

divest additional related assets to a Commission-approved purchaser.

The Order also requires Reckitt & Colman to provide to the Commission a report of compliance with the divestiture provisions of the Decision & Order within thirty (30) days following the date the Decision & Order becomes final, every thirty (30) days thereafter until Reckitt & Colman has completed the required divestiture, and every ninety (90) days thereafter until Reckitt & Colman has completed its divestiture obligations under the Order.

The purpose of this analysis is to facilitate public comment on the Consent Agreement and it is not intended to constitute an official interpretation of the Consent Agreement or to modify its terms in any way.

By direction of the Commission.

**Benjamin I. Berman,**

*Acting Secretary.*

[FR Doc. 99-31183 Filed 11-30-99; 8:45 am]

BILLING CODE 6750-01-M

## 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 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), U.S. Public Health Service. The meeting will be held from 8:45 a.m. to 5 p.m. on January 27, 2000 at the University of Maryland, School of Nursing, 655 W. Lombard Street, Baltimore, Maryland 21201. The meeting will be open to the public from 8:45a.m. to adjournment with attendance limited to space available. The public is encouraged to register for the meeting through the SACGT website or by contacting the SACGT at 301-496-9838. Further information about the meeting is available at the following website address: <http://www4.od.nih.gov/oba/sacgt.htm>. A draft meeting agenda will be posted to the website prior to the meeting. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should inform the contact person listed below in advance of the meeting. All comments received before the end of the consultation period will be considered by SACGT and will be available for

public inspection at the SACGT office between the hours of 8:30 a.m. and 5:00 p.m. The SACGT office is located at 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892. Questions about this request for public comments can be directed to Susanne Haga, Ph.D., Program Analyst, SACGT, by email ([hagas@od.nih.gov](mailto:hagas@od.nih.gov)) or telephone (301-496-9838).

The Secretary's Advisory Committee on Genetic Testing (SACGT) is seeking diverse public perspectives on the adequacy of current oversight of genetic testing in the United States. SACGT was chartered to advise the Department of Health and Human Services on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests. This notice provides background information prepared by SACGT about genetic tests, including their current limitations, benefits and risks, and the provisions for oversight now in place. It presents five specific issues for public comment along with related questions and a sixth set of questions to enable the public to comment on other issues relevant to genetic testing. SACGT is also seeking public comments through a website consultation, a targeted mailing, and a public meeting on January 27, 2000 in Baltimore, Maryland.

The public is encouraged to submit written comments on the oversight of genetic testing to SACGT. In order to be considered by SACGT, public comments need to be received by January 31, 2000. Comments can be submitted by mail or facsimile. Members of the public with Internet access can submit comments through email or the SACGT website consultation. The SACGT mailing address is: SACGT, National Institutes of Health, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892. SACGT's facsimile number is 301-496-9839. Comments can be sent via email to: [sc112c@nih.gov](mailto:sc112c@nih.gov). To participate in SACGT's website consultation, please visit the SACGT website: <http://www4.od.nih.gov/oba/sacgt.htm>. Questions about this request for public comments can be directed to Susanne Haga, Ph.D., Program Analyst, SACGT, by email ([hagas@od.nih.gov](mailto:hagas@od.nih.gov)) or telephone (301-496-9838).

### A Public Consultation on Oversight of Genetic Testing

#### Part I: Introduction

##### Overview

Decades of research in genetics have brought about many important medical and public health benefits. Gene discoveries have provided a better understanding of the genetic basis of

disease and opened new avenues for diagnosis, treatment, and prevention of disease. The pace of the discovery of new genes and the development of new genetic tests is expected to increase in the future. The Human Genome Project, a major international collaborative effort established and supported by public and private groups, including the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH), is expected to complete the sequencing of the human genome by the year 2003. The unprecedented amount of genetic information produced by the Human Genome Project will enable scientists to make more rapid progress in understanding the role of genetics in many common complex diseases and conditions—such as heart disease, cancer, and diabetes—and to increase knowledge that may lead to the development of individually tailored medical treatments. These scientific and technological advances are expected to bring about revolutionary changes in clinical and public health practice and to have a significant impact on society.

The Secretary's Advisory Committee on Genetic Testing (SACGT) was established 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 NIH-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, the 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.

##### Statement of the Issue

Advances in knowledge about the structures and functions of human genes and the development of new laboratory technologies for the analysis of genetic material are helping to produce many new genetic tests for a wide range of conditions and purposes. Genetic tests can be used to diagnose disease, confirm a diagnosis, provide prognostic information about the course of disease, confirm the existence of a disease in individuals who do not yet have symptoms, and, with varying degrees of effectiveness, predict the risk of future disease in healthy individuals. Currently, several hundred genetic tests are in clinical use, with many more under development, and their number and variety are expected to increase rapidly over the next decade. These

advances stem in large part from research funded and conducted by agencies within DHHS, especially NIH.

