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Department of Health and Human Services

Secretary's Advisory Committee on Genetic Testing; Notice of Meeting

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Genetic Testing

AGENCY: Office of the Secretary, DHHS.

ACTION: Notice of Meeting and Request for Public Comments on Preliminary Final Recommendations on Oversight of Genetic Testing.

Pursuant to Public Law 92–463 notice is hereby given of a meeting of the Secretary's Advisory Committee on Genetic Testing (SACGT). The meeting will be held from 8:45 a.m. to 5:00 p.m June 5, 2000 to June 7, 2000 at the Governor's House Hotel, 1615 Rhode Island Avenue, NW, Washington, DC 20036. In addition to completing its report on oversight, the Committee will also be exploring the impact of gene patenting and restrictive licensing on the cost, quality, and accessibility of genetic testing, Federal regulatory requirements regarding informed consent in genetic research involving information-gathering about family members, and genetics education of health professionals. The meeting will be open to the public, with attendance limited to space available. Individuals who wish to provide public comment on the oversight recommendations of genetic tests or other issues should contact Susanne Haga at 301–496–9838. A draft agenda will be posted at the following website address http://www4.od.nih.gov/oba/sacgt.htm prior to the meeting.

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 of and use of genetic tests. SACGT is presently assessing the adequacy of current oversight of genetic testing in the United States, in consultation with the public. After careful analysis of the issues and an effort to gather and consider public comments, SACGT drafted preliminary conclusions and recommendations on oversight of genetic tests. It is now seeking further public comments on these preliminary conclusions and recommendations. The preliminary recommendations will also be posted on SACGT's website and sent to groups and individuals who submitted comments in the prior comment period.

The public is encouraged to submit written comments on this preliminary report by May 22, 2000. SACGT's mailing address is: SACGT, National Institutes of Health, 6000 Executive Blvd., Suite 302, 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. Questions about this request for public comment can be directed to Susanne Haga, Ph.D., Program Analyst, SACGT, by e-mail (hagas@od.nih.gov) or telephone (301–496–9838).

Adequacy of Oversight of Genetic Tests

Preliminary Conclusions and Recommendations of the Secretary's Advisory Committee on Genetic Testing

Executive Summary

The Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered in 1998 to advise the Department of Health and Human Services (DHHS) on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests. In June 1999, Dr. David Satcher, Assistant Secretary for Health and Surgeon General, asked SACGT to assess, in consultation with the public, the adequacy of oversight of genetic tests and, if warranted, based on a consideration of the public comments and an analysis of the issues, to recommend options for additional oversight and to ensure public access to quality genetic tests. Dr. Satcher asked the Committee to report back by March 15, 2000, and to organize its report around five major issues:

- What criteria should be used to assess the benefits and risks of genetic tests?
- How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories, and what kind of mechanism could be used to assign tests to the different categories?
- What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?
- What are the options for oversight of genetic tests and the advantages and disadvantages of each option?
- What is an appropriate level of oversight for each category of genetic test?

SACGT worked intensely through the summer and fall of 1999 to design a multifaceted process to gather public comments on genetic testing oversight issues. The public consultation process was carried out during a 60-day period from December 1, 1999, to January 31, 2000, and involved a **Federal Register** notice, a targeted mailing to 2,500 individuals and organizations, a website consultation, and a public meeting that was held on January 27, 2000. In addition, SACGT conducted a literature review and analysis of scholarly articles on genetic testing.

On February 24–25, 2000, SACGT met to review public comments received and to develop recommendations on the adequacy of oversight of genetic testing. SACGT carefully reviewed the public input received, which highlighted the importance of ensuring the quality of, and access to, genetic tests. In addition, many of the public comments expressed concern about the potential for genetic test results to be used to discriminate against people in areas such as employment and health insurance. After considering the public comments, SACGT developed the following preliminary overarching principles and recommendations.

Overarching Principles

- One of the main goals of genetic testing is to improve the health and well-being of individuals and families. No test should be introduced in the market before it is established that it can diagnose and/or predict a health-related condition accurately and safely. Thus, the public is best served by ensuring both the appropriate oversight of genetic tests and the continued development of genetic tests.
- The public, through involvement of advocacy groups, organizations, and individuals, needs to be involved in the ongoing consideration of issues surrounding genetic testing. This will be particularly important in addressing the concerns of minority populations and diverse communities regarding the purposes and uses of genetic testing.
- Since genetic education and counseling are critical to the appropriate use, interpretation, and understanding of genetic test results, efforts to ensure the education of the public and of health providers about genetics are necessary.
- Federal legislation is needed to prohibit discrimination in employment and health insurance based on genetic information. Federal legislation is also needed to protect the privacy of genetic information in medical records. Without these protections, the public will be reluctant to undergo genetic tests that might be beneficial to its health and well-being.

Recommendations

Issue 1: What criteria should be used to assess the benefits and risks of genetic tests?

- Analytical validity, clinical validity, clinical utility, and social issues should be the major criteria used

to assess the benefits and risks of genetic tests.

Issue 2: How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories, and what kind of mechanism could be used to assign tests to the different categories?

- For the purposes of review, a useful way to consider tests is to assess them across several dimensions. These criteria are necessary but may not be sufficient for all tests.
- Is the test at this stage of development primarily diagnostic or predictive?
- Is the mutation being tested for highly or weakly penetrant?
- Is a proven intervention available to prevent or treat the disease for which the test is being conducted?
- Is the test used for population-based screening or testing of individuals?
- Is the prevalence of the disorder for which the test is used high or low?
- Is there potential for stigmatization of individuals or groups from the test results?
- Is the test designed or able to identify more than one condition?

For example, predictive tests require more scrutiny than do diagnostic tests. Similarly, tests for weakly penetrant mutations require more assessment than do those for highly penetrant genes. Tests for conditions for which no interventions are available would be more problematic than tests for conditions for which interventions exist. Thus, for example, a high-scrutiny test would be one that is predictive, detects a mutation that is weakly penetrant, and for which a proven intervention is not available. These dimensions should be considered in the review of genetic tests, and test developers should indicate the categories into which their test(s) fit.

Issue 3: What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?

- The responsibility for collecting initial data on the analytical validity of a test lies with the test developer.
- Initial knowledge of the clinical validity of a genetic test is essential to assess its safety and efficacy. Further knowledge will depend on additional research and the long-term systematic collection and analysis of additional data. Researchers and test developers should gather and share initial data on the clinical validity and utility of genetic tests.
- Since data sharing and analysis are critical, relevant DHHS agencies should work collaboratively with researchers and test developers to advance data collection and provide this information to health care providers and the public. Initial exploratory data collection efforts among DHHS agencies, which have been coordinated by the Centers for Disease Control and Prevention, have been of value and should continue.
- Protecting the confidentiality of data and the privacy of individuals is essential to the progress of data collection efforts.
- Laboratories should be encouraged or required to make pre- and post-marketing data on genetic tests available in a timely, accurate, and understandable manner.
- Post-market data collection can enhance understanding of current applications of a genetic test and is important for any expansion of the use of a genetic test beyond the initial indications approved when the test is made available. Laboratories providing clinical genetic services should commit to post-market data collection efforts.

Issue 4: What are the options for oversight of genetic tests and the advantages and disadvantages of each option?

- Based on the rapidly evolving nature of genetic tests, their anticipated widespread use, and extensive concerns expressed by the public about their potential for misuse or misinterpretation, additional oversight is warranted for all genetic tests.
- The Food and Drug Administration (FDA) should be the lead federal agency responsible for reviewing, approving, and labeling of all new genetic tests. FDA review should focus on the claims of analytical and clinical validity made by the developer of the test and be appropriate to the level of scrutiny warranted by the test. The agency should develop flexible mechanisms for review of new genetic tests that minimize both the time and the cost of review without jeopardizing the quality of the assessment of test validity. These mechanisms should, for example, include the use of deemed reviewers and standards developed in concert with professional organizations.
- Clinical Laboratory Improvement Amendment regulations should be augmented to provide more specific provisions for ensuring the quality of laboratories conducting genetic tests.
- DHHS agencies should be provided with sufficient resources to carry out expanded oversight of genetic tests, including coordinated data collection, review, and information dissemination.

Issue 5: What is an appropriate level of oversight for each category of genetic test?

- Institutional Review Board review should be conducted of all research protocols for genetic tests in which individually identifiable human subjects or samples are used, regardless of the funding source. Institutions that lack an IRB must obtain the services of a qualified board. Efforts will be needed to ensure that IRBs are suitably equipped to carry out these reviews. In addition, informed consent must be obtained from all subjects participating in such research.
- FDA should give particular attention to the review of genetic tests that are used to predict diseases and conditions for which no safe and effective interventions are available. Other tests may also warrant a higher level of scrutiny in the FDA review process.
- In the future, tests may be developed that raise major social and ethical concerns. Because FDA's review will focus on assuring the analytical and clinical validity of a test, the agency's capacity to assess the ethical and social implications of a test may not be sufficient. The Secretary should consider the development of a mechanism to ensure the identification, and appropriate review, of tests that raise major social and ethical concerns.
- The U.S. Preventive Services Task Force with augmented resources, or a similar body set up or given deemed status for this purpose, should review genetic tests that are already on the market for evaluation of clinical efficacy and development of guidelines about their appropriate use.

Additional Recommendations for the Appropriate Use of Genetic Tests

- Individual and family members considering a genetic test should have access to appropriate genetic education and counseling resources to ensure their ability to make an informed decision about being tested.
- Written informed consent should be obtained for tests used for predictive purposes. The extent to which written informed consent should be obtained for all other genetic tests requires further deliberation.
- Current regulations under FDA and the Federal Trade Commission should be enforced in the area of genetic test promotion and marketing.

