and there is no financial incentive for them to do so. She asked the Committee to consider what could be done from a public health perspective to encourage pharmacogenetic research on marketed drugs.

Returning to the topic of informed consent and biorepositories, Dr. Deverka said that ethical issues arise because researchers other than those who collected samples may be the conducting research on the samples. Informed consent is complicated in these situations because future studies will likely be conducted by unspecified investigators. There is concern that a number of different groups may want to access these biorepositories. The traditional emphasis on protecting subjects from physical harm through the informed consent process is moving to the need for protection from informational harm. Although these studies would be facilitated by blanket consent, which would allow any future use of the specimens, Dr. Deverka said that blanket consent might be too broad to meet the ethical standards of informed consent. She stated that informed consent processes are needed that will protect subjects, while at the same time minimizing the need to contact them repeatedly in the future to obtain consent for various studies.

Dr. Deverka suggested that informed consent's traditionally exclusive focus on the individual research subject is arbitrary from an ethical point of view. She suggested that researchers should be addressing risks to groups. She used the example of specific population groups that could be stigmatized if genetic findings re made available on their group's responses to drugs.

Turning to the topic of pharmacogenetics and race, Dr. Deverka stated that there is no precise biological

or genetic definition of race. The prevailing thinking is that race is a social construct. However, researchers have found that certain pharmacogenetic variants are more common in some ethnic and racial groups than in others. Published studies demonstrate differences in response to conventional treatments across various racial groups. However, some people debate the scientific validity of these studies because they claim that self-identification of one's race is imprecise. She pointed out that this type of research can be harmful if it reinforces the notion that racial differences have a genetic basis. Drugs could be marketed to particular racial groups in a misleading manner or leave the impression that all members of a group would benefit. For instance, a drug like BiDil could be incorrectly claimed to be more effective than other non-racially defined medicines. If certain genotypes are linked to poor medication response in specific racial minorities, those groups could be stigmatized by the implication that they are more difficult or more expensive to treat. Dr. Deverka said that, ultimately, the primary concern is that physicians will "take shortcuts" and use race, rather than genotype, as the basis for drug selection.

Addressing the topic of orphan genotypes, Dr. Deverka explained that there are two kinds. First, through pharmacogenetic data, it can be shown that a particular drug is unlikely to be safe or effective for a particular genotypic subgroup within a general population or disease group. The second type of orphan genotype occurs when a disease that was formerly thought of as attractive from a commercial perspective has no genotypic subgroups large enough to attract commercial investment. The potential concern is that drugs will not be developed for these genetically defined subgroups. Although large pharmaceutical companies may not be interested in these diseases, she believes that they will be of interest to small start-up companies. Ethical concerns may arise if there is no other safe and effective treatment available for the disease. Dr. Deverka believes it is unlikely that a subgroup will be so small that it will never attract investors.

Dr. Deverka expressed concern that pharmacogenomics is entering the marketplace and clinical practice without adequate validation, due to the lack of a regulatory framework or an evidence base. She spoke about the problems that could arise from a rapid and unmanaged introduction of genetic tests into the marketplace. She said the predictive value of many pharmacogenomic tests is likely to be too low to be clinically useful. Excitement about pharmacogenomics could cause resources to be diverted away from more effective ways of improving public health.

She said there will be suboptimal access to and use of pharmacogenomic testing because professionals and payers have significant knowledge gaps about genetics as well as difficulty interpreting probabilistic information. In addition, it is not clear when physicians are obligated to offer pharmacogenetic tests. Physicians and pharmacists could be considered negligent if they do not offer "a reasonable standard of care," and pharmaceutical companies could be liable if they do not disclose a knowable safety problem with a drug.

Another clinical practice issue relates to the need to determine when informed consent is needed for pharmacogenetic testing. She believes that pharmacogenetic testing will not be very controversial because it will be viewed as therapeutic drug monitoring to inform dosing decisions. Dr. Deverka noted that many believe Federal nondiscrimination legislation will be necessary to help people feel comfortable with genetic testing. She also expressed concern that higher drug costs would lead to access barriers. Pharmaceutical companies may not pass the savings gained in the drug development process on to the

consumer.