The Task Force on Genetic Testing, which was charged to review genetic testing in the United States and to make recommendations to ensure the development of safe and effective genetic tests, began its work in 1995 and published its final report two years later. In its final report, the Task Force concluded that although genetic testing is developing successfully in the United States, some concerns about it exist. These can be grouped into four main areas:

- The way in which tests are introduced into clinical practice;
- The adequacy and appropriate regulation of laboratory quality assurance;
- The understanding of genetics on the part of health care providers and patients; and
- The continued availability and quality of testing for rare diseases.

The Task Force recommendations were intended primarily to enhance 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, considered how comprehensive data gathering efforts could incorporate new data, and made suggestions about the need for external review of tests. Although the Task Force recommended that revisions to the current review process may be needed to assess the effectiveness and usefulness of genetic tests, it did not specify how the review of laboratory-based genetic tests should be changed.

DHHS requested that SACGT build 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. This assessment requires consideration of the potential benefits and risks (including socioeconomic, 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. If, after public consultation and analysis, SACGT finds that other oversight measures for genetic tests are warranted, it has been asked to recommend options for such oversight.

It is important to note that although this paper focuses on Federal oversight of genetic tests in laboratory and clinical settings, the training and education of

health care providers and the promotion of greater public understanding of genetics are also critical issues. More genetics training and education of health care providers who prescribe genetic tests and use the results for clinical decision-making is widely regarded as another way in which to enhance the safe and effective development and use of genetic tests. It is helpful to keep training and education of health care providers and promotion of public understanding in mind while considering the Federal role in oversight. SACGT intends to address the training and education issue after this current assignment is completed.

#### *Importance of Public Consultation*

The question of whether more oversight of genetic tests is needed has significant medical, social, ethical, legal, economic, and public policy implications. Additional oversight may ensure that genetic tests are appropriately used and accurately interpreted, and it may increase the confidence of providers and individuals in using or having genetic tests. Such oversight might increase the willingness of health insurers to cover the costs of genetic tests if their usefulness can be established, but might also increase the costs of those tests. On the other hand, subsequent acceptance and widespread use of a genetic test may increase the demand for it and thereby lower the costs of a test. The development of genetic tests and their use in clinical practice may be slowed by more oversight measures. Finally, further oversight can be expected to require additional funds.

Because this issue may 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, DHHS has sought to ensure that public perspectives on oversight for genetic testing are considered. Such public involvement in this process will enhance SACGT's analysis of the issues and the advice it provides to DHHS. SACGT is hoping to reach a broad audience and to receive a wide range of perspectives from both professionals and the general public, including diverse communities. SACGT is using five approaches to gather public perspectives: (1) A notice in the **Federal Register**; (2) a targeted mailing to interested organizations and individuals; (3) a website consultation (<http://www4.od.nih.gov/oba/sacgt.htm>); (4) a public consultation meeting on January 27, 2000 in Baltimore, Maryland; and, (5) a retrospective review and analysis of the

literature. The Committee looks forward to receiving public comments and to being informed by the public's perspectives on oversight of genetic testing.

#### *Organization of This Paper*

Because the issues surrounding genetic testing are complex and highly technical, this paper first provides basic background information about genetic tests, including a discussion of their current limitations, benefits and risks. The provisions for oversight that currently are in place are outlined. Then, the paper presents the specific issues that SACGT and the public have been asked to consider, along with some possible approaches or options for addressing them.

### **Part II: Background Information About Genes, Genetics Research, and Genetic Testing**

#### *Overview*

Much of the information presented in the following sections 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>.

#### *Genes and Gene Mutations*

Genes are made of DNA, a long, threadlike molecule coiled inside cells. Within the cell, the DNA is packaged into 23 pairs of chromosomes. Each chromosome, in turn, contains thousands of genes. Genes, which are segments of DNA, are packets of instructions that tell cells how to behave. They do so by specifying the instructions for making particular proteins. The gene instructions are written in a four-letter code, with each letter corresponding to one of the chemical constituents, or bases, of DNA: A, G, C, T. The number of bases in the human genome (the complete sequence of the DNA molecule) is estimated to be 3 billion to 4 billion. The human genome is estimated to contain 100,000 to 140,000 genes.

If the DNA sequence, the order of the four-letter code, becomes altered in any way, the cell may make the wrong protein, or too much or too little of the right one—mistakes that often result in disease. In some cases, such as sickle cell anemia, just a single misplaced base is sufficient to cause the disease. Genetic mistakes can be inherited (called an inherited mutation) or they can develop during an individual's

lifetime (an acquired mutation). Inherited mutations are found in every cell of the body, while acquired mutations occur sporadically in individual cells.

Mutations in genes are responsible for an estimated 3000 to 4000 clearly hereditary diseases and conditions. Some of these—including Huntington disease, cystic fibrosis, neurofibromatosis, Duchenne muscular dystrophy—are caused by the mutation of a single gene. Gene mutations also play a role in cancer, heart disease, diabetes, and many other complex diseases. Genetic alterations may increase a person's risk of developing one of these more complex disorders, although it is the cumulative effects of the interaction of genetic and environmental factors, such as diet and smoking, that result in the development of disease.