On March 15, 2000, SACGT forwarded preliminary recommendations to Dr. Satcher. At this time, the Committee invites public comment on this preliminary draft of its conclusions and recommendations, and at its next meeting, June 5–7, 2000, the Committee will review the comments received and will then develop a final

report to the Secretary. With the completion of this assignment, SACGT will move on to consider a number of other high-priority issues raised by genetic tests that are not the subject of this report.

Adequacy of Oversight of Genetic Tests

Preliminary Conclusions and Recommendations of the Secretary's Advisory Committee on Genetic Testing

Introduction

The Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered in June 1998 to advise the Department of Health and Human Services (DHHS) on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests. The formation of SACGT was recommended by the National Institutes of Health (NIH)-Department of Energy (DOE) Task Force on Genetic Testing and the Joint NIH-DOE Committee to Evaluate the Ethical, Legal, and Social Implications Program of the Human Genome Project. At SACGT's first meeting in June 1999, Dr. David Satcher, Assistant Secretary for Health and Surgeon General, asked the Committee to assess, in consultation with the public, the adequacy of current oversight of genetic tests and, if warranted, to recommend options for additional oversight.

Dr. Satcher provided SACGT with a framework of five central questions around which to organize the assessment and requested that SACGT report back by March 15, 2000. During the summer and fall of 1999, the Committee gathered background information on genetic testing, designed five approaches to gather professional and public opinions on oversight of genetic testing, and prepared a document for soliciting public comment. The public consultation was held from December 1, 1999, to January 31, 2000. On February 24–25, 2000, the Committee met to review the public input received and to develop conclusions and recommendations on the adequacy of oversight of genetic testing. SACGT submitted a brief report of its preliminary recommendations to Dr. Satcher on March 15, 2000.

This report presents for public comment SACGT's preliminary conclusions and recommendations. Public comments will be reviewed at SACGT's next meeting, June 5–7, 2000, after which the Committee will submit its final conclusions and recommendations to the Secretary.

Background

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

Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, and/or gene products to determine whether an alteration is present that is causing or is likely to cause a specific disease or condition. Genetic tests can be performed for a number of purposes. Moreover, a test can be used in more than one way. For example, a test used for diagnostic purposes could also be used to predict risk of disease.

- *Preimplantation diagnosis* is used following *in vitro* fertilization to diagnose a genetic disease or condition in a preimplantation embryo.
- *Prenatal diagnosis* is used to diagnose a genetic disease or condition in a developing fetus.
- *Newborn screening* is performed in newborns in state public health programs to detect certain genetic diseases for which early diagnosis and treatment are available.
- *Carrier testing* is performed to determine whether an individual carries one copy of an altered gene for a particular recessive disease. The term ''recessive'' refers to diseases that will occur only if both copies of a gene that an individual receives have a disease-associated mutation; thus, each child born to two carriers of a mutation in the same gene has a 25-percent risk of being affected with the disorder.
- *Diagnostic/confirmatory testing* is used to identify or confirm the diagnosis of a disease or condition in an affected individual. Diagnostic testing may also be useful to help determine the course of a disease and choice of treatment.
- *Presymptomatic testing* is used to determine whether individuals who have a family history of a disease but no current symptoms have the gene alteration associated with the disease.
- *Predictive testing* determines the probability that a healthy individual with or without a family history of a certain disease might develop that disease.

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. In general, such tests are not recommended for individuals without a family history of the disease.

The process of discovering and understanding genetic mutations and their role in disease is extremely complex and can involve many years of investigation. In addition, because the genome is vast, discovering a specific disease-related gene has, up to now, been a difficult and time-consuming process. Nevertheless, the development and clinical use of genetic tests is expected to increase rapidly over the next decade, driven in large part by research funded and conducted by agencies within DHHS, especially NIH, as well as by work in the private sector. The Human Genome Project, a major international collaborative effort established and supported by public groups, including NIH and DOE, is expected to have a major impact on gene discovery and genetic test development. The results of the Human Genome Project, along with new technical advances, such as tandem mass spectrometry, microarrays, and gene chips, will speed the pace of disease gene discovery.

Once the entire sequence of the human genome has been determined, scientists will have a critical tool to better understand the contribution of each gene to the development and function of the human body. Even then, however, the role played by a specific gene mutation in disease will not be completely understood because of the effects of confounding factors such as gene-gene interactions and environmental influences (smoking and diet, for example). A full understanding of the role of genetic mutation in the current and future health of individuals will require more research, ranging from detailed biochemical studies to population-based studies that focus on clarifying and elucidating the significance of how genes interact with each other and with the environment.

A rising new area in medicine is pharmacogenomics, the combination of the fields of genomics and pharmacology that builds on the work of the Human Genome Project. Much of human variation is due to small differences in a person's DNA, referred to as single nucleotide polymorphisms (SNPs). Pharmacogenomics is the

application of genetic science and technology to understand how these genetic variations influence responses to medicines. Because individuals may not react in the same way to a given drug, understanding the correlation between a person's unique SNPs and his or her drug response will be of great benefit. This knowledge will help health professionals determine a person's likely response to a medicine before it is prescribed. Other potential benefits of pharmacogenomics include the development of effective therapies, prescribed with less trial and error, and the ability to target beneficial drugs and reduce adverse drug reactions.

At present, genetic testing is clinically available for more than 300 diseases or conditions in more than 200 laboratories in the United States, and investigators are exploring the development of tests for an additional 325 diseases or conditions.[i] A recent survey of genetic testing laboratories found that over a three-year period, the total number of genetic tests performed increased by at least 30 percent each year, rising from nearly 100,000 in 1994 to more than 175,000 in 1996.[ii]

In 1997, the NIH–DOE Task Force on Genetic Testing'charged to review genetic testing in the United States and to make recommendations to ensure the development of safe and effective genetic tests—concluded that although genetic testing was developing successfully in the United States, some concerns about it exist.[iii] The Task Force grouped the concerns into four major categories: (1) The manner in which tests are introduced into clinical practice; (2) the adequacy and appropriate regulation of laboratory quality assurance; (3) the degree of understanding of genetics on the part of health care providers, patients, and the public; and (4) the continued availability and quality of testing for rare diseases.

A number of the Task Force recommendations were aimed at enhancing the way in which tests are developed, reviewed, and used in clinical practice. The Task Force explored the question of how tests should be assessed and made suggestions about the need for additional data and external review of genetic tests. While recommending that revisions to the current review process may be needed to assess the effectiveness and usefulness of genetic tests, the Task Force did not specify how the review of laboratory-based genetic tests should be changed.

DHHS established SACGT to help the nation prepare for some of the revolutionary changes in clinical and public health practice resulting from the continued and increasing use of genetic testing. SACGT builds on the work of the Task Force by assessing whether current programs for assuring the accuracy and effectiveness of genetic tests are satisfactory or whether other measures are needed.

It is critical for the public to understand that while genetic tests can be extremely beneficial, they also can pose risks, including medical and psychological risks, risks to families, and social and economic risks that may affect entire groups as well as individuals. As the diagnostic and predictive uses of genetic testing continue to increase, and as the effects of testing on society become clearer, its impact will become broader and ultimately will affect all of our lives. Because the use and ramifications of these tests are not yet fully realized, additional consideration is needed regarding whether current programs for assuring the safety and effectiveness of genetic tests are satisfactory or whether additional oversight measures are needed before such tests are introduced for wide-scale use.

Charge to the Committee

SACGT was asked to frame its recommendations around the following five issues:

- What criteria should be used to assess the benefits and risks of genetic tests?
- How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories, and what kind of mechanism could be used to assign tests to the different categories?
- What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?
- What are the options for oversight of genetic tests and the advantages and disadvantages of each option?
- What is an appropriate level of oversight for each category of genetic test?

The level of oversight of genetic tests has significant medical, social, ethical, legal, economic, and public policy implications. Because the system of oversight can greatly affect those who undergo genetic testing, those who provide tests in health care practice, and those who work or invest in the development of such tests—SACGT actively sought public input on the five questions listed above. The Committee concluded that to fully respond to its charge, it was especially important to reach out to diverse communities that might have particular concerns about genetic testing and members of the public who have not yet undergone genetic testing, but are likely to face decisions about these tests in the future.

Public Consultation Process

SACGT employed several mechanisms for gathering public comment and assessing the status of prior debate about the issues surrounding genetic testing. A **Federal Register** notice, a targeted mailing to interested individuals and organizations, a web-based consultation, and a public meeting provided several venues in which the public could submit comments.[iv] To provide a framework for receiving input on the five questions in the Committee's charge, SACGT developed a document, A Public Consultation on Oversight of Genetic Tests, which provided background information about genetic tests, including their current limitations, benefits and risks, and provisions for oversight currently in place. A summary of the consultation document was prepared in English and Spanish.

SACGT received nearly 400 comments from the general public, health professionals, individuals and families affected with genetic conditions, religious groups, state health departments, industry, professional organizations, academia, and patient advocacy organizations. The comments were analyzed qualitatively with respect to the five specific issues SACGT was asked to address. (Because the comments were not a representative sample of the U.S. population, no attempt was made to perform statistical analysis.) SACGT was enormously impressed with the effort people made to participate in this process and believes that its recommendations are strengthened and enriched by the views, opinions, and perspectives the public has shared.

As part of its effort to gather broad-based perspectives on the oversight of genetic testing, SACGT also conducted a literature review and analysis of more than 70 published scholarly articles on genetic testing. Most of the articles were published within the last five years and were written by professionals in the fields of law, science, and bioethics.