Dr. Deverka described payers' hopes concerning the use of pharmacogenomics in the real world, including decreased health care costs, improved compliance, better health care outcomes, and a reduction in patients' adverse effects. However, payers are also concerned that, as is usually the case with new technologies, pharmacogenomics will increase costs. Although ultimately they will be more cost effective and provide more information, advances in this field may not initially result in cost savings.

Dr. Deverka said that pharmacogenomics discoveries will only become an important element of clinical practice if they are reimbursed. Therefore, pharmacogenomics must be evaluated in the context of current cost containment practices. She said that from an ethical standpoint, pharmacogenomics is clearly on a par with, if not superior to, current practices but has the added benefit of being tailored to an individual. She said that at the individual and group levels, there is a stewardship obligation to manage resources by not paying for drugs that are unsafe or ineffective. However, this will be difficult to operationalize in clinical practice because of the probabilistic nature of the results.

She proposed the idea that direct-to-consumer access to pharmacogenomic testing is permissible in some situations. However, there must be appropriate standards for analytic and clinical validity, and the results must be conveyed in an accurate and understandable manner. She felt it could be unethical to restrict access to pharmacogenomic tests for over-the-counter drugs or dietary regimens. She also felt that individuals should have direct access to testing when they have insurance coverage for the drug but not for the test. In other cases, individuals may not want to go through their employers' health plans to obtain testing due to concerns about discrimination or stigmatization.

Dr. Deverka discussed reasons for and against the idea that pharmacogenomics is unique relative to other medical technologies. Her opinion is that the ethical, legal and policy issues are the same as in other areas of medicine. Some argue that it is different because DNA is uniquely identifying and predictive, the sample can be kept indefinitely, and there is a tremendous amount of information involved. Dr. Deverka acknowledged the concerns about stigmatization by race or ethnicity because of the likelihood of genetic variability in those groups. She said it is important to see genetic variation as only one factor that impacts drug response otherwise, the negative ideas of genetic determinism and exceptionalism will be reinforced and will make patients less willing to be tested.

In conclusion, Dr. Deverka recommended that the field look at pharmacogenomics as a prescribing tool that helps physicians decide on the best intervention for a specific patient. She stated that pharmacogenomics emphasizes the need to resolve longstanding problems concerning ways to integrate new technologies into clinical practice. She suggested areas in which more information needed, including an extensive information technology infrastructure, regulatory requirements, and cost-effectiveness data.

Questions and Answers

Dr. Licinio asked about the standard of ethics that should be used if it becomes known that a person has a gene variant that can cause adverse drug reactions or that can result in no response to treatment for a life-threatening disease. Should the subject be recontacted even if they specified that they did not want

further contact? Dr. Deverka said it is important to allow people the option of not being recontacted but agreed that pharmacogenetics is different. She said this question could arise if a researcher has information that would affect a patient's outcome but there is no other treatment option. She noted, however, that in most cases, researchers don't have a means of recontacting subjects. From an ethical standpoint, she said that she would follow the expressed wishes of the subject.

Mr. Leshan asked if studies have been done indicating that there are higher costs associated with implementing privacy standards. Dr. Deverka pointed to the cost of implementing HIPAA, but acknowledged that there are no studies on this. She noted that it seems logical that if information is being treated differently, there will be costs associated with it.

Dr. Fitzgerald asked how the technology can be supported without concomitantly raising fear of genetic reductionism and determinism. Dr. Deverka said how the vocabulary is used is critically important. Some have suggested not using the word "genetics" when talking about drug response profiles. For example, in the clinical setting, a patient could be told that a test will help the physician decide which drug is best for them.