#### *Genetics Research*

The process of discovering and understanding genetic mutations is an extremely complex one. Reaching a complete understanding of the relationship between a mutation and a disease or condition can involve many years of investigation, and the discovery of a mutation usually is only the first step. Scientists looking for a gene that contributes to a particular disease or condition typically begin by studying DNA samples from members of families in which many relatives over several generations have developed the same illness—colon cancer, for example. Scientists start looking for detectable traits or distinctive segments of DNA (called genetic markers) that are consistently inherited by relatives with the disease or condition but that are not found in relatives who do not have it. Then, scientists work to narrow down the target DNA area, identify possible genes, and look for specific mutations within those genes.

Because the genome is vast, discovering a specific disease gene has, up to now, been a difficult and time consuming effort. In the case of Huntington disease, for example, scientists worked for ten years before they found the gene that causes the disease. The Human Genome Project combined with new developments in technology, such as tandem mass spectrometry, microarrays, and gene chips, will speed up the pace of the discovery of disease genes and mutations.

Once the entire sequence of the human genome has been mapped, scientists will have the tools they need 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 complicating factors such as gene-gene interactions and environmental influences (for example, smoking and diet). As a result, understanding what gene mutations mean for a person's future health and well-being will require more research, including population-based studies that focus on clarifying the significance of gene-gene and gene-environment interactions.

#### *Genetic Testing*

Genetic testing involves the analysis of chromosomes, genes, and/or gene products to determine whether a mutation is present that is causing or will cause a certain disease or condition. It does not involve treatment for disease, such as gene therapy, although test results can sometimes suggest treatment options.

Genetic tests are performed for a number of purposes, including prenatal diagnosis, newborn screening, carrier testing, diagnosis/prognosis, presymptomatic testing, and predictive testing. Prenatal diagnosis is used to diagnose a genetic disorder or condition in a developing fetus. Newborn screening is used to detect certain genetic diseases in newborns, and it is performed on a public health basis by the States. The disorders screened for are those that, if detected early, have significant treatment or prevention benefits. Carrier screening is performed to determine whether an individual carries a copy of a mutated gene for a recessive disease (recessive means that the disease will occur only if both copies of a gene are mutated). Carriers are not affected with the disease, but they have a 50 percent risk of passing the mutation on to their children. If the partner of a carrier is screened and found also to be a carrier, each child they conceive will have a 25 percent risk of being affected with the disorder. Diagnostic testing is used to identify or confirm the diagnosis of a disease or condition in an affected individual. Diagnostic testing can also be used for prognostic purposes to help determine the course of a disease. Presymptomatic testing is used to determine whether individuals who have a family history of a disease, but no current symptoms, have the gene mutation. Predictive testing determines the probability that a healthy individual with or without a family history of a certain disease might develop that disease.

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. (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>). A recent survey of genetic testing laboratories found that over a recent three-year period, the total number of genetic tests performed increased by at least 30 percent each year, rising from 97,518 in 1994 to 175,314 in 1996. Most of the tests are conducted for diagnostic, carrier, and presymptomatic purposes for rare genetic disorders. Recently, tests have been developed to detect mutations for about 25 more common, complex conditions—such as breast, ovarian, and colon cancer—whose effects generally do not appear until later in life. These tests are currently used for presymptomatic purposes in individuals with a family history of the disorder. Although the tests could be used for predictive purposes, they are not recommended for this purpose because more must be learned about the significance of the mutation in someone without a family history of the disease.

A concern has recently been raised about the impact that patenting human genes may be having on genetic testing. The Patent and Trademark Office has been issuing patents on gene sequences since 1980. Approximately 12,000 patents have been issued on plant, animal, and human genes and patent applications have been made on another 30,000 genes. While patenting genes generally provides incentives for the development of useful gene-based products, some gene patent holders have begun to restrict the use of their gene discoveries by charging high fees for the license rights, establishing exclusive licenses, or refusing to license the discovery altogether. These restrictions can have an adverse effect on the accessibility, price, and quality assurance of genetic tests. A recent survey conducted by the American College of Medical Genetics, a professional organization representing clinical and laboratory geneticists, found that 25 percent of its members had discontinued offering certain genetic tests because of patent/licensing complexities.

#### *Important Concepts About the Accuracy and Effectiveness of Genetic Tests*

Several standard terms are used in discussing the accuracy and effectiveness of laboratory tests. These terms—analytical validity, clinical validity, and clinical utility—apply not

only to genetic tests but also to other kinds of tests, such as cholesterol or pap smear tests. An understanding of these terms is helpful in considering the possibilities for oversight of genetic tests.

Analytical validity is an indicator of how well a 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.) An analytically valid test would be positive when the relevant gene mutation is present (analytical sensitivity) and negative when the gene mutation is absent (analytical specificity). Another element of the test's analytical validity is reliability—meaning that the test obtains the same result each time. 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.

Clinical validity is a measurement of the accuracy with which a test identifies or predicts a clinical condition. A clinically valid test would be positive if the individual being tested has the disease or predisposition (clinical sensitivity) and negative if the individual does not have the disease or predisposition (clinical specificity). To be clinically valid, a test would be positive if the individual being tested has or will get the disease or condition (positive predictive value) and negative if the individual being tested does not have or will not get the disease or condition (negative predictive value). Determining the clinical validity of a test may be more challenging when different mutations within the same gene cause the same disease and different mutations can result in different degrees of disease severity. In addition, gene mutations may or may not lead to disease depending on how “penetrant” or completely expressed they are.