Characteristics of Genetic Tests and Implications for Oversight

Genetic tests currently have certain limitations that are relevant to the issue of oversight.[v] One important limitation is that a test may not detect every mutation a gene may have. (A single gene can have many different mutations, and they can occur anywhere along the gene.) Moreover, not all mutations have

the same effects. For example, more than 800 different mutations of the cystic fibrosis gene have been identified, some of which cause varying degrees of disease severity and some of which appear to cause no symptoms at all. This means that a positive test for a specific cystic fibrosis mutation may not provide a clear picture of how the disease is likely to affect an individual. A negative test result cannot completely rule out the disease because the test will usually focus only on the more common mutations and will not detect rare ones. In addition, the frequency of common cystic fibrosis mutations varies among population groups.

Complexity of Human Disease

Another current limitation of genetic tests, especially if used for predictive purposes, relates to the complexities of how diseases develop. Diseases and conditions can be caused by the interaction of many genetic and environmental factors. Thus, predictive tests cannot provide absolute answers for everyone who might be at risk for a disease such as breast or colon cancer. For example, mutations in the breast cancer 1 gene (BRCA1) occur in about half of families with histories of multiple cases of breast and ovarian cancer. If a woman with no family history of the disease has the BRCA1 mutation, it may not mean that she will develop breast or ovarian cancer. Likewise, if she does not have the mutation, she still cannot be sure she will never develop breast or ovarian cancer. Furthermore, because of varying genetic and environmental factors, even the same mutations may present different risks to different people and to different populations. The same mutation in the cystic fibrosis gene in individuals from different populations may have different clinical effects as a result of variations in other genetic and environmental factors.

Gap Between Diagnosis and Treatment

Another important consideration related to the limitations of genetic testing is that effective treatments are not available for many diseases and conditions now being diagnosed or predicted through genetic testing, and, in some instances, they may not be available for some time—a situation sometimes called the ''therapeutic gap.'' However, while knowledge that a disease or condition will or could develop may not provide any direct clinical benefit, it may lead to increased monitoring that could help manage the disease or condition more effectively. At the same time, information about risk of future disease can have significant emotional and psychological effects, and, in the absence of privacy and anti-discrimination protections, that information can also lead to discrimination or other forms of misuse of personal genetic information.

The Changing Nature of Genetic Information

In addition to the limitations of genetic tests, information provided by genetic tests also has potential benefits and risks. Understanding the benefits and risks of a genetic test to individuals or particular populations, which may change over time as more information is gathered, is critical in determining its appropriate use in clinical and public health practice. As further research is conducted and knowledge gained, the validity of test results may increase or decrease.

Potential Benefits of Genetic Tests

Individuals with a family history of a disease live with uncertainties about their own lives as well as their children's futures that may be relieved by having a genetic test. For example, if the test result is positive, it can provide an opportunity for psychological counseling and for the introduction of risk-reducing interventions, such as regular screening practices and healthier lifestyles. Early interventions (such as annual colonoscopies to check for precancerous polyps, the earliest signs of colon cancer) could help prevent deaths from colon cancer. If the test result is negative (the mutation is not present), in addition to feeling tremendous relief, individuals may also no longer need frequent checkups and screening tests, some of which may be uncomfortable and/or expensive.

Genetic tests can sometimes provide important information about the course a disease may take. For example, certain cystic fibrosis mutations are predictive of a mild form of the disease. Other gene mutations may identify cancers that are likely to grow aggressively.

Genetic tests also can provide information to improve treatment strategies. Because genetic factors may affect how individuals respond to drugs, the knowledge that an individual carries a particular genetic mutation can help health care providers tailor therapy. For example, individuals with Alzheimer disease who have two copies of a certain gene do not respond to a drug used in some Alzheimer's patients. [vi] In individuals with the disease who do not have both copies of that gene, however, the drug seems to slow progression of the disease.

Potential Risks of Genetic Tests

However, at the same time that genetic tests offer great potential benefits, they can also pose risks. Genetic testing poses potential physical, medical, psychological, and social and economic risks to individuals being tested and to members of their families. For the most part, the physical risks of genetic testing are minimal, because most genetic tests are performed on blood samples or cells obtained by swabbing the lining of the cheek. The procedures required to carry out prenatal genetic testing can cause miscarriage in 1 in 200 to 400 cases.

The medical risks of genetic testing relate to actions taken in response to the results of a genetic test. Positive test results can have an impact on a person's reproductive and other life choices. For example, individuals with positive test results may choose not to have children or may opt to take extraordinary preventive measures, such as surgical removal of the breasts to prevent the possible development of cancer. Individuals with negative test results may forgo screening or preventive care because they mistakenly believe they are no longer at risk for developing a given disease. Substantial risks are posed by incorrect test results or the misinterpretation of test results. False negative test results can mean delays in diagnosis and treatment, while false positive results can lead to follow-up testing and therapeutic interventions that are unnecessary, inappropriate, and sometimes irreversible.

Genetic test results have potential psychological and emotional risks. Predictive testing of healthy individuals may have significant psychological and social impacts. The knowledge about disease risk may prove burdensome because of uncertainty about how to manage risk when data about the efficacy or preventive measures is constantly changing, such as controversies about dietary interventions or the use of hormone replacement therapy in preventing heart disease.

The emotional impact of positive test results can be significant and can cause persistent worry, confusion, anger, depression, and even despair. Individuals who have relatives with a disorder may have developed a frightening picture of what their own future may hold. Negative test results also can have significant emotional effects. While most people will feel greatly relieved by a negative result, they may also feel guilty for escaping a disease that others in the family have developed (known as survival guilt). A

negative test result may provide a false sense of security because an individual may not understand that even with a negative test result, he or she still bears the same risk of disease as the general population.

Because genetic test results reveal information about the individual and the individual's family, test results can shift family dynamics in pronounced ways. For example, if a child tests positive for sickle cell trait (having one copy of the sickle cell gene) during newborn screening, it implies that one of the parents is a carrier. It is also possible for genetic tests to inadvertently disclose information about a child's parentage.

Genetic test results can pose risks for groups if they lead to stigmatization of that group and discrimination of its members. Concerns about the potential risks of discrimination and stigmatization, based on information gained from genetic testing are particularly acute among groups who have experienced genetic discrimination in the past and other forms of discrimination.

It is important to point out that the potential risks described above relate to genetic testing for conditions that are solely health-related. In the future, it may be possible to develop tests that could be used to diagnose conditions that are related to certain predispositions that also have a behavioral component, such as alcohol abuse, nicotine addiction, or eating disorders, or to predict future behavior. Although the assumption that single genes, or even many genes, can predict complex human actions is simplistic, the possibility of such tests raises profound concerns because their potential psychological, social and economic harms are so significant and the potential misuse of such information is so great. Because of these complexities, SACGT focused its discussions on the use of genetic tests to determine health-related information about individuals and/or families.

Current System of Oversight of Genetic Tests

As part of its charge, SACGT reviewed the provisions for oversight of genetic tests already in place. Currently, government agencies accord genetic and nongenetic tests the same level of oversight. Genetic tests are regulated at the federal level through three mechanisms:

(1) the Clinical Laboratory Improvement Amendments (CLIA);

(2) the Federal Food, Drug, and Cosmetic Act; and

(3) during investigational phases, the Federal Policy for the Protection of Human Subjects (45 CFR part 46, 21 CFR part 50, and 21 CFR part 56).

Four DHHS organizations have roles in the oversight of genetic tests: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Care Financing Administration (HCFA), and the Office for Protection from Research Risks (OPRR). Although they do not have regulatory functions, NIH, the Health Resources and Services Administration (HRSA), and the Agency for Healthcare Research and Quality (AHRQ) support research activities and demonstration projects that generate knowledge about and experience with genetics and genetic testing. In addition, some states regulate genetic tests, and some professional organizations have issued relevant guidelines for professional practice.

The Roles of CDC and HCFA

All laboratory tests performed for the purpose of providing information about the health of an individual must be conducted in laboratories certified under CLIA. The regulatory requirements applied to these laboratories increase in stringency with the complexity of the tests performed. Under CLIA, HCFA's Division of Laboratories and Acute Care, in partnership with CDC's Division of Laboratory Systems, develops standards for laboratory certification. In addition, CDC conducts studies and convenes conferences to help determine when changes in regulatory requirements are needed. The advice of the Clinical Laboratory Improvement Advisory Committee may also be sought regarding these matters.

The CLIA program provides oversight of laboratories through on-site inspections conducted every two years by HCFA, using its own scientific surveyors or surveyors of deemed organizations or state-operated CLIA programs approved for this purpose. This oversight includes a comprehensive evaluation of the laboratory's operating environment, personnel, proficiency testing, quality control, and quality assurance. The laboratory director plays a critical role in assuring the safe and appropriate use of laboratory tests. The laboratory director must meet the required CLIA qualifications for laboratory director and must ensure that the test methodologies selected are capable of providing the quality of results required for patient care. Laboratory directors are required to take specific actions to establish a comprehensive quality assurance program, as outlined by CLIA, that ensures that the continued performance of all steps in the testing process is accurate. Although laboratories under CLIA are responsible for all aspects of the testing process (from specimen collection through analysis and reporting of the results), CLIA oversight has emphasized intra-laboratory processes as opposed to the clinical uses of test results.

CLIA has not specifically outlined in its current review processes additional aspects of oversight that are critical to the appropriate use of genetic tests, such as clinical validity and clinical utility. Also unaddressed are the issues of informed consent for clinical genetic testing after the research phase and adequate access to genetic counseling to assure the appropriate transfer of information. HCFA and CDC are taking steps to develop more specific laboratory requirements for genetic testing under CLIA, including provisions for the pre- and post-analytical phases of the testing process, and CDC will be issuing a Notice of Intent in the **Federal Register** to gather public comment on the proposed changes to CLIA.

