Highlights of the Eleventh Meeting of the
Secretary's Advisory Committee on Genetic Testing
November 15-16, 2001
Bethesda, Maryland

The eleventh meeting of the Secretary's Advisory Committee on Genetic Testing (SACGT) was held in public session on November 15-16, 2001, in Bethesda, Maryland. The Committee was briefed on the outcomes of a roundtable meeting convened the previous day by the Education Work Group and discussed ideas for the upcoming Education Summit. The Rare Diseases Work Group organized a series of presentations on issues related to the development, translation, availability, and accessibility of genetic tests for rare diseases. SACGT was also updated on the status of Federal genetic discrimination legislation by Congressional staff. SACGT heard progress reports from the Access Work Group and Informed Consent/IRB Work Group, including a presentation of the draft information brochure developed by the Informed Consent/IRB Work Group.

DAY ONE

Dr. Joann Boughman, chair of the Education Work Group, briefed SACGT on the outcomes of a roundtable meeting. On November 14, 2001, the Education Work Group convened a roundtable meeting to discuss and gather input on genetics educational issues faced by health professionals. The goals of the meeting were to explore the integration of genetics into current and future healthcare practice; discuss the major curricular needs of the various health disciplines; and identify obstacles and gaps towards enhancing genetics education of all health professionals. The participants represented a wide range of health professional disciplines and organizations and included SACGT and Work Group members.

The roundtable participants provided the Work Group with a deeper understanding of the issues and offered helpful guidance in the planning of an Education Summit to be held in conjunction with the next SACGT meeting. Regarding the integration of genetics into professional practice, participants emphasized the need for health professionals to acknowledge the importance of genetics to their disciplines. Awareness of genetics by the various disciplines needs to be increased and the desired behavior change should be clearly defined. The need for evidence-based practice in genetics and clinical tools for family history taking and point of care technology was emphasized by several participants.

Regarding content and curricular needs, the meeting participants agreed that in addition to the promotion of genetics knowledge and skills, a change in attitude was required in order for genetics to be successfully integrated into medical practice. The community of general genetics needs to take a leadership role to assist the integration of genetics into clinical and public health practice. The usefulness of the core competencies developed by the National Coalition for Health Professional Education in Genetics (NCHPEG) was affirmed by several participants, but with the caveat that it needed to be tailored as appropriate for various disciplines and that each discipline should take some responsibility to include genetics in their curricula and training

programs. Several model programs were highlighted, including the Genetics in Primary Care project supported by the Health Resources and Services Administration, the recently developed public health core competencies in genetics developed by the Centers for Disease Control and Prevention (CDC), and combined specialty residencies and fellowships.

The roundtable participants made several suggestions to address the gaps in genetics education of health professionals including the need for discipline-based guidelines, faculty development programs, expansion of the genetics workforce, additional support for model programs and special fellowships in genetics, and development of a list of credible genetics resources for health professionals. There was general agreement that additional support for translational research is needed, which would help in the development of evidence-based practice guidelines. Several participants recommended continued or enhanced support for Title VII funds to support continued training and educational programs for various health professions.

Following SACGT's discussion regarding plans for the proposed Education Summit, the Committee decided that due to the proximity of NCHPEG's annual meeting to the proposed summit date in February 2002, the Education Summit should be held at a later date in the Spring or perhaps in conjunction with SACGT's May meeting. The proposed agenda would include an introduction defining the desired change or outcome, followed by a plenary session with a focus on family history, panel(s) using case scenarios to define the roles of various healthcare professionals in the integration of genetics into clinical and public health practice and to promote a team approach in genetics, and focus groups on specific topics or tracks. The Education Work Group will confer further to discuss and finalize the summit agenda.

Next, the Committee reviewed a demonstration of a CD-ROM educational tool, *Genetic Testing in Clinical Practice: A Team Approach*. Mr. Andrew Faucett, a genetic counselor from CDC's Office of Genetic Testing, opened the presentation with a brief introduction and overview of the project funded by CDC. Dr. Joseph Henderson, Director of the Interactive Media Laboratory and Professor of Community and Family Medicine at Dartmouth Medical School, demonstrated this novel educational tool and discussed its utility for health professionals. As reflected in the work of the Education Work Group, the preparedness of health care professionals to adapt to changes in medicine that are expected to result from the expansion of genetic technologies is a critical issue for SACGT. The need for new modes of teaching and learning is apparent, and SACGT members were impressed with the project's innovative approach to genetics education of health care providers.