Clinical utility refers to the degree to which benefits are provided by positive and negative test results. If a test has utility, it means that the results—positive or negative—provide information that is of value to the person who is tested. The availability of an effective treatment or preventive strategy, for example, would make such information valuable. However, even if no interventions are available to treat or prevent the disease or condition, there may be benefits associated with knowledge of a result. On the other

hand, social, psychological, and economic harms can result from such knowledge, particularly in the absence of privacy and discrimination protections. Thus, determining the clinical utility of a test requires obtaining information about the benefits and risks of both positive and negative test results.

A final point can be made about the challenge of assessing the clinical validity and utility of genetic tests used for predictive purposes and for rare diseases. For genetic tests used for predictive purposes in diseases or conditions whose effects do not become apparent for many years, clinical validity and utility will need to be evaluated over time. For genetic tests for rare diseases, gathering sufficient data to assess clinical validity and utility may never be possible because of the low prevalence of the diseases. Consequently, different approaches to the evaluation of clinical validity and utility for predictive tests and for rare disease tests may be necessary.

#### *Current Limitations of Genetic Testing*

Genetic tests currently have certain limitations that are relevant to the issue of oversight. 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 the 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. 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 genetic and environmental factors. In addition, the frequency of common cystic fibrosis mutations varies among population groups. Determining the clinical validity of a genetic test requires a thorough analysis of all these factors without which the likelihood of error may be high.

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 certain 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 cancer.

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 never be available—a situation sometimes called the “therapeutic gap.” While knowledge that a disease or condition will or could develop may not provide any direct clinical benefit, it may lead to increased monitoring which 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, can also lead to discrimination or other forms of misuse of personal genetic information.

#### *Potential Benefits and Risks of Genetic Tests*

Information provided by genetic tests has potential benefits and risks. Understanding the benefits and risks of a genetic test is critical in determining its appropriate use in clinical and public health practice. The benefits and risks of any particular test to individuals or particular populations may change over time as more information is gathered.

*Potential Benefits.* Individuals with a family history of a disease live with troubling uncertainties about their and their children's futures. Having a genetic test may relieve some of those uncertainties. If the test result is positive, it can provide an opportunity for counseling and for the introduction of risk-reducing interventions such as regular screening practices and healthier lifestyles. Early interventions (for example, annual colonoscopies to check for precancerous polyps, the earliest signs of colon cancer) could prevent thousands of colon cancer deaths each

year. If the test result is negative (they do not have the mutation), 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 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 (AD) who have two copies of a certain gene mutation do not respond to the drug Tacrine. In individuals with AD who do not have both copies of the mutation, however, the drug seems to slow progression of the disease.

*Potential Risks.* Genetic testing poses potential physical, medical, psychological, and socioeconomic 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, in rare circumstances, cause miscarriage.

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. Individuals with positive test results may choose not to have children. They 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. Incorrect test results or misinterpretation of test results have substantial risks. False negative test results can mean delays in diagnosis and treatment. 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 risks. 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 have a fairly clear, and perhaps 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 (survivor guilt) for escaping a disease that others in the family have developed. A negative test result may provide a false sense of security because the individual may still bear 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 baby tests positive for sickle-cell trait during newborn screening, it means that one of the parents is a carrier. It is also possible for genetic tests to inadvertently disclose information about a child's paternity.

Genetic test results present potential socioeconomic risks for individuals. Some people have reported being denied health insurance and losing jobs or promotions as a result of genetic test results. People have reported being rejected as adoptive parents because of their genetic status. Some people seeking adoptions have requested genetic testing for the child before finalizing the adoption.

Genetic test results can pose risks for groups if they lead to group stigmatization and discrimination. Concerns about the potential risks of discrimination and stigmatization are particularly acute among minority groups who have experienced other forms of discrimination. Regrettably, the African American experience with sickle cell anemia screening provides an example of the potential for and consequences of discrimination and is one of the reasons why the particular risks of genetic testing for minority groups must be considered. In the 1970s, a major effort was made in many States, with Federal Government support, to screen African American children and young adults for sickle cell disease. Many of the screening programs were based on an inadequate knowledge of the genetics of sickle cell disease, and in some instances, the accuracy and validity of the test itself was in question. Also, many programs were implemented without sufficient sensitivity to ethnocultural issues and the potential for misuse of personal test results. Individuals who were actually carriers of the mutation were incorrectly identified as having sickle cell disease. Carriers were ostracized, deprived of employment and educational

opportunities, and denied health and life insurance.

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, such as to obesity, alcohol abuse, or nicotine addiction, 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 and socioeconomic harms are so significant and the potential misuse of such information is so great.