Dr. Winn-Deen stated that it seemed, from the comments on TPMT and in the white paper on companion diagnostics, that there is no formal recognition or utilization by FDA of laboratory-developed tests as a way of providing pharmacogenetic services. Yet the only way certain tests are available is through laboratory-developed tests. She asked if there is a requirement that an IVD assay be developed before FDA labeling will recognize a pharmacogenetic test. Dr. Hackett said that anything other than a biomarker must go through the regular approval process, because it is considered similar to a research product. Dr. Winn-Deen expressed concern that in these tests cannot be clinically recommended in a practice guideline or on a drug label. Dr. Frueh stated that two separate issues were being raised. One concerned a combination product or co-developed product that requires a test for the drug to be used. Those tests must be FDA approved. He said that in more than 100 other cases, the pharmacogenomic information is provided on the drug labels, even in the absence of an FDA-approved test.

Full Committee Discussion and Next Steps for Pharmacogenomics

Dr. Winn-Deen led a discussion on next steps on the pharmacogenomics issue. Dr. Willard suggested that the Committee provide direction to the Pharmacogenomics Task Force so they could prepare for the October meeting and decide whether there were remaining gaps in knowledge. Dr. Fitzgerald stated that he would like more information from industry on the financial issues involved in pharmacogenomics and to hear more about partnerships among academia, Government, and industry partners. He also said the Committee had not yet heard the legal perspective on potential lawsuits and other red flags. Dr. Winn-Deen added that the Committee had not yet heard from insurers. Ms. Masny suggested finding out more about the electronic health infrastructure. She asked if the Large Population Studies Task Force saw areas of overlap. Dr. Willard said there were clearly some questions in common and substantial overlap in the work of the two Task Forces.

Ms. Berry said she divided the themes that arose during the day into a flow chart. One path represented research needs in pharmacogenetics and the second represented ways to integrate the conclusions of this research into practice. She said there are large gaps in the research and she divided that area further, into

research on existing drugs that have received FDA approval and research on pipeline drugs. Each area has its own questions that must be answered, e.g., Who conducts the research? How can incentives be developed to encourage research? She added that a mechanism must be developed to coordinate these efforts. She suggested that the Committee contemplate how they could best advise the Secretary in a way that will encourage research both for existing drugs and pipeline drugs. Dr. Winn-Deen added that under the category of "approved drugs," she would distinguish between those for which the biomarker is known and those for which the biomarker is not known, but for which adverse events have occurred and researchers would like to know the biomarker.

Dr. Leonard pointed out that Japan has mandated that all existing drugs be evaluated for their pharmacogenetic impact on the Japanese population. She thought it would be useful to hear how they are implementing this process, how it is funded, and what they are looking at. She also was interested in hearing more about the status of the submissions of pharmacogenetic information to FDA. Dr. Frueh said that he recently developed a presentation on these submissions and would be happy to share it. Dr. Winn-Deen and Dr. Leonard said they would like additional clarity on how decisions are made about including pharmacogenomic information on drug labels.

Dr. Winn-Deen said she was told during the break by Mr. Yocher that there are different regulations for informed consent and the handling of samples for Government agencies versus private entities. Mr. Yocher explained that Government agencies operate under 45 CFR Part 46, while industry operates under 21 CFR, Parts 50 and 56. He said this difference has been an issue for some time and that it creates difficulties when public and private consortiums attempt to work together on pharmacogenomics projects. Ms. Carr noted that NIH's Clinical Research Policy, Analysis, and Coordination Program, which works to harmonize Government policies and procedures, is addressing the problem and talking with FDA. Dr. Winn-Deen stated that public/private partnerships should work under one set of rules. She suggested that the Committee use its advisory role to ask the Secretary to address this issue.

Dr. Fitzgerald expressed his fear that there will be widespread public misconceptions about pharmacogenomics because it is difficult to communicate the benefits of new medical technologies effectively. He said sociologists have been studying the different ways in which different groups interpret the same words and data and suggested the Committee look at this body of work.