In the afternoon, Dr. Barbara Koenig, Co-Chair of the Informed Consent/IRB Work Group, reported on the status of the group's current projects. Dr. Koenig presented a final draft of the general information brochure on genetic testing for the Committee's consideration with a recommendation that public comment be solicited on the brochure's utility, content, tone, readability, and dissemination. The brochure provides general information about genetic tests and genetic testing. It discusses different kinds of test categories, but does not provide specific information about specific tests. The goal of the brochure is to broaden awareness of genetic testing and provide the public with general information about genetic tests and issues that should be understood about these types of tests. It is intended to serve as a model for communicating

information about genetic tests, but it is not to be a model informed consent document. At the same time, if it is successful in increasing general understanding of genetic tests, it ultimately may facilitate informed consent discussions.

The brochure provides an overview of genetic tests and outlines some questions to consider before having a genetic test. Using a question and answer format, the brochure explains: what genetic tests are, the different purposes to which they are put, how they are similar to and different from other medical tests, and some of their limitations and possible outcomes (potential benefits and risks); addresses insurance policy implications, privacy, confidentiality and discrimination; provides a number of information and services resources; and spells out questions to ask oneself and one's healthcare provider when considering a genetic test.

Following a discussion of the information brochure, SACGT agreed that public comment on the brochure's content and utility should be solicited. However, the Committee recommended that a professional writer with expertise in writing for a general audience be hired to ensure the brochure's readability for a lay audience before, not after, seeking public comment. Members concluded that the brochure's utility was inextricability linked to its readability and public comment should be sought on a final version of the document.

Dr. Koenig next described the work group's progress in formulating a framework or points to consider to help determine the degree of informed consent needed for new genetic tests as they are introduced into clinical and public health practice. She reviewed the reasons such a report is needed, the underlying principles for its development, the contribution it could make to ensure appropriate test use, and its potential audiences. After summarizing the work group's current thinking and approach and outlining some of the challenges and questions that the group has encountered, she sought the Committee's input on several outstanding issues.

Committee members commended Dr. Koenig for the work group's efforts to develop such a framework and they agreed that the development of guidance regarding informed consent for genetic tests in clinical and public health practice was needed. They urged the work group to continue to develop the recommendations and offered several ideas for the work group to consider:

- While there is currently enormous diversity in genetic test types and purposes and different consent processes may be warranted depending on the type of test, making a case for the use of multiple (four) models of consent will be very difficult. Any tool to guide the process of deciding which model to use for which test must be simple and straightforward if it is to work in practice. Two to three models may be more practical.
- Although guidance on how to determine what type of consent is needed for a particular test would be a significant contribution to the field, in practice the approach must be flexible and tailored to each patient's needs (an individual patient-centered approach).
- The idea of recommending that FDA play a role in requiring consent practices as part of the pre-market review process needs to be thought through carefully.

Ensuring appropriate consent for genetic testing may be more achievable in practice through the education of health providers and consumers.

- With regard to the four proposed models of consent, genetic counseling should be an explicit component of at least the most comprehensive consent model.

Two key Congressional staffers briefed SACGT on the status of genetic discrimination legislation. Ms. Kim Monk is a member of the Minority Staff of the Senate Health, Education, Labor, and Pensions (HELP) Committee; Senator Judd Gregg is the HELP Committee's ranking minority member. Ms. Cindy Pelligrini is Chief of Staff and Legislative Director for Representative Louise Slaughter, sponsor of H.R. 602, the Genetic Nondiscrimination in Health Insurance and Employment Act. They reviewed the history of genetic discrimination bills, explained the way in which the several pending bills differ on particular provisions and the implications of those differences, discussed the substantive issues that are the current focus of negotiation, including the definition of genetic information and scope of protections, and suggested that, notwithstanding changes in national priorities since the September 11th attacks, prospects were good for the passage of a compromise bill in 2002.

The final presentation of the day was by Dr. Steven Gutman, director of the Division of Clinical Laboratory Devices at the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA). Dr. Gutman updated the Committee on the agency's progress in implementing oversight of genetic tests at FDA. His presentation focused on quantitative and qualitative data elements to be considered in the review of genetic tests and the use of the pre-market review template for submission of analytical and clinical data. Dr. Gutman indicated that the review template is being piloted in nine laboratories that offer a range of testing services to evaluate the ease of preparation and submission. He expected to be able to present the results of the pilot study at SACGT's February meeting.