#### *Case Studies: From Gene Discovery to the Development and Use of Genetic Tests*

After a gene has been shown to cause or play a role in a specific disease or condition (through analysis of DNA from affected individuals), the function of this gene in both healthy and disease states must then be understood. Each step along the research path adds to and reshapes existing knowledge in this constantly evolving area of study. In the following sections, seven case studies are provided to illustrate the different kinds of genetic testing that are performed, the way in which genetic tests evolve from research to clinical and public health practice, and some of the difficulties that can arise when a test moves from research to clinical use due to limitations in the data on clinical validity and utility. Although each example primarily describes one use of the test, it is possible that the same test could be used for other purposes. For example, a diagnostic test also may be used for predictive purposes. Indeed, the fact that tests may be used for multiple and overlapping purposes is one of the significant challenges of any effort to identify distinct categories of genetic tests.

*Prenatal Diagnosis.* An example of a genetic test used for prenatal diagnosis is the test for the recessive disorder called Tay-Sachs disease. (Genetic tests are also used for Tay-Sachs carrier screening, but this case study focuses on its use in prenatal diagnosis.) Tay-Sachs is a neurological disease that results from a buildup of sugar fats in brain cells and is caused by a defect in a gene that is responsible for the breakdown of those fats. Infants with Tay Sachs generally appear healthy at birth, but begin to develop motor weakness between 3 and 5 months of age. Progressive weakness continues,

characterized by poor head control and failure to achieve major developmental milestones, such as crawling or sitting unsupported. After 8 to 10 months of age, the disease progresses rapidly, and the child becomes completely unresponsive. Most children with Tay-Sachs survive to 2 to 4 years of age; most succumb to pneumonia. Currently, palliative and supportive treatment is the only therapy for Tay-Sachs disease.

Prenatal diagnosis of Tay-Sachs disease was first achieved in 1970. The test involves measuring the activity of a particular enzyme in cells from a developing fetus. The fetal cells are obtained through two principal methods—chorionic villus sampling (CVS) and amniocentesis. CVS, which is performed at 9 to 12 weeks of pregnancy, involves examining a sample of fetal cells taken from the placenta. Amniocentesis is a procedure, done at 16 to 18 weeks of pregnancy, in which a sample of the fluid surrounding the fetus (the amniotic fluid) is withdrawn from the womb and examined. These procedures carry a risk of miscarriage (1 case in 100 for CVS and 1 case in 200 to 300 for amniocentesis). When the results of the Tay-Sachs test are positive, many couples face an agonizing decision about whether to continue the pregnancy. Most, but not all, elect to terminate the pregnancy. Although prenatal diagnosis for Tay-Sachs disease initially was used only for couples to whom affected children had already been born, it is now also offered to couples who are identified by carrier screening to be at risk.

Over the last two decades, the analytical validity and clinical validity of prenatal testing for Tay-Sachs disease have been established, and the clinical utility of the test is now also fairly well understood. Tay-Sachs disease testing is limited primarily to populations in which the disease is known to be prevalent, including people of Ashkenazi Jewish or French Canadian descent. The incidence of Tay-Sachs disease in the Ashkenazi Jewish population is approximately 1 in 4,000 births; in the general population the incidence is tenfold less (1 in 40,000).

**Newborn Screening.** Phenylketonuria (PKU) results from a defect in a gene that encodes for a liver enzyme that is important for the breakdown of an essential protein building block, phenylalanine. The defect leads to the buildup of phenylalanine levels in the blood, resulting in brain damage. It was first described in 1934, when an association was observed between mental retardation and the presence of chemicals known as phenylketones in the urine of two siblings. In 1953, it was

demonstrated that lowering blood phenylalanine levels by placing affected persons on a phenylalanine-restricted diet improves outcomes for individuals with PKU. In 1959, the introduction of a restricted diet in PKU-affected newborns was shown to prevent brain damage. The overall incidence of PKU is approximately 1 in 10,000 live births.

In 1963, a simple, inexpensive test to screen for elevated phenylalanine in the blood of newborns became available. A trial test was conducted on a group of individuals with mental retardation, and it identified correctly all persons who were previously diagnosed with PKU. After publication of the test method, the PKU screening test was accepted by the medical and scientific communities and became part of routine neonatal screening programs across the country. In fact, PKU was the first genetic disease for which newborn screening was developed. Newborn PKU screening is required by law in nearly all States.

The gene responsible for the major form of PKU was found in 1986, and since then more than 100 different mutations in the gene have been identified. Because DNA analysis of the PKU gene cannot always be correlated with disease severity, analysis of enzyme function and measurement of phenylalanine metabolites are more reliable indicators of clinical severity.

In the nearly 40 years since the PKU screening test was first used, a significant amount of data has been collected to establish its analytical and clinical validity and clinical utility. The test's clinical utility is especially significant because the most serious consequence of untreated PKU—mental retardation—can be prevented through a phenylalanine-restricted diet.

**Carrier Screening.** Cystic fibrosis (CF), which was first described in the 1930s, primarily affects the lungs and pancreas and often results in the onset of chronic lung disease. Recurrent infections and deficiencies of pancreatic enzymes can prevent normal digestive function. The median survival of individuals with CF has increased from 18 years in 1976 to 30 years in 1995, thanks to aggressive management of disease complications. CF is most common in people of northern and central European origin, with an incidence of 1 in 2,000, but it is much less common in other populations.

