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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Genetic Testing

AGENCY: Office of the Secretary, DHHS.

ACTION: Request for public comment on a proposed template of genetic test information for use by health professionals.

SUMMARY: The Secretary's Advisory Committee on Genetic Testing (**SACGT**) was chartered to advise the Department of Health and Human Services on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests. **SACGT** recently completed its first report, Enhancing the Oversight of Genetic Tests (available at http://www4.od.nih.gov/oba/ **sacgt**.htm). **SACGT** stated in the report's overarching principles that genetics education of health professionals and the public about the appropriate use, interpretation, and understanding of genetic test results is critical to the successful implementation of genetic testing into health care.

To inform and educate health professionals on genetic testing and their appropriate uses, **SACGT** is developing a template of essential information elements about genetic tests. A **SACGT** working group, composed of **SACGT** members and ad hoc experts, identified seven key data elements about a genetic test that may be valuable to health professionals considering using a genetic test for patient care. At its November 2-3, 2000 meeting, **SACGT** reviewed the proposed genetic test information template and recommended public comment be solicited. After consideration of public comments, **SACGT**'s final draft of the template will be submitted to the Assistant Secretary of Health for transmittal to the Secretary of Health and Human Services.

DATES: The public is encouraged to provide written comments on the proposed genetic test information template by January 31, 2001. The following mailing address should be used: **SACGT**, National Institutes of Health, 9000 Rockville Pike, Building 1, Room 103, Bethesda, Maryland, 20892. **SACGT**'s facsimile number is 301-496-9839. Comments can also be sent via e-mail to hagas@od.nih.gov . All public comments received will be available for public inspection at the **SACGT** office between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION: Questions about this request for public comment can be directed to Dr. Susanne Haga, by e-mail (hagas@od.nih.gov .) or telephone (301-496-9838). The proposed template will also be posted on **SACGT**'s website for review and comment.

SUPPLEMENTARY INFORMATION: Decades of genetics research have brought about many important medical and public health advances. The pace of discovery

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in this area has enabled scientists to make rapid progress in understanding the role of genetics in many common yet complex diseases and conditions, such as heart disease, cancer, and diabetes. It also has increased knowledge that may lead to the development of new tests to identify these disease conditions in individuals, sometimes before symptoms occur. According to GeneTests, a genetic testing laboratory directory, genetic testing is clinically available for more than 400 diseases or conditions in more than 200 laboratories in the United States, and investigators are exploring the development of tests for an additional 338 diseases or conditions. However, most of the current genetic testing is for single gene disorders such as Huntington disease and cystic fibrosis.

Genetic tests can be performed for a number of purposes. Moreover, a test can be used in more than one way, such as when a test used for diagnostic purposes is also used to predict risk of disease. **SACGT** included the following types of testing within its definition: (1) An analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition; and (2) the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes. The purposes of both these types of genetic tests include directing clinical management, screening of newborns, predicting risks of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. Not included in this definition are tests that are used primarily for other purposes, but that may contribute to diagnosing a genetic disease (e.g., blood smear, certain serum chemistries), and tests conducted exclusively for forensic identification purposes.

In the past, many tests were developed to detect or confirm rare genetic diseases. More recently, tests have been developed to detect mutations that may be involved in or contribute to more common, complex conditions (such as breast, ovarian, and colon cancer and cardiovascular disease), the effects of which generally do not appear until later in life. Optimally, these tests are used to predict a person's predisposition to disease where there is a family history of the disease, and, in general, such tests are not recommended for individuals without such a history. However, in the future, the use of predictive tests may expand and be offered to individuals without a family history of certain diseases and conditions, e.g., common adult-onset disorders.

Proposed Template of Genetic Test Information

Due to the wide range of genetic tests, their multiple uses and complexities, and the rapidity with which they are being developed and introduced into clinical practice, health professionals should be knowledgeable about the basic elements of a genetic test to ensure their appropriate use. A **SACGT** working group developed a template of seven key essential data elements about genetic tests that could serve as a framework for an informational fact sheet. This fact sheet would be analogous to reference books or fact sheets describing intended uses, risks, and benefits of drugs for health professionals. Fact sheets for genetic tests could help encourage important information exchanges between health professionals who order genetic tests and laboratorians who provide the testing services. Information that is known about a genetic test in these seven areas should be included or referenced on the fact sheet. Equally important, when data are not available for a given element, the absence of such data should be specifically noted. It will also be important for the fact sheets to be updated periodically to reflect new scientific or clinical data. If the Food and Drug Administration (FDA) or other oversight bodies become involved in the review of genetic tests prior to clinical introduction,

the approved claims of the test should be stated as well.

The seven elements relate to the following areas: purpose of the test; clinical condition for which the test is performed; definition of the test; analytical validity, clinical validity, and clinical utility of the test; cost of the test and billing/reimbursement information. The seven elements are described in detail below along with the proposed sources for each element.

A. Purpose of the Test. **SACGT** proposes that the purpose of the test and the appropriate settings for offering the test should be clearly described. Examples of categories of test purposes could include predictive, carrier, prenatal, preimplantation, newborn, and diagnostic testing. Each category of test use represents a different test, even when the laboratory measurement(s) are the same. Therefore, all appropriate categories should be clearly described.

SACGT suggests that the laboratory providing the testing services should define the proper use of the test. Peer-reviewed literature as well as the laboratory's own data should be used to substantiate the appropriateness of the intended use(s) of a test. In addition, relevant clinical, professional, and health policy communities and government agencies should contribute to defining the appropriate uses of genetic tests through the development of practice standards and guidance documents.