Through its Office of Genetics and Disease Prevention, CDC also has a role in addressing the public health impact of advances in genetic research, furthering the collection, analysis, dissemination, and use of peer-reviewed epidemiologic information on human genes and coordinating the translation of genetic information into public health research, policy, and practice. CDC is also leading an interagency effort to explore how voluntary, public/private partnerships might help encourage and facilitate the gathering, review, and dissemination of data on the clinical validity of genetic tests. Two pilot data collection efforts, one for cystic fibrosis and one for hereditary hemochromatosis, are in the preliminary stages.

The Role of FDA

All laboratory tests and their components are subject to FDA oversight under the Federal Food, Drug, and Cosmetic Act. Under this law, laboratory tests are considered to be diagnostic devices, and tests that are packaged and sold as kits to multiple laboratories require pre-market approval or clearance by FDA. This pre-market review involves an analysis of the device's accuracy as well as its analytical sensitivity and specificity. Pre-market review is performed based on data submitted by sponsors to scientific reviewers in the Division of Clinical Laboratory Devices in FDA's

Office of Device Evaluation. In addition, for devices for which the link between clinical performance and analytical performance has not been well established, FDA requires that additional analyses be conducted to determine the test's clinical characteristics, that is, its clinical sensitivity and specificity. In some cases, FDA requires that the predictive value of the test be analyzed for positive and negative results.

The majority of new genetic tests are being developed by laboratories and are being provided as clinical laboratory services. These tests are referred to as in-house tests or ''home brews.'' FDA has stated that it has authority, by law, to regulate such tests, but the agency has elected as a matter of enforcement discretion to not exercise that authority, in part because the number of such tests is estimated to exceed the agency's current review capacity.

However, FDA has taken steps to establish a measure of regulation of home brew tests by instituting controls over the active ingredients (analyte-specific reagents) used by laboratories to perform genetic tests. This regulation subjects reagent manufacturers to certain general controls, such as good manufacturing practices.

With few exceptions, however, the current regulatory process does not require a pre-market review of the reagents. (The exceptions involve certain reagents that are used to ensure the safety of the blood supply and to test for high-risk public health problems such as HIV and tuberculosis.) The regulation restricts the sale of reagents to laboratories performing high-complexity tests and requires that certain information accompany both the reagents and the test results. The labels for the reagents must, among other things, state that ''analytical and performance characteristics are not established.'' Also, the test results must identify the laboratory that developed the test and its performance characteristics and must include a statement that the test ''has not been cleared or approved by the U.S. FDA.'' In addition, the regulation prohibits direct marketing of home brew tests to consumers. In 1999, FDA established the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee to serve as a source of independent advice in the area of DNA-based diagnostics.

The Role of Regulations Protecting Human Subjects

Additional oversight is provided during the research phase of genetic testing if the research involves human subjects or identifiable samples of their DNA. OPRR and FDA administer regulations governing the protection of human research subjects. OPRR oversees the protection of human research subjects in DHHS-funded research. FDA oversees the protection of human research subjects in trials of investigational (not yet approved) devices, drugs, or biologics being developed for eventual commercial use.

Fundamental requirements of these regulations are that experimental protocols involving human subjects must be reviewed by an organization's Institutional Review Board (IRB) to assure the safety of the subjects, to review and approve the informed consent process, and to evaluate whether risks outweigh potential benefits. The regulations apply if the trial is funded in whole or in part by a DHHS agency or if the trial is conducted with the intent to develop a test for commercial use. However, FDA regulations do not apply to laboratories developing home brew genetic tests, because at present FDA has elected not to exercise its enforcement authority. CLIA requirements apply to DHHS-funded research only if the results of the genetic test are used for patient care, meaning that results are provided to a subject, to the subject's family, or to the subject's health care provider. OPRR regulations would apply if the laboratory was funded by DHHS or was conducting research at an institution that receives DHHS funding.

The Role of NIH

The mission of NIH is to support and conduct medical research to improve health. This research encompasses basic, clinical, behavioral, population-based, and health services research. In addition to funding a substantial amount of genetics research, including the Human Genome Project, and assuring that the research is conducted in accordance with human subject regulations and other pertinent guidelines, NIH supports a number of other programs that have an important role in disseminating knowledge and technology to the public and private sectors. NIH also produces consensus statements and technology assessment reports on issues important to health care providers, patients, and the general public. Topics related to genetic testing have included the development and assessment of newborn screening for sickle cell disease, genetic testing for cystic fibrosis, and screening for and management of phenylketonuria (PKU).

The Role of AHRQ

As the lead federal agency in health care quality, AHRQ is expected to play a greater role in promoting research on optimal methods of organizing, delivering, and financing genetic services and measuring the impact of these factors on the quality of patient care. AHRQ now plays an important role in making better health-related information available to health plans, purchasers of health care, clinicians, and patients, and in developing methods for facilitating shared patient-physician decision-making. In particular, the agency has developed an instrument (Consumer Assessment of Health Plans, or CAHPS) that allows consumers to assess their current health plan and a website that catalogues clinical practice guidelines. The Technology Assessment Program of the agency has a role in rigorously evaluating the beneficial and adverse outcomes associated with health care interventions (both diagnostic and therapeutic) in order to inform consumers, health professionals, and payors. AHRQ also supports the U.S. Preventive Services Task Force, which rigorously reviews evidence for the effectiveness of more than 100 interventions to prevent illnesses and conditions, including screening tests for genetically determined conditions such as PKU and Down Syndrome, and recommends which of these interventions clinicians should provide to their patients.

The Role of HRSA

The mission of HRSA is to assure access to health care, including genetic services, for those who are medically underserved. Access is attained through a broad range of programs including support for community health centers, maternal and child programs, health professional training programs, and state public health agency infrastructure (Maternal and Child Health Block Grants). The Genetic Services Program of HRSA promotes support and leadership for assurance, assessment and policy development for utilization of genetic medicine and technology within health care and public health practice. In this role, HRSA has supported the development and quality assurance of screening tests for PKU, congenital hypothyroidism, and sickle cell anemia and for the management of these conditions within the health care setting and within newborn screening programs. In addition, HRSA has provided funding to assist public health systems develop genetic medicine and technology and demonstration projects

related to the translation of genetic technology into practice. With a special focus on underserved populations, these programs have evaluated how genetic tests are used in practice and have identified barriers to access and use.

The Role of the States

State health agencies, particularly state public health laboratories, have an oversight role in genetic testing, including the licensure of personnel and facilities that perform genetic tests. State public health laboratories and state-operated CLIA programs, which have been deemed equivalent to the federal CLIA program, are responsible for quality assurance activities. A few states, such as New York and California, have promulgated regulations that go beyond the requirements of CLIA. States also administer newborn screening programs and provide other genetic services through maternal and child health programs.

The state newborn screening laboratories must meet the requirements of CLIA's quality control and proficiency testing programs, but in general there is little Federal oversight of their programs. State newborn screening laboratories and many commercial laboratories that perform testing for state newborn screening programs have used the National Newborn Screening Quality Assurance Program for verifying test accuracy and for meeting CLIA quality assurance requirements. This is particularly important because of the absence of a requirement for HCFA-approved proficiency testing programs for newborn screening.

The Role of the Private Sector

Recognized professional organizations provide oversight in voluntary partnership with HCFA and CDC, some of which serve as agents for the government in accreditation activities. These groups also develop laboratory and clinical guidelines and standards. A number of organizations are involved in helping to assure the quality of laboratory practices and in developing clinical practice guidelines to ensure the appropriate use of genetic tests. These organizations include the following:

- the College of American Pathologists (CAP), which develops standards for its membership and establishes and operates proficiency testing programs;
- the NCCLS (formerly called the National Committee on Clinical Laboratory Standards), which develops standards for test methodologies;
- the American College of Medical Genetics (ACMG), which develops guidelines for the use of particular tests and test methodologies and works with CAP to provide proficiency tests for certain genetic tests; and
- COLA, a nonprofit, physician-directed, national accrediting organization whose purpose is to promote excellence in medicine and patient care through programs of voluntary education, achievement, and accreditation.

Other organizations, such as the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, the American Society of Human Genetics, and the National Society of Genetic Counselors, are also involved in the development of guidelines and recommendations regarding the appropriate use of genetic tests. Patient advocacy groups, as well as individuals and families affected with genetic conditions, also play an important role in setting standards and in developing guidelines through advocacy and monitoring of health care practices.

Conclusions and Recommendations

SACGT was asked to assess whether current programs for assuring the accuracy and effectiveness of genetic tests are satisfactory or whether other measures are needed. This assessment requires consideration of the potential benefits and risks (including social, economic, psychological, and medical harms) to individuals, families, and society, and, if necessary, the development of a method to categorize genetic tests according to these benefits and risks. Considering the benefits and risks of each genetic test is critical in determining its appropriate use in clinical and public health practice.

Genetic tests offer great promise and provide hope for many people who wish to improve the health of their families and themselves. At the same time, if introduced prematurely or applied inappropriately, the outcomes of genetic testing could place some individuals and groups at risk. Thus, an important balance must be struck between the need to encourage the development and dissemination of new tests and the need to ensure that their introduction yields more benefit than harm.

SAGCT was guided by a recurrent theme that emerged from the public comments. Although many citizens believe that the risks and potential benefits of genetic tests are no different than those posed by any other type of medical test, there is a widespread perception that these tests are different and that people experience genetic testing in a way that is dissimilar to the experience of other forms of medical testing.

Comments received from the public by SACGT highlighted lingering and persistent concerns about the risks of inappropriate disclosure of genetic information about individuals and the potential that such disclosure would result in stigma and discrimination. One individual wrote that the public ''will not be able to utilize fully the promise of genetic testing without assurances of the privacy of test results and safeguards against discrimination in health care and employment.''