The CF gene was identified in 1989. Seventy percent of affected individuals carry the same mutation in the CF gene, and about 30 other mutations account for another 20 percent of CF cases. The remaining 10 percent have been found to have one of at least 800 additional

mutations, and new mutations are still being identified. More than 85 percent of individuals with CF are born to parents who have no family histories of the disorder.

Results from a CF carrier test can only reduce—not eliminate—the risk that one may be a carrier, because it is not practical to test for all of the possible rare mutations. Carrier screening is recommended for those individuals with family histories of CF or for those who have a relative identified as a CF carrier. An NIH consensus development conference in 1997 concluded that carrier screening should be offered to all pregnant women and couples contemplating pregnancy, but this recommendation is in the early stages of implementation. Further research is needed to correlate the many different gene mutations with disease severity, population differences, and penetrance. Information from these studies may aid in an assessment of the clinical validity and clinical utility of broader based carrier screening.

**Diagnostic/Presymptomatic Testing.** Testing for myotonic dystrophy can be both diagnostic and presymptomatic. First described in 1908, myotonic dystrophy is an autosomal dominant, multisystem disorder mainly involving the heart, smooth and skeletal muscle, central nervous system, and eyes. The incidence of myotonic dystrophy is 1 in 8,000. It is characterized by a symptom known as myotonia—delayed muscular relaxation or stiffness and is extremely variable in severity both within and between families. The disease has been shown to have an earlier onset and increasingly severe clinical features as it is passed from one generation to the next.

The gene for myotonic dystrophy was identified in 1985. The mutation is located at one end of the gene, where a series of duplicate DNA sequences called repeats is found. In the normal gene, the number of repeats is fewer than 50. Carriers of the myotonic dystrophy gene have 50 to 80 repeats; affected adults have between 100 to 500 repeats. Several studies have found a correlation between a higher number of repeats and earlier age of onset and disease severity.

Molecular testing for diagnostic and presymptomatic purposes has been used for myotonic dystrophy since 1990, and DNA testing is now an acceptable form of diagnosis for this disease. More than 1,000 individuals have been studied through DNA analysis, and thus far, no mutation other than the increased number of repeat sequences has been found. Data on the analytical validity and clinical validity of this test are

fairly complete, but unfortunately, no specific therapy is available that will slow or significantly modify the progressive muscular changes that occur in individuals with myotonic dystrophy. Although the test is able to provide a definitive diagnosis and is considered useful for some individuals, the clinical utility of the test is less clear-cut because of the lack of effective treatment. Scientists are hopeful that further research on the function of the myotonic dystrophy gene may explain the underlying causes of the disease and lead to the development of new therapies.

*Diagnostic Testing (with effective treatment).* Genetic testing for hereditary hemochromatosis (HH) is currently conducted for diagnostic purposes. Studies are underway to determine whether the genetic test should be used for predictive purposes in the general population. HH was first described in 1889. It is an autosomal recessive disease that results in increased accumulation of iron in the body. When the body's storage capacity for iron is surpassed, the iron is deposited in the tissues of multiple organs, causing tissue damage. This iron overload can cause cirrhosis of the liver, diabetes, fatigue, and heart disease, among other conditions, and persons with HH are more likely to die from liver failure or primary liver cancer. However, HH is one of the few genetic diseases for which an effective and relatively simple therapy exists if the disease is diagnosed before tissue damage has occurred. The therapy involves removing excess iron by periodic phlebotomy, or bloodletting.

In 1972, a simple biochemical test was developed to measure iron levels in the blood. The accuracy of the test was evaluated through several investigational studies. It is currently the most common screening strategy for the disease. The incidence of HH is estimated to be about 3 in 1,000 in people of northern European descent, an estimate that is based on screening trials that used biochemical measures of iron overload to identify affected persons. The proportion of people with positive test results who progress to symptomatic disease or life-threatening complications is unknown, however, and information on the incidence of HH in other populations is less complete.

In 1996, more than 100 years after HH was first described, the gene responsible for HH was identified. Based on research studies of HH affected individuals, one specific mutation in the gene has been found to be responsible for 85 percent of HH cases, and a second mutation is responsible for

a much smaller proportion of cases. More than a dozen different genetic testing methods are now available for the detection of the two described mutations. Genetic testing for HH has been used to identify presymptomatic persons with a family history, and it may eventually replace liver biopsy as the definitive test for HH because it is safer and noninvasive. Broad-based population screening by DNA analysis has not been implemented for HH because of the uncertain link between positive test results and severity of disease, the environmental and other genetic factors that may be involved in the disease process, and the possibility that other mutations may exist that have not yet been identified. Studies are underway to address these knowledge gaps and to assess the clinical validity of the DNA based test.

*Diagnostic/Predictive Testing (without effective treatment).* Alzheimer disease (AD), which was first described in the early 1900s, is a progressive disease that causes impairment in multiple brain functions, including memory, language, orientation, and judgment. The only definitive diagnosis for AD is the examination of brain tissue after death. At the present time, a checklist of clinical symptoms is used to diagnose AD and to rule out other possible disorders. Thus, a definitive diagnostic test for AD would be an important medical advance. Three genes have recently been associated with AD, although inherited cases of AD make up only a small proportion (less than two to five percent) of AD sufferers. Diagnostic and presymptomatic testing based on DNA analysis is recommended only for the small number of families that have a dominant pattern of inheritance of AD in multiple generations. A fourth gene, known as APOE, is the most recent gene found to be associated with AD. One variant of the gene, referred to as APOE4, is thought to be a risk factor for AD. Although the majority of AD cases occur at random, individuals with one or two copies of this gene are thought to be at greater risk for developing AD than the general population.