DAY TWO

Dr. Judith Lewis, chair of the Access Work Group, began the second morning with an update of the group's activities. The Work Group is currently working on two reports--coverage of patient education and counseling services and guiding principles for healthcare payers regarding coverage of and reimbursement for genetic tests and services. With regard to the coverage paper, the Group will be conducting a small survey of nine medical institutions/laboratories to gather information about how the broad range of providers bill and are reimbursed for genetic education and counseling services. The guiding principles report will address a broad array of issues relating to genetic testing for healthcare payers to consider now and in the future. It is intended to serve as a model to health insurance providers as they encounter genetics services. A stepwise approach is being taken in preparing the report to ensure that several sensitive and complex issues, such as the effect of public concerns about genetic discrimination on test use, are properly addressed. The Work Group will also be conferring with outside experts before submitting the report for review by the full Committee. In conjunction with the Data Work Group, a session on how population data are collected, organized, and reported will be convened at an upcoming meeting to provide clarification on the health care disparities issues as they relate to genetic testing. The group also plans to gather input from public interest and advocacy groups on specific issues SACGT should be addressing related to health disparities.

Ms. Mary Davidson and Dr. Michael Watson, Co-chairs of the Rare Diseases Work Group, led a session on the development, translation, availability, accessibility, and oversight of genetic tests for rare diseases. The purpose of the session was to gather information from various stakeholders and government agencies in order to assess the adequacy of activities and oversight in the areas mentioned above that will culminate in a white paper.

Dr. Vicky Whittemore, Executive Director of the Tuberous Sclerosis Alliance's Center Without Walls, reviewed her organization's experiences with the development and provision of a genetic test for tuberous sclerosis and described her group's role in facilitating the provision of the test through CLIA-certified laboratories and supporting the costs of the test as well as serving as a resource for both patients and researchers.

Dr. Marlene Haffner, Director of FDA's Office of Orphan Products Development (OPD), presented an overview of OPD's role in supporting the development of products for orphan diseases. Dr. Haffner began by defining an orphan drug as a drug intended to treat a condition affecting less than 200,000 persons in the U.S. or which will not be profitable within seven years following FDA approval, as defined in the 1984 amendments of the Orphan Drug Act. Dr. Haffner described the designation process of products as orphan and the incentives available to manufacturers, including tax incentives and exclusivity provisions. She explained the Orphan Products Grant Program, which funds clinical research for the purposes of accelerating or assisting in the approval of unapproved products or unapproved uses of approved products. The grant program has resulted in the approval of 27 orphan products to date. Dr. Haffner also briefly reviewed the Humanitarian Use Devices (HUD) provisions of the 1990 Safe Medical Devices Act.

Dr. Joanne Less, Director of the Investigational Device Exemption (IDE) and Humanitarian Device Exemption (HDE) Programs at the Office of Device Evaluation at FDA's CDRH, described the HUD provisions and HDE application and review process in more detail. Marketing approval of products with a HUD designation is based on the provision that the device does not expose patients to an unreasonable risk of illness or injury and that the probable benefits outweigh the risks of using the device. Dr. Less noted the dearth of HDE applications submitted to FDA for review and raised several issues that may need to be considered in order to increase the use of the HDE provisions.

Dr. Henrietta Hyatt-Knorr, Acting Director of the National Institutes of Health's (NIH) Office of Rare Diseases (ORD), presented an overview of ORD's history, mission, and activities. ORD's current activities include the implementation of recommendations of the National Commission of Orphan Diseases and the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research, support of scientific workshops and symposia, and maintenance of the medical genetics and rare disorders section of the Combined Health Information Database. She reported that legislation introduced this year (the Rare Diseases Act of 2001) would provide a statutory authorization for ORD and, if enacted, could enable the office to play a greater role in the support of rare disease research funded by NIH.

Dr. Glenn Miller, Associate Scientific Director of Genetics Applications at Genzyme, discussed three main issues in the development of genetic tests: information quality, assay quality, and process quality. Some of the challenges posed in the development of genetic tests for rare diseases include having an adequate number of clinical samples obtained with informed consent for research as well as having a sufficient variety of mutations to assay the sensitivity of the test. Other challenges related to the scope of knowledge about specific mutations and polymorphisms of a particular disease allele. Dr. Miller concluded that there are no shortcuts in the development of tests for rare diseases and that each test must meet the same high standards as set for other tests.