Based on these and other concerns, SACGT arrived at several overarching principles that address public concerns and relate to the establishment of enhanced oversight.

- One of the main goals of genetic testing is to improve the health and well-being of individuals and families. No test should be introduced in the market before it is established that it can diagnose and/or predict a health-related condition accurately and safely. Thus, the public is best served by ensuring both the appropriate oversight of genetic tests and the continued development of genetic tests.
- The public, through involvement of advocacy groups, organizations, and individuals, needs to be involved in the ongoing consideration of issues surrounding genetic testing. This will be particularly important in addressing the concerns of minority populations and diverse communities regarding the purposes and uses of genetic testing.
- Since genetic education and counseling are critical to the appropriate use, interpretation, and understanding of genetic test results, efforts to ensure the education of the public and of health providers about genetics are necessary.
- Federal legislation is needed to prohibit discrimination in employment and health insurance based on genetic information. Federal legislation is also needed to protect the privacy of genetic information in medical records. Without these protections, the public will be reluctant to undergo genetic tests that might be beneficial to its health and well-being.

In addition to developing these basic principles, SACGT considered each of the five questions in its charge separately, recognizing that there is tremendous overlap in the issues raised under each question. The Committee's conclusions and recommendations are based on its analysis of the public input received, the literature reviewed, and discussions held on these issues at each of its four public meetings.

Issue 1. What criteria should be used to assess the benefits and risks of genetic tests?

• Analytical validity, clinical validity, clinical utility, and social considerations should be the major criteria used to assess the benefits and risks of genetic tests.

SACGT identified four criteria'analytical validity,[vii] clinical validity,[viii] clinical utility,[ix] and societal issues—that can be used to assess the benefits and risks of a genetic test. The importance of these criteria was confirmed in the public comment process. Assessing the potential benefits and risks of a genetic test is a process that occurs in stages. Before a test is used in clinical or public health practice, a determination must be made regarding the test's effectiveness in the laboratory—that is, whether a test is analytically valid. The degree of complexity of the test is a particularly important factor in assessing analytical validity.

Analytical Validity

Analytical validity is an indicator of how well a test measures the property or characteristic it is intended to measure. In a DNA-based test, an analytically valid test would be positive when the particular gene mutation is present (*analytical sensitivity*) and negative when the gene mutation is absent (*analytical specificity*). A key measure of a test's analytical validity is its accuracy, or the probability that the measured value will be within a predefined range or the true activity or level. Another measure of analytical validity is reliability, or the probability of repeatedly getting the same test result. During the process of validating a new genetic test, how well it performs will be compared to how well the best existing method or ''gold standard'' performs. Sometimes, if a gold standard does not exist for a new genetic test, the test's performance must be based on how well it performs in samples from individuals known to have the disease.

While the analytical validity of a test must be determined, it is not a sufficient criterion for assessing the potential benefits and risks of a test. Members of the public noted that the availability of treatment options or the opportunity for prevention or amelioration of disease through lifestyle change are key requirements in assessing benefits and that in the absence of such interventions, benefits diminish. It is important to remember, however, that for some individuals, knowledge of a condition—even without options for prevention or treatment—can be of value. The possibility that a genetic test can resolve uncertainty is an important benefit for some individuals. Conversely, some individuals find value in not knowing the results of a test for which no intervention is available.

Clinical Validity and Utility

Once the analytical validity of a test is established, the second step in assessing the benefits and risks of a genetic test is to evaluate how well it performs in the clinical environment. This involves evaluating a test's clinical validity and clinical utility. Clinical validity refers to the accuracy of the test in diagnosing or predicting risk for a health condition and is measured by the sensitivity, specificity, and predictive value of the test for a given health condition. Clinical utility involves identifying the outcomes associated with positive and negative test results. Because the clinical validity and clinical utility of a genetic test may vary depending upon the health condition and the population to be tested, these criteria must be assessed on an individual basis for each test.

Thus, in considering a system for assessing benefits and risks, it is crucial to recognize that only individuals can weigh the balance between negatives and positives once a test is deemed safe and efficacious and that not everyone will make the same choice. Participants at the public meeting stated that one of the major benefits of genetic testing is that it enables patients to make informed medical decisions and life choices. One participant summed up this view by noting that ''Individuals expect a high level of accuracy and to be able to use the genetic information obtained to make medical or personal decisions.''

The complexity of the interpretation of a test result is a critical determinant of risk, and the contribution of other genetic factors as well as environmental factors to disease development can complicate the interpretation of a test result. The more complex the interpretation, the greater the possibility for harm. For example, a test might be clinically valid and useful in one population, but not in another. Or, a test might be appropriate for use in adults, but not in newborns. In addition, genotype/phenotype correlations vary within a given disease category, even for single gene disorders.

An important distinction in considering the risks and potential benefits of a test is that between the technical aspects of a given test—that is, its clinical validity and utility—versus how it is interpreted by health care providers and the individuals undergoing testing. A clinically valid test in the hands of a poorly trained health care provider can pose as much risk as a less valid or accurate test that is correctly interpreted. A clinically valid test administered to individuals without involving them in an informed decision-making process can also pose considerable risk to that individual or family. Thus, one way to minimize harms is to ensure that tests are administered by qualified professionals and that appropriate education and genetic counseling is provided.

Individuals submitting comments to SACGT frequently mentioned the need for health care providers to demonstrate competence in understanding the information and its implications, and a number of individuals suggested that availability of and access to genetic counseling would reduce the public's concerns about genetic testing. One commenter noted that the issues of benefits and risks are ''the reason that genetic counseling and evaluation is so necessary for genetic testing.'' In addition, one private laboratory that offers genetic testing services stated that ''many of the questions we receive from client health care providers and patients relate to the translation and interpretation of genetic information in our medical reports.'' In fact, commenters often mentioned that inadequate public understanding and physician education are causes of the confusion and risks associated with genetic testing. One commenter urged ''more emphasis * * * on improving the education and influencing the attitudes of health professionals regarding genetic matters.'' Participants in the public meeting also emphasized the importance of education in minimizing the potential harms of genetic testing and in maximizing its potential benefits to diverse communities.

Factors to Be Considered in Assessing Clinical Validity

A test's clinical validity is influenced by a number of factors, including the purpose of the test, the prevalence of the disease or condition for which the test is being conducted, and the adequacy of the information available to determine clinical validity.[x] Genetic tests have a number of purposes, and some are used for more than one purpose. The acceptable level of the predictive value of a genetic test may vary depending on the purpose for which the test is used (for example, for diagnosing a condition in a person with symptoms or for predicting a future health risk in an otherwise asymptomatic individual).[xi] In addition, a higher predictive value may be required of a test for which no

other confirmatory test or clinical measure is available.

Clinical validity, particularly predictive value, is influenced by the prevalence of the condition in the population. Assessing clinical validity may be particularly challenging in the case of tests for rare diseases. This is because gathering statistically significant data may be difficult, as relatively few people have these diseases. Thus, prevalence may be a factor in determining how much data on test performance should be available before a test is offered in patient care.

For many genetic tests, particularly those that are predictive or presymptomatic, knowledge of the test's clinical validity may be incomplete for many years after the test is developed. When information that may affect clinical validity is incomplete, the potential harms of the test may increase and must be considered more carefully.

Factors to Be Considered in Assessing Clinical Utility

Clinical utility takes into account the impact and usefulness of the test results to the individual, the family, and society. The benefits and risks to be considered include the psychological, social, and economic consequences of testing as well as the implications for health outcomes. Decisions about the use of a genetic test should be based upon a consideration of the risks of any follow-up tests required to confirm an initial positive test, the efficacy of available treatments, the degree of certainty with which a diagnosis can be made, and the potential for adverse psychological and social and economic effects versus beneficial treatment if a diagnosis is made. Factors affecting clinical utility include (1) the purpose of the test; (2) the quality of evidence for assessing outcomes; (3) the potential benefits and risks of test results; (4) the nature of the health condition and its potential outcomes; (5) uncertainties of genetic test results; and (6) the provision of information concerning other family members.

Purpose of the Test

As in assessing clinical validity, the purpose of the test is an important factor in assessing clinical utility. Different risks and uncertainties are associated with genetic tests that are used to predict a future disease or condition than with those that are used for diagnostic purposes. For example, the use of a test for a specific mutation to aid in the diagnosis of cystic fibrosis in a person who has symptoms has different implications than the use of a test to determine whether a woman with no symptoms has a risk for breast and ovarian cancer because she has a BRCA1 or BRCA2 mutation that might alter her risks. Tests used for diagnostic purposes will most likely be conducted as part of a clinical evaluation to diagnose a specific disease, or they will be used for diseases or conditions that are clearly inherited.

The use of a genetic test in population screening may raise greater concern than the use of the same test in an individual seeking information about his or her health. In population screening, a large number of healthy people may receive unexpected test results that may or may not provide definitive information. Decisions about whether to use genetic tests for screening should take into account the prevalence of the condition, because the higher the prevalence of the genetic condition, the greater the number of people who may receive unnecessary treatment or false reassurance if the test produces false positive or false negative results. On the other hand, if treatment options are available, screening for highly prevalent conditions may have significant public health value.

The Quality of the Evidence for Assessing Outcomes

The quality of evidence for assessing outcomes of genetic test results is a factor to consider in determining the clinical utility of a genetic test. Often, the evidence needed to assess clinical utility is limited or lacking. Established methods for evaluating the quality of the evidence should be used to assess outcomes. (Issues pertaining to data collection and analysis are addressed more fully in Issue 3, below.)