Not long after the discovery of this association, the test was commercialized as a tool to predict heightened risk for AD, although the clinical validity and clinical utility of the test had not yet been established. Subsequently, APOE4 predictive testing was withdrawn from the market, and the test is now available only to aid in the confirmation of a diagnosis of AD in a patient showing signs of dementia. APOE4 predictive DNA testing for AD is not recommended for several reasons. First, it is associated

at a population level with an increased risk of AD, but its predictive value for individuals is limited because many people with one or two copies of APOE4 will never develop AD, and conversely, many people with AD do not carry the gene variant. In addition, science's understanding of other risk factors that may play a role in the development of the disease in people who carry APOE4 is limited. Finally, the social and psychological burdens of predictive AD testing are not understood fully, and treatment and preventive strategies are lacking. More research into the genetic basis of AD will be necessary before predictive genetic testing of AD in the general population would be appropriate.

The ongoing commercial availability of this test as a tool in diagnosing AD complicates oversight issues, because without appropriate oversight, the APOE4 test could be used for predictive purposes, even though this use is not recommended. In addition, a positive result from APOE4 testing in an individual suspected of having AD automatically provides information to relatives about their probability of developing the disease, information that could be misused. As this example shows, the boundary between predictive and diagnostic uses of tests often is not distinct.

*Presymptomatic/Predictive Testing.* Breast cancer is an example of a disease in which genetic testing is used to predict disease in individuals with a family history of the disease. According to recent estimates, breast cancer is the second leading cause of cancer death in women in the United States. One out of every eight American women is at risk for developing breast cancer during her lifetime. There are a number of treatment options for breast cancer, including radiation, lumpectomy or mastectomy, and multiple drug treatments for both first diagnosis and metastatic disease. However, there is no guaranteed cure, and, once diagnosed, women never know whether they will be able to overcome the disease. Women with a strong family history of breast cancer, which may suggest the presence of a genetic factor, are at greater risk, although only 5 to 10 percent of breast cancer cases are believed to be related to genetic predisposition.

Because of the strong family history documented in some women who develop breast cancer, scientists began an intensive search for the gene that contributes to the development of this disease. DNA from women with familial breast cancer was analyzed, and in 1990, a region on chromosome 17 was found to be linked to increased risk for

the development of breast and ovarian cancer. In 1994, the BRCA1 gene was identified as a cancer-susceptibility gene. A second gene, BRCA2, was later discovered. Mutations in these two genes account for a significant portion of inherited cases of breast and ovarian cancer.

Development of commercial tests for these genes quickly followed. However, difficulties in assessing the analytical and clinical validity of BRCA1/2 test results have been demonstrated in some studies. Hundreds of mutations have been detected in the two BRCA genes, and different mutations in these genes may have different risks for breast cancer and ovarian cancer, or possibly different affects of tumor progression or severity. This suggests that further research is necessary to clarify the relationship between gene mutations in BRCA1/2 and the risk of developing breast and/or ovarian cancer. Studies have shown that the same mutations in different families have resulted in different disease outcomes, and environmental and other modifying factors also may determine how a particular mutation behaves, further contributing to the difficulty in interpreting BRCA 1/2 test results.

The complexities associated with genetic testing of BRCA1/2 raise further concerns, because some of the options a woman may choose if she tests positive, such as the surgical removal of breasts or ovaries, are irreversible. Further research on different populations and on women with no family history of breast cancer are necessary to establish analytical and clinical validity for BRCA1/2 testing in the general population. Such research should also increase understanding of the risks and benefits of testing for these groups, which may be different for women with no family history of the disease.

### **Part III: Current Oversight of Genetic Tests**

In considering whether additional oversight measures for genetic tests are needed, it is important to understand the provisions for oversight that already are in place. Currently, genetic and non-genetic tests receive the same level of oversight from governmental agencies. 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, regulations for the Protection of Human Subjects (45 CFR 46, 21 CFR 50, and 21 CFR 56). In addition to the Federal role, oversight of genetic tests is provided by States and private sector organizations.

This section summarizes the roles of five DHHS organizations in providing oversight of genetic tests: the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Care Financing Administration (HCFA), Office for Protection from Research Risks (OPRR), and National Institutes of Health (NIH). Although it does not have a regulatory function, the NIH supports research activities that generate knowledge about genetics and genetic testing. The roles of the States and the private sector in oversight also are described.