Ms. Masny encouraged the Task Force to keep education issues in mind. Dr. Winn-Deen agreed, but stated that the Committee had heard from several people that education alone is not sufficient to create clinical implementation. She said she would like the Committee to explore mechanisms that could be proposed for effectively moving a body of evidence forward into clinical practice. She reminded the group that existing pharmacogenomic knowledge has been slow to move into practice.

Dr. Howard stated that the Committee might want to hear from CMS about the effects of FDA approval on their reimbursement policies, especially now that a drug benefit has recently been added. She noted that Medicaid also will be affected.

Dr. Leonard asked what could be done to have a resource available to support pharmacogenetic analysis of patients from various clinical trials in a centralized way, similar to the model used by NCI. She suggested that this function be taken on by PGRN. Dr. Willard stated that he did not see a lack of core

resources or access to technology, but rather, he said there is a conceptual block that prevents information from large studies from being translated into clinical practice. Dr. Leonard disagreed with Dr. Willard, maintaining that a general sequencing facility or genotyping facility would not have the pharmacogenetic and pharmacologic information necessary to assist investigators in designing genotyping or resequencing projects. She said a more focused pharmacogenetics core, rather than generic sequencing core, would better facilitate such research. Dr. Willard said their disagreement was one of terminology. He stated that a facility ceases to be "core" if it is driven intellectually and conceptually by physicians and clinicians around the country who are obtaining data on patient cohorts to derive pharmacogenetics conclusions. He said he would not call that a core, but he agreed that such a system is needed. Dr. Winn-Deen said that many labs both collect clinical samples that are well characterized and provide a mechanism for resequencing or genotyping them. They benefit from the mixed expertise of the clinicians and the high-throughput genotyping and sequencing support team. Dr. Licinio noted that a PGRN Request for Applications for translational centers had been proposed but was cancelled.

Dr. Licinio also said that, based on his experience, there are significant deficiencies in the field, both on the part of those who work in genetics and those who work in the clinic. He said those with genetics backgrounds do not understand the clinical issues and the costs of pharmacogenetics trials. It is common to see sophisticated genotyping and sequencing being performed on clinical samples that are of questionable value. However, he said many clinicians collect very good samples and have good trials, but do not know a great deal about genetics. They test only a few polymorphisms and their studies do not have sufficient power. He indicated that more interface between clinicians and geneticists is needed and suggested the Committee try to bring the two communities together through a core facility or another mechanism.

Dr. Willard said that Dr. Davis made a very rational and impassioned plea in his presentation to link translational pharmacogenomics to health outcomes. These translational research networks may not be appropriate to bridge the gap. He suggested that the Task Force look more closely at mechanisms that push new discoveries forward through a series of studies that would address clinical analysis, pharmacoeconomics, health system design and financing, and other key issues. He said there are many avenues that must come into play for technological advances to be successfully integrated into medical practice.

Dr. Willard said the Task Force also might want to look at the issue of genetic exceptionalism in the new context of pharmacogenomics. He also suggested that the Committee advise the Secretary on the developing issues and knowledge gaps related to race and genomics.

Dr. Guttmacher noted that pharmacogenomics is an edifying example of interdisciplinary research in an era when no one group has enough knowledge to do research on their own. He said this poses a challenge to NIH, academia, and private industry. The PharmGKB network is one example of a means to move forward. He recommended that the Committee look not only at the funders, but consider other kinds of changes that could be made. Dr. Winn-Deen noted that the Committee's focus on funders related to their charge to make recommendations to the Secretary, but said the Committee could address the role of HHS agencies in doing outreach and working jointly with non-HHS entities.

Ms. Carr asked if the Committee if they were ready to begin working on a report or other product. Dr. Winn-Deen said she was not sure what form the product would take. No one objected to giving the Task Force the latitude to think about what form the products would take.

The meeting was adjourned.

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

Reed V. Tuckson, M.D.
SACGHS Chair

Sarah Carr
SACGHS Executive Secretary