Dr. David Wenger, Professor of Neurology and Biochemistry and Molecular Genetic Pathology, and Director of the Lysosomal Diseases Testing Laboratory at Jefferson Medical College, reviewed the origin, history and development of a diagnostic program for testing for lysosomal storage disorders. Since 1973, Dr. Wenger has screened to diagnose approximately 30,000 patients for one of about 20 lysosomal storage disorders. Most of the genetic tests conducted in his laboratory are enzyme-based assays and only a small proportion are DNA-based. Dr. Wenger identified several major problems he has encountered in providing genetic testing for rare diseases, including a lack of physician awareness of available testing, receipt of inadequate clinical information or family history needed to determine appropriate tests to run, and requests for inappropriate tests. Dr. Wenger emphasized that only interested and skilled personnel should be allowed to process samples and perform assays and that knowledgeable persons handle inquiries regarding pending tests and interpretation of results. Dr. Wenger suggested that in many instances research laboratories are scientifically the best place to provide testing for rare diseases.

Lastly, Dr. David Ledbetter, Professor and Chair of the Department of Human Genetics at the University of Chicago, reviewed his experience in rare disease testing and partnering with research laboratories to develop and offer rare disease tests. Dr. Ledbetter emphasized the importance of providing testing through a CLIA-certified clinical laboratory to ensure the highest level of accuracy through trained or credentialed laboratory specialists and to minimize error. Dr. Ledbetter commented that funding for rare diseases has not increased appreciably, particularly research support to translate basic discoveries to clinical applications. Dr. Ledbetter also described the National Laboratory Network for Rare Disease Genetic Testing, a new program he has initiated to serve the genetic testing needs of families and individuals affected by rare diseases for which genetic testing is available.

A roundtable discussion following the presentations was held with the panelists and Committee members. Among the recommendations suggested by the panelists for consideration by the Rare Diseases Work Group included reimbursement for the professional services of laboratory consultations, enhanced support for translational research to apply scientific knowledge to clinical practice, and a rare disease database for genotype/phenotype correlation data.

Dr. Patricia Charache, liaison to the CLIAC, reviewed an issue she reported on in August regarding oversight of waived tests. CLIA oversight is not applied to laboratories with a certificate of waiver. The accurate performance of these tests is dependent on the laboratories following the manufacturer's instructions. However, a study by the Centers for Medicaid and

Medicare Services found that more than one third of waived test laboratories surveyed did not have instructions from manufacturers and another third did not follow the supplied instructions. Currently, only one genetic test is classified as waived but there is significant pressure on FDA to increase the number of tests classified as waived. CLIAC established a waived test working group and reviewed new guidance documents that were considered to be too permissive. FDA has signaled its intention to withdraw the guidance document and is currently re-considering how tests should be categorized as waived and who should be reviewing those tests.

Before adjourning, Dr. McCabe reviewed the information SACGT has requested from the HHS agencies represented on the Committee regarding their efforts to advance knowledge of the clinical validity and utility of genetic tests in four types of core activities: primary research studies; secondary analyses of existing data from multiple studies; projects involving the development or updating of information summaries for clinicians, laboratory personnel, policy-makers, patients/consumers and the general public; and information dissemination projects for professionals and the public. The request also asked for a description of each agency's specific role in increasing knowledge of the validity and utility of genetic tests through the four core activities; summaries of all projects (or if this is not feasible, a representative sample of projects) underway for increasing knowledge of validity and utility of genetic tests; the amount of resources devoted in fiscal years 1996 through 2000 to these activities; and coordination of core activities with other agencies and the extent to, and mechanisms by, which the agency shares relevant information with other agencies in order to increase knowledge of the validity and utility of genetic tests. The agencies will report back to the Committee at the February meeting.

Dr. McCabe also noted that SACGT has requested additional information from FDA about the Agency's specific plans for pre-market review of genetic tests. The questions include the anticipated steps in the pre-market review process and when is each step expected to be implemented; how the template information will be reviewed; what thresholds will genetic test developers be expected to meet in order to gain approval to market the test; how professional organizations may (both legally and practically) be involved in the pre-market review process and the process for granting deemed status to a professional organization; and whether FDA has the discretionary authority to apply its regulatory tools selectively for old and new genetic tests and to apply its regulatory tools selectively to test kits (developed by manufacturers) and not to in-house tests (performed by laboratories).