Potential Benefits and Risks

A number of potential benefits and risks of genetic testing can be associated with positive or negative test results. For example, potential benefits of a positive test result include the possibility that it may provide knowledge of diagnosis or risk status, it could allow preventive steps or treatment interventions to be taken, or it may identify information about risk status in other family members (also a potential harm). The potential benefits of a negative test result include ruling out a specific genetic diagnosis or risk and/or eliminating the need for unnecessary screening or treatment.

The potential risks of a positive test result include exposure of individuals to unproven treatments; potential for social, psychological, and economic harms, including altered self-image, impact on family relationships, stigmatization, and potential exclusion from health insurance and employment; and identification of risk status in other family members (also a potential benefit). For false positive test results, individuals may be exposed to unnecessary screening or treatment. A negative test result could give false reassurance regarding risk due to nongenetic causes or induce psychological effects such as survivor guilt. False negative test results may delay diagnosis, screening, and treatment.

The Nature of the Health Condition

In determining the relative risks and benefits of a given test, these outcomes also must be considered in light of the nature (severity, degree of associated disability, or potentially stigmatizing characteristics) of the disorder being tested for, which is an important factor in assessing clinical utility. For example, a genetic test for periodontal disease may raise less concern than a test for cancer, and genetic tests developed for conditions such as alcoholism or mental illness might cause even greater concern because of possible misuse of such information. Health outcomes, as measured by such indicators as morbidity and mortality, are important in assessing clinical utility of genetic testing, and they can be affected by both the nature of the health condition as well as the availability, nature, and efficacy of treatment. The greater the uncertainty about the health outcomes associated with a test result, the greater the potential harms of the test. This is an important consideration in genetic testing for common health problems such as cancer and cardiovascular disease, since health outcomes typically are the result of the combined effects of genetic, environmental, and behavioral risk factors.

Uncertainties of Genetic Test Results

Genetic tests used to predict a specific disease or condition in otherwise healthy persons are associated with greater uncertainties and risks than are those used to diagnose a disease or condition. Currently, tests used for predictive purposes will provide an estimate of a person's risk of developing a particular disease or condition. However, the risk assessment may be inaccurate because of other genetic and environmental factors that have not been accounted for or are not yet known. Even so, predictive genetic tests may have profound effects on the lives of otherwise healthy individuals.

False negative results are more common in the early stages of the development of diagnostic tests,

including genetic tests. Genetic tests in early development may identify only a portion of mutations associated with a given health outcome. The role of other genetic and environmental factors is still unknown for many conditions and will also affect the certainty of genetic test results.

Implications for Family

Because genetic information may have implications for relatives of the individual being tested, the potential of the test to reveal information about family members or to alter interfamilial relationships are additional factors to be considered in assessing a test's clinical utility. For example, DNA-based tests for cystic fibrosis, sickle cell anemia, or other conditions will identify carriers for the condition as well as those who are affected. If an individual tests positive for Huntington's disease, first-degree relatives are then known to have a 50 percent chance of carrying the same mutation. Some of these relatives may not wish to discover their risk, while others may wish to use the test results of their relatives to make a decision about their own genetic testing.

Factors to Be Considered in Assessing Social Issues

Important social considerations may heighten the risks of certain tests, even if they are accurate and clinically meaningful. Tests for certain health conditions may carry special risks because of the social implications of the health condition, for example, conditions associated with mental illness or dementia. Thus, some dimensions of genetic testing may affect society as a whole and certain social groups as well as individuals, and this requires that special consideration be given to the potential for further stigmatization and discrimination of members of vulnerable or at-risk groups.

Genetic test results can change how people are viewed by their family, friends, and society as well as how people view themselves. People diagnosed with or at risk for genetic diseases or conditions may be affected by the way others begin to see and interact with them. Having or being at risk for a disease or condition that is viewed by society in a negative light can result in stigmatization, and emotional and psychological harms. In addition to changes in how they are seen by others, social influences can affect self-perception and have a profound impact on life decisions.

Diagnostic or predictive genetic information about an individual could lead to discrimination in health insurance, life insurance, education, and employment, a fear expressed repeatedly in public comments to SACGT. The fear of discrimination may be particularly acute for people with or at risk for diseases or conditions that are chronic and severely disabling and that lack effective or affordable treatments. Educational opportunities may be restricted, further limiting life possibilities. Fears of genetic discrimination have made the establishment of federal privacy and anti-discrimination protections a high priority for many. In addition to concern about discrimination, there may be downstream effects of a transformation in medicine to a focus on predicting future disease risks that are not yet fully understood.

Significant social concerns have grown out of painful memories of the American eugenics movement and the more recent history of programs that tested African Americans for sickle cell disease and disadvantaged populations for ''feeble-mindedness.'' Because these programs heightened discrimination against those tested, tests developed for use in certain targeted population groups may carry higher risks.

In addition, because social categories used to classify ethnocultural differences often do not accurately reflect actual genetic variation within a population, care should be taken to ensure accurate interpretation of genetic test results by obtaining, to the extent possible, accurate knowledge regarding the ethnocultural and/or genetic background of the individuals being tested. A further note of caution is also necessary. In developing genetic tests, it will be important to ensure that they are accurate when used in different populations, even though doing so may inadvertently reinforce the erroneous assumption that there is a straightforward, one-to-one relationship between one's genes and one's ethnocultural identity, possible resulting in stigmatization. Even accurate tests can reinforce misguided cultural notions.

Issue 2: How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories and what kind of mechanism could be used to assign tests to the different categories?

SACGT considered whether analytical validity, clinical validity, clinical utility, and social issues could be used to characterize the potential benefits and risks associated with a given test. Using this information, SACGT suggested in the public consultation document that tests might be organized into categories such as ''high risk'' and ''low risk,'' while acknowledging that this would not be a simple or straightforward task. Categorization would depend on the consideration of a combination of factors, including test characteristics, availability of safe and effective treatments, and the social consequences of a diagnosis or identification of risk status. In 1975, the National Academy of Sciences recommended that genetic tests be considered in terms of three categories, based on the complexity and usefulness of the information to the individual being tested.[xii]

The difficulty of arriving at a straightforward schema was reflected in the public comments received. Some individuals suggested categorizing genetic tests by the purpose of the test, such as newborn screening, prenatal, carrier, predictive, or diagnostic testing. Others suggested categorizing tests by the availability of treatment or preventive measures, by the demonstration of clinical validity, or by the stage of development of the test.

A number of public commenters believed that certain genetic tests raise more ethical, legal, and social concerns than do others. In this category, they identified prenatal, presymptomatic, and predictive tests, especially when no treatment measures are available. Commenters viewed diagnostic and confirmatory tests and tests for diseases for which treatment is available as raising less concern.

Additional considerations for the level of review of genetic tests include gene frequency—that is, whether the test would be for a common or an orphan (rare) disease; whether the test will be used for population-based screening or individual testing; the potential for stigmatization of individuals or groups; and the availability of independent methods of confirmation to reduce the occurrence of false-positive test results.

For the purposes of review, a useful way to consider tests is to assess them across several dimensions. These criteria are necessary but may not be sufficient for all tests.

- Is the test at this stage of development primarily diagnostic or predictive?
- Is the mutation being tested for highly or weakly penetrant? [xiii]
- Is a proven intervention available to prevent or treat the disease for which the test is being conducted?
- Is the test used for population-based screening or testing of individuals?
- Is the prevalence of the disorder for which the test is used high or low?

• Is there potential for stigmatization of individuals or groups from the test results?

• Is the test designed or able to identify more than one condition?

For example, predictive tests require more scrutiny than do diagnostic tests. Similarly, tests for weakly penetrant mutations require more assessment than do those for highly penetrant genes. Tests for conditions for which no interventions are available would be more problematic than tests for conditions for which interventions exist. Thus, for example, a high-scrutiny test would be one that is predictive, detects a mutation that is weakly penetrant, and for which a proven intervention is not available. These dimensions should be considered in the review of genetic tests, and test developers should indicate the categories into which their test(s) fit.

Issue 3: What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?

Currently, data about genetic tests are collected by a number of different organizations. While some of these data are publicly available, others are not. Data on clinical application of a test could be collected and evaluated by a number of sources, including professional organizations, individual laboratories, academic institutions, and/or governmental agencies. Inherent in any extension of data collection requirements is an added burden to the delivery system as well as an added cost for provision of health care. These are important considerations that must be carefully understood and resolved.

SACGT considered many options for collection, evaluation, and dissemination of data on genetic tests, including the following:

• Continuing reliance on the current practice of allowing laboratories to base decisions on information they collect and analyze, including their own data or data they glean from other sources, such as research publications or consensus conferences.

• Requiring that each laboratory that offers a test be responsible for collecting and analyzing the information that is necessary to support its claims, according to national standards.

• Establishing that a government agency take primary responsibility for collecting information on clinical applications of tests that detect particular mutations and defining the appropriate claims for such tests.

• Forming a consortium of government, professional associations, and industry to create, collect, and analyze information about clinical applications.

Regardless of the option chosen for data collection, once the data have been collected and evaluated, they must be disseminated in an appropriate manner to health care practitioners and the public. One public commenter stated that ''the public needs to be informed about general information that evolves from the data about genetic tests, at the same time as the practitioners are informed.'' Others suggested that information should be easily accessible by all and recommended an Internet-based database system. One commenter supported ''the concept of developing peer reviewed Internet resources that provide information on genetic tests for health providers and the public.''

SACGT concludes that databases on genetic tests should include not only data generated prior to offering the test for clinical use, but also data generated as part of any post-market evaluation. One option for dissemination is to require laboratories to release summaries of data on clinical application as part of the process of offering the test. Such summaries could be directed to health care professionals, to the general public, or to both. In addition, different methods of collection and distribution of information may be used for different tests. Guidelines or regulations might be required to make those distinctions. One method would be to rely upon publications and professional societies to inform readers and members, with the expectation that practitioners will inform the public over time. Alternatively, the federal government or a consortium could be responsible for ensuring that relevant data are available for both professional and public use.