B. Clinical Condition for Which Test is Performed. **SACGT** recommends that the clinical condition for which the test is to be performed be described. The prevalence or incidence of the disease or condition, its clinical manifestations, and prognosis to the extent known should be included in the description of the clinical condition. The testing laboratory should cite the clinical condition as part of its description of the intended use(s) of the test. Peer-reviewed literature should be referenced as appropriate. In addition, relevant clinical, professional, and health policy communities and government agencies should contribute to describing clinical manifestations, prevalence, and prognosis as appropriate.

C. Definition of Test. **SACGT** proposes that the specific laboratory measurement(s) of the test, e.g., specific mutation, metabolite, enzyme activity, be described in the information template for health professionals. The description should be written in a language that would be understandable to non- laboratorians. A description of what the test measures may also assist health professionals in interpreting the results.

D. Analytical Validity. **SACGT** recommends that information regarding the analytical validity of a test be provided in the information template to health professionals. **SACGT** believes that a genetic test should demonstrate analytical validity before the test is used for clinical purposes. Analytical validity is defined as the ability of a test to measure or detect the analyte it is intended to measure or detect. An analyte is defined as the substance measured by a laboratory test, e.g., DNA--mutation, allele, or chromosome, metabolites, or enzyme activity. Analytical validity includes analytical sensitivity (the probability that a test will detect an analyte when it is present in the sample) and analytical specificity (the probability that a test will be negative when an analyte is absent from a sample). Health professionals as well as patients should know whether a test can accurately detect the presence or absence of its intended target.

SACGT proposes that the laboratory providing the testing services supply specific information related to its assay.

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As with other elements, peer-reviewed literature may be referenced to substantiate claims of test performance.

E. Clinical Validity. **SACGT** proposes that information on the clinical validity of a test be provided to health professionals. **SACGT** defines clinical validity as the accuracy with which a laboratory

measurement predicts the presence or absence of a clinical condition. For diagnostic, prenatal, and carrier tests, accuracy could be expressed as clinical sensitivity (the probability a person with the disease, or who will get the disease, will have a positive result), clinical specificity (the probability that a test will be negative in a person who does not have or will not get the disease), positive predictive value (the probability that a person with a positive result has, or will get, the disease), and negative predictive value (the probability that a person with a negative test result does not have, or will not get, the disease). For predictive tests, **SACGT** proposes to define accuracy as the prediction of expressivity (the range of phenotypes associated with positive and negative test results) and age-related penetrance (likelihood of disease at a given age in test-positive individuals). In addition, health professionals should be made aware of other factors, such as environment or lifestyle, that may influence the development or prognosis of a disease or condition in an individual with a positive test result, as they may assist in their clinical management approaches.

SACGT suggests that the testing laboratory should define clinical validity as relevant to the proposed uses of the test. Peer-reviewed literature as well as the laboratory's own data should be used to substantiate the claims of clinical validity of the test. Information about the clinical validity should include, as necessary, a statement about the limitations of the available data. For example, if a test has been evaluated in only high-risk families, the absence of population-based data should be noted. More detailed consideration of clinical validity through research studies and clinical experience may contribute to the development of practice standards over time by the professional, medical, and health policy communities.

F. Clinical Utility. **SACGT** proposes that information relating to the clinical utility of a test be provided to health professionals. **SACGT** defines clinical utility as the contribution of the test result to improved outcome in the person tested. Clinical utility usually reflects the efficacy of clinical interventions for persons with positive test results. However, even when no interventions are available to treat or prevent the disease or condition, there may be other benefits associated with the knowledge of positive or negative test results.

If a clinical intervention is available for individuals who test positive for the disease or condition, this information should be provided to health professionals, along with the level of evidence regarding its efficacy. Other potential benefits associated with the knowledge of test results should also be described.

SACGT has not identified a specific source that would be responsible for providing information related to clinical utility. References to peer-reviewed literature or contact information for professional or patient advocacy organizations in the relevant field could be listed. Health professionals should also be active in investigating possible clinical interventions or preventive strategies. In-depth consideration of clinical utility through research studies and clinical experience will contribute to the development of practice standards and guidelines over time by professional medical and health policy communities and patient and disease advocacy organizations.

G. Cost of Test and Billing/Reimbursement Information. **SACGT** suggests that the testing laboratory provide information to health professionals on the cost of the test. At present, some genetic tests are very expensive, though, as technology advances and the use of these tests increases, it is expected that costs will decrease. If possible, the laboratory could also provide any information on billing and reimbursement policies for the test. For example, the laboratory may indicate which CPT codes should be used for billing purposes. In addition, since patients may wish to pay for the test directly due to concerns related to the confidentiality and privacy of test results, information on direct payments should be included. **SACGT** recognizes

that laboratories may have limited information regarding reimbursement policies since these are variable and often decided over time by third-party payors. Many health insurers provide information on their reimbursement policies via their web-site or customer information services.

Questions on Which Comment Is Being Solicited

1. Do the proposed elements sufficiently address the relevant information that should be made available to health professionals about a genetic test? Are there other elements that should be added to the template? If so, please define the element and propose a specific source for the element.
2. Are the proposed sources of information appropriate for each element?
3. Who should provide information regarding the clinical utility of a genetic test?
4. Would this information template be useful to you? If so, how?
5. How would this information best be disseminated to health professionals?
6.If FDA becomes involved in the oversight of genetic tests, much of the content of the proposed fact sheets will be considered during FDA's review process. In the interim, what other review mechanisms should be considered to ensure the accuracy of the material provided in the information sheets?

Dated: December 6, 2000.
Sarah Carr,
Executive Secretary, Secretary's Advisory Committee on Genetic Testing.
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