Through the public comment process, SACGT learned that the issues of privacy and confidentiality of data collected for research is a major concern of individuals participating in such studies. One commenter noted that ''collection of data to establish analytic and clinical validity is severely compromised by fear of discrimination.'' Many individuals indicated that they would be willing to share genetic test results and individually identifiable information if informed consent were obtained and assurances of confidentiality were provided. Many commenters recommended that data collected for research should be anonymized or coded to protect the privacy and confidentiality of the individual and the data. Participants at the public meeting suggested that individuals involved in research studies should receive feedback on the outcomes and findings of the study. Others have suggested that there are risks involved in receiving investigational tests results before the meaning of the information is understood.

• The responsibility for collecting initial data on the analytical validity of a test lies with the test developer.

• Initial knowledge of the clinical validity of a genetic test is essential to assess its safety and efficacy. Further knowledge will depend on additional research and the long-term systematic collection and analysis of additional data. Researchers and test developers should gather and share initial data on the clinical validity and utility of genetic tests.

• Since data sharing and analysis are critical, relevant DHHS agencies should work collaboratively with researchers and test developers to advance data collection and provide this information to health care providers and the public. Initial exploratory data collection efforts among DHHS agencies, which have been coordinated by the Centers for Disease Control and Prevention, have been of value and should continue.

• Protecting the confidentiality of data and the privacy of individuals is essential to the progress of data collection efforts.

Need for Post-Market Data Collection and Dissemination

SACGT believes that it is critical that data continue to be collected after genetic tests reach the market. In addition, there is no current requirement that data about a test's analytical validity, clinical validity, or clinical utility, or lack thereof, should be disclosed to health care providers or patients. BRCA1 is an example of a test that should have been released with disclaimers about the limited knowledge about the test's clinical validity, which was based on data from a small and highly selected group of families in which multiple cases of cancer had occurred. Better post-market data collection and analysis will allow for expansion of the use of the test after it has been proven and understood in the initial target population. There should be some assurance that additional data will be collected after a test is preliminarily approved, using some minimal standards, and that data will be continuously reported, so that at any given point in time the level of knowledge about any test is sufficient and that for a selective few tests, more intensive studies are needed.

• Laboratories should be encouraged or required to make pre- and post-marketing data on genetic tests available

in a timely, accurate, and understandable manner.

• Post-market data collection can enhance understanding of current applications of a genetic test and is important for any expansion of the use of a genetic test beyond the initial indications approved when the test is made available. Laboratories providing clinical genetic services should commit to post-market data collection efforts.

Issue 4: What are the options for oversight of genetic tests and the advantages and disadvantages of each option?

Oversight of genetic tests can occur through multiple approaches. SACGT identified a number of possible directions that could be taken to improve oversight of genetic tests, including (1) strengthening and expanding current CLIA or FDA regulations or voluntary standards and guidelines; (2) forming interagency review boards; or (3) forming a consortium of representatives from government, industry, and professional organizations.

In assessing whether further oversight is warranted, SACGT emphasized the importance of considering the implications that further oversight may have on the current system and all parties involved as well as the trade-offs and the evolving nature of genetic research and technology. SACGT also recognized that there are many areas beyond test development, use, and marketing, such as the training and education of health care providers and public understanding of genetics that might have an equally important impact on assuring the safety and effectiveness of a genetic test.

The public comments were evenly divided between favoring a greater federal role in oversight versus forming a public/private consortium that would be responsible for oversight. Commenters noted the advantages of a consortium, including flexibility and broad representation of stakeholders. The advantages of a greater federal role cited in public comments are increased resources, centralization of oversight, and the provision of rigorous standards. Some commenters specifically recommended FDA as the federal agency of choice to oversee genetic tests. One said that ''FDA should use the authority it has to regulate all genetic tests and any kits that might be developed as part of gene sequencing.'' Others suggested that strengthening current CLIA regulations was preferable. Still others favored integrating all three approaches, with expansion of a consortium approach integrated with enhanced roles for FDA oversight of test validity and expanded CLIA oversight of testing practices, including enforcement of requirements for pre- and post-analytical test functions. Participants in the public meeting suggested that oversight should not be limited to the tests themselves, but should also apply to the manner in which the tests are used.

• Based on the rapidly evolving nature of genetic tests, their anticipated widespread use, and extensive concerns expressed by the public about their potential for misuse or misinterpretation, additional oversight is warranted for all genetic tests.

The type of oversight required will differ depending on the stage of development of the test and whether it falls into the ''high-scrutiny'' or ''low-scrutiny'' categories. However, several actions could be taken to strengthen the federal oversight role to ensure that some level of review occurs for all tests. In particular, the roles of CLIA and FDA in oversight should be strengthened and expanded.

• The Food and Drug Administration (FDA) should be the lead federal agency responsible for reviewing, approving, and labeling of all new genetic tests. FDA review should focus on the claims of analytical and clinical validity made by the developer of the test and be appropriate to the level of scrutiny warranted by the test. The agency should develop flexible mechanisms for review of new genetic tests that minimize both the time and the cost of review without jeopardizing the quality of the assessment of test validity. These mechanisms should, for example, include the use of deemed reviewers and standards developed in concert with professional organizations.

Various elements of a genetic test (analytical validity, clinical validity, clinical utility, and test methodology) raise different issues that require further oversight. A genetic test should not be used in clinical practice (that is, for other than research purposes) unless it has been shown to detect reliably the mutation that it is intended to detect. CLIA requires a laboratory that offers a test to determine the analytical validity of the test before it is used in clinical practice. In the current system, the laboratory intending to offer a test decides when it has met CLIA's requirement, a judgment that may later be evaluated during a CLIA inspection. SACGT believes that the current system requires review. Standards should be enhanced to assist laboratories in deciding when a test's analytical validity has been determined and is acceptable, or laboratories should be required to obtain the concurrence of an independent third party before a test is offered for use in clinical practice.

• Clinical Laboratory Improvement Amendment regulations should be augmented to provide more specific provisions for ensuring the quality of laboratories conducting genetic tests.

The additional oversight and data collection efforts recommended by SACGT will require enhanced resources.

• DHHS agencies should be provided with sufficient resources to carry out expanded oversight of genetic tests, including coordinated data collection, review, and information dissemination.

Finally, professional organizations and state health departments can provide additional oversight protections. Organizations such as CAP, ACMG, and NCCLS have developed guidelines and standards for the development and use of genetic tests, and they continue to do so; state health departments may require laboratory facilities and personnel that perform genetic tests be licensed, and importantly, patient advocacy groups as well as individuals and families affected with a genetic condition will continue to play an important role in setting standards and in developing guidelines.

Issue 5: What is an appropriate level of oversight for each category of genetic test?

At this time, no systematic or credible mechanism is in place for reviewing evidence about genetic tests before they are introduced into clinical practice using standardized methodologies. Thus, it is difficult to determine with great certainty when a test is ready to move from research to clinical practice. (In clinical practice, test results go back to the patient or the patient's family, as opposed to only being part of data collection.) In addition, once tests enter the health care system, it is difficult to retrieve data on their use and outcomes. SACGT concluded that although genetic tests should be evaluated at all stages, from development through clinical application, the level and focus of review should be appropriate to the stage and complexity of the test itself. For example, diagnostic tests for a disease with high penetrance and for which an intervention is available may require less scrutiny than predictive tests for a disease for which no proven intervention is available.

Also important is the degree to which benefits are provided by positive and negative test results. In general, genetic tests should provide information that people will find useful in making decisions relating to their health and well-being. Some consumers might assume that a test would not be made

available unless it has a health benefit. For example, a negative genetic test result may provide a useful basis of information for informed decision-making. Others have argued that access to information, even it if does not lead to a health-related intervention, is itself useful. There is currently no requirement that the clinical utility of a genetic test be assessed before it is used in clinical practice, and additional oversight may be needed to ensure greater awareness of the utility of the test.

In considering the level of oversight warranted, the risks, benefits, and economic implications (both short- and long-term) associated with oversight must be considered. More stringent oversight, for example, may ensure greater certainty that a test has been shown to be accurate and useful, that patient safeguards are in place, and that health care dollars are not spent on tests of little value. On the other hand, additional oversight may unnecessarily delay the introduction of new tests (or improvements to existing tests) into clinical practice and increase the costs of test development, which may in turn discourage the development of new tests. The provision of any type of additional oversight is likely to have implications for resources that may affect the costs of genetic tests and public access to them.

The public comments emphasized a need for guidelines or national standards to determine when a test is ready for clinical use. Many commenters stated that a test should be considered ready for clinical use when clinical validity and utility have been demonstrated. One said that investigational tests are ready for general use ''only when sufficient data has been collected and evaluated to determine accuracy, validity, and utility in different populations.'' Participants in the public meeting said that it was important that the benefits of immediate test application be weighed against what might be lost if the test is not available. In general, commenters thought that tests for rare diseases should be given special considerations so that their availability would not be limited. One said that special consideration for genetic tests for rare diseases ''must be given in order to ensure access to such tests, even before validity is confirmed.''

Systematic and ongoing review of genetic tests would provide information to health care providers and individuals to assist their decision-making about the usefulness of the test and its potential risks and benefits. The level of confidence in the information presented to individuals on genetic tests should be high.

Making information available and understandable about a test's accuracy and predictive power and the availability of therapy for the disease the test is designed to test for is important to the public, but most commenters thought that this would not be a sufficient form of oversight. Similarly, while commenters believed that the review of promotional materials would be an important part of the oversight process of genetic tests, this alone would not be sufficient for oversight.

Ongoing review is essential, because when test manufacturing methods and materials change, either deliberately or inadvertently, the performance characteristics of a test can change as well, altering its analytical validity. Although CLIA requires reevaluation of tests when the methodology changes, stronger incentives are needed to re-qualify tests when methods and materials change to demonstrate equivalent analytical validity performance.

In addition to considering the levels of oversight required, SACGT considered the timing of such oversight. Because the clinical validity of tests changes as it is used in a population, oversight must consider the entire continuum of test introduction and use over time, from the earliest stages of research to wide-scale clinical application.

SACGT determined that different levels of oversight are warranted for different phases and types of genetic tests. Specific recommendations are made for tests in the research phase of development, the review of tests prior to clinical and public health use, and tests already on the market.

Oversight of Tests in the Research Phase of Development

Analytical validity should be determined in the research phase. Clinical validity can be established only by the expansion of testing to larger numbers of people. Thus, a test in the research phase must satisfy somewhat different standards than one that has been widely used in clinical settings. There must also be a rationale for a test's clinical application and for establishing a population in which testing would be appropriate. In some cases, laboratories that are developing genetic tests for eventual use in clinical practice conduct studies using identifiable patient samples. [xiv] Unless the study is conducted with federal funding or is intended for submission to FDA, there is no federal requirement that laboratories obtain informed consent from a patient participating in that study. Further, at present, not all facilities developing genetic tests have IRB oversight bodies in place, because IRBs are not legally required for institutions that do not conduct DHHS-funded research.

- Institutional Review Board review should be conducted of all research protocols for genetic tests in which individually identifiable human subjects or samples are used, regardless of the funding source. Institutions that lack an IRB must obtain the services of a qualified board. Efforts will be needed to ensure that IRBs are suitably equipped to carry out these reviews. In addition, informed consent must be obtained from all subjects participating in such research.

Transition of Genetic Tests to Clinical and Public Health Use

Once a laboratory has established the analytical validity of a test, its clinical validity and utility can be established only by testing in human populations. Questions must be answered about a test's ability to generate information about the presence, or possibility of future occurrence, of a disease. Determining a genetic test's clinical validity is a complex process, often requiring years of work. At the same time, many would like to see gene discoveries quickly translated into practical use as soon as the discoveries are made, often before the clinical validity of the test is fully established. The use of the test is then refined as new information becomes available. No federal standards guide how laboratories determine when enough is known about a genetic test for it to be used in clinical practice or the extent to which uncertainties about a test's characteristics must be disclosed. FDA should play a central role in serving as the ''gatekeeper'' for the introduction of new tests and should have the resources to carry out timely reviews.

Many tests are likely to fall into the ''low-scrutiny'' category and would receive expedited review. For those tests that raise concerns—because they are predictive rather than diagnostic, weakly penetrant, detect a disorder for which no proven intervention exists, or detect a gene mutation in a subpopulation at greater risk for stigma or discrimination—greater scrutiny is warranted.

- FDA should give particular attention to the review of genetic tests that are used to predict diseases and conditions for which no safe and effective interventions are available. Other tests may also warrant a higher

level of scrutiny in the FDA review process.

• In the future, tests may be developed that raise major social and ethical concerns. Because FDA's review will focus on assuring the analytical and clinical validity of a test, the agency's capacity to assess the ethical and social implications of a test may not be sufficient. The Secretary should consider the development of a mechanism to ensure the identification, and appropriate review, of tests that raise major social and ethical concerns.

SACGT can play an important coordinating role in the oversight of genetic tests. The Committee, which includes nonvoting liaison members from AHRQ, CDC, FDA, HCFA, HRSA, and NIH, made a commitment to follow the progress of DHHS in implementing enhanced oversight and to provide ongoing advice about the oversight issues as necessary. SACGT should not engage in case-by-case review of genetic tests, but should serve as a forum for public discussion of evolving concerns about the issues raised in the approval, release, and ongoing review of genetic tests.

Review of Tests Already on the Market

SACGT believes that some tests already on the market should be further evaluated for clinical efficacy and that guidelines should be developed for their appropriate use. A body similar to the U.S. Preventive Services Task Force could be constituted to conduct such reviews. Such a group could develop methodology that emphasizes systematic analytic procedures to review scientific evidence for the purpose of developing sound practice guidelines for genetic testing. Evaluations could be submitted for consideration by medical organizations, specialty societies, government agencies, and other groups concerned with the delivery of genetic services and could be published in peer-reviewed medical journals and other publications.

• The U.S. Preventive Services Task Force with augmented resources, or a similar body set up or given deemed status for this purpose, should review genetic tests that are already on the market for evaluation of clinical efficacy and development of guidelines about their appropriate use.

Additional Recommendations for the Appropriate Use of Genetic Tests

In addition to responding to the five questions in its charge, SACGT developed several recommendations directed toward improving the safe and responsible introduction of genetic tests to the public.

• Individual and family members considering a genetic test should have access to appropriate genetic education and counseling resources to ensure their ability to make an informed decision about being tested.

Current oversight does not specifically address whether genetic education and qualified counseling should be made available for all genetic tests. Genetic test results may be difficult to interpret and present in an understandable manner, raise important questions related to disclosure of test results to family members, and sometimes involve difficult treatment decisions. Because of these intricate issues, some have suggested that those who offer genetic tests should be encouraged or required to make genetic education or counseling available to those considering genetic testing and their family members.

• Written informed consent should be obtained for tests used for predictive purposes. The extent to which written informed consent should be obtained for all other genetic tests requires further deliberation.

Even after a test has been accepted into clinical practice, some observers have suggested that because of the predictive power of genetic tests and the impact that test results may have on individuals and their families, tests should not be administered unless the individual has been fully informed of the test's risks and benefits and a written informed consent has been obtained. There is currently no requirement for such an informed consent.

• Current regulations under FDA and the Federal Trade Commission should be enforced in the area of genetic test promotion and marketing.

Although the federal government requires that promotion and marketing of products and services (which sometimes takes the form of educational materials) be truthful and not deceptive, federal agencies have taken little enforcement action against false or deceptive claims involving genetic tests. While some believe that false or deceptive claims are not currently a problem, others have suggested that promoting or advertising genetic tests, especially to patients/consumers, should be prohibited. Another suggestion is to permit the promotion and advertising of genetic tests, while also emphasizing taking action against those who make false or deceptive claims.

Conclusion

On March 15, 2000, SACGT forwarded its preliminary draft recommendations to Dr. Satcher. The Committee invites public comment on this preliminary draft of its conclusions and recommendations, and at its next meeting, June 5–7, 2000, the Committee will review the comments received and will develop a final report to the Secretary. With the completion of this assignment, SACGT will move on to consider a number of other high-priority issues, relevant to genetic tests and not addressed in this report.

[i] These statistics were provided by GeneTests, a directory of clinical laboratories providing testing for genetic disorders, which can be found at the following website: *http://www.genetests.org*

[ii] McGovern, M.M.; Benach, M.O.; Wallenstein, S.; *et al.* Quality assurance in molecular genetic testing laboratories. JAMA 281(9): 835–40, 1999.

[iii] Holtzman, N.A.; Watson, M.S. (eds.) Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing. Baltimore: Johns Hopkins University Press, 1997.

[iv] The consultation document was mailed to 2,500 individuals and organizations in late November 1999, and comments were received until January 31, 2000. A public meeting was held at the University of Maryland, Baltimore, on January 27, 2000, which was planned and organized by a steering group composed of SACGT members and additional experts knowledgeable about issues of concern to diverse communities.

[v] Some of the information presented in this section regarding genes, genetics research, and genetic testing is adapted from Understanding Gene Testing, a booklet produced by the National Cancer Institute and the National Human Genome Research Institute. The booklet is available at *http://www.accessexcellence.org/AE/AEPC/NIH/index.html*.

[vi] Farlow, M.R.; *et al.* Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology 50(3): 669–77, 1998.

[vii] The term analytical validity refers to how well a test performs in the laboratory, that is, how well the test measures the property or characteristic it is intended to measure. (In the case of a genetic test, the property can be DNA, proteins, or metabolites.) In other words, does the test do what its makers claim it does? If so, it must produce the same results repeatedly and in different laboratories (given the same set of procedures).

[viii] Clinical validity refers to the accuracy with which a test predicts the presence or absence of a clinical condition or predisposition. Thus, a test would be clinically valid if it successfully detects the disease or predisposition. Initially, the test has to be conducted on individuals who are known to have the condition (as well as those who do not) to determine its success rate.

[ix] Clinical utility refers to the usefulness of the test and the value of the information to the person being tested. If a test has utility, it means that the results—positive or negative—provide information that is of

value to the person being tested because he or she can use that information to seek an effective treatment or preventive strategy. Even if no interventions are available to treat or prevent the disease or condition, there may be benefits associated with knowledge of a result.

[x] Prevalence refers to the percentage of a population that is affected with a particular disease at any given time.

[xi] A genetic test may either have positive predictive value (the probability that an individual with a positive test result will develop the disease) or negative predictive value (the probability that an individual with a negative result will not get the disease), depending upon its clinical sensitivity and specificity (clinical validity).

[xii] National Research Council. Committee for the Study of Inborn Errors of Metabolism. Genetic Screening: Programs, Principles, and Research. Washington, DC: National Academy of Sciences, 1975.

[xiii] Penetrance is a concept indicating the likelihood that a given gene will result in disease. For example, if a condition is not expressed in every person who carries the mutation, it is said to have reduced penetrance.

[xiv] The National Bioethics Advisory Commission has addressed ethical issues concerning the use of human biological materials in research and made a number of recommendations relevant to some of the issues discussed here. National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Report and Recommendations of the National Bioethics Advisory Commission. 1999.

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