#### *The Roles of CDC and HCFA*

All laboratory tests performed for the purpose of providing information for the health of an individual must be conducted in laboratories certified under CLIA. Tests are regulated according to their level of complexity: waived, moderate, and high complexity. 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, the 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 (CLIAC) 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 employing surveyors of deemed organizations or State-operated CLIA programs that have been approved for this purpose. The oversight provided includes a comprehensive evaluation of the laboratory's operating environment, personnel, proficiency testing, quality control, and quality assurance. The laboratory director, who must be certified, plays a critical role in assuring the safe and appropriate use of laboratory tests. Laboratory directors are required to take specific actions to establish a comprehensive quality assurance program, which 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 specimen analysis and reporting of the results), to date, CLIA oversight has emphasized intra-laboratory processes as opposed to the clinical uses of test results. CLIA has not specifically addressed other aspects of

oversight that are critical to the appropriate use of a genetic test, including the clinical validity and clinical utility of a given test. Also unaddressed to date are other important issues such as informed consent and genetic counseling. (See Part IV for a discussion of steps being taken by CDC and HCFA to strengthen CLIA regulations for genetic testing.)

#### *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 premarket approval or clearance by the FDA. This premarket review involves an analysis of the device's accuracy as well as its analytical sensitivity and specificity. Premarket review is performed based on data submitted by sponsors to scientific reviewers in the Division of Clinical Laboratory Devices in the FDA's Office of Device Evaluation. In addition, for devices in which the link between clinical performance and analytical performance has not been well established, the FDA requires that additional analyses be conducted to determine the test's clinical characteristics, or its clinical sensitivity and specificity. In some cases, the 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 for their own use. These are referred to as in-house tests or "home brews." The FDA has stated that it has authority, by law, to regulate home brew laboratory tests, but the agency has elected, as a matter of enforcement discretion, not to exercise that authority. However, the 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. However, with few exceptions, the current regulatory process does not require a premarket 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 capable of 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.

#### *The Role of Human Subjects Regulations*

Additional oversight is provided during the research phase of genetic testing if the research involves human subjects or identifiable samples of their DNA. Regulations governing the protection of human research subjects are administered by the OPRR and FDA. OPRR oversees the protection of human research subjects in DHHS-funded research. The FDA oversees the protection of human research subjects in trials of investigational (unapproved) 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 and that risks do not 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 these tests are not subject to the FDA's enforcement authority. OPRR regulations would apply if the laboratory was DHHS-funded or was carrying out the research at an institution that receives DHHS funding. In a 1995 survey of biotechnology companies, the Task Force on Genetic Testing found that 46 percent of respondents did not routinely submit protocols to an IRB for any aspect of genetic test development.

#### *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 subjects 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. These activities help promote the appropriate integration and application of scientific knowledge into clinical and public health practice. The following are examples of research, dissemination, and integration activities supported wholly or in part by NIH that might specifically contribute to a better understanding of the validity and utility of genetic tests.

- The Ethical, Legal, Social Issues (ELSI) Program, a major program established as an integral part of the Human Genome Project, supports research on the ethical, legal, and social implications of human genetics research.
- A five-year epidemiologic study of iron overload and hereditary hemochromatosis is beginning to gather data on the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of the disorder. The knowledge gained from this study will be used to determine the feasibility, benefits, and risks of a broad-based screening program.
- The Cancer Genetics Network, a consortium of academic cancer centers around the country, serves as a national resource to support multi-center investigations into the genetic basis of cancer susceptibility, to integrate new research data into medical practice, and to identify psychological, ethical, legal, and public health issues related to cancer genetics.
- GeneTests, a directory of clinical laboratories providing testing for genetic disorders, disseminates information about diseases and diagnostic and treatment options to health care providers and the public.
- The National Coalition for Health Professional Education in Genetics promotes genetics education and information dissemination to health professionals.

NIH also produces consensus statements and technology assessment statements on issues important to health care providers, patients, and the general public. Topics related to genetic testing have included newborn screening for sickle cell disease, genetic testing for cystic fibrosis, and screening for and management of PKU.

#### *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, 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 Role of the Private Sector*

The private sector provides oversight in partnership with HCFA and the CDC by serving as agents for the Government in accreditation activities. The private sector also develops 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 College of American Pathology (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 consensus recommendations for the standardization of test methodologies; and, 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. Other organizations, such as the American Academy of Pediatrics, American College of Obstetrics and Gynecology, American Society of Human Genetics, and National Society of Genetic Counselors, are also involved in the development of guidelines and recommendations regarding the appropriate use of genetic tests.

#### *The Roles Combined*

It is likely that no single agency or organization will be able to address all the issues raised by genetic tests. Instead, the combined expertise of all entities may be needed.

#### **Part IV: Recommendations of the NIH-DOE Task Force on Genetic Testing**

The Task Force on Genetic Testing made a number of recommendations related to the oversight of genetic tests. The Task Force identified the type of data needed in order to assess the validity and utility of genetic tests, methods of data collection, preliminary criteria for tests that require stringent scrutiny, the need for external review of genetic tests, steps for enhancing

laboratory quality assurance, and special concerns related to rare diseases. These recommendations are summarized below, and the full report of the Task Force is available at [www.nhgri.nih.gov/ELSI/TFGT\\_final/](http://www.nhgri.nih.gov/ELSI/TFGT_final/). The actions taken by the Federal agencies in response to the Task Force recommendations are also outlined.

*Data needed for assessing tests.* The Task Force recommended that data regarding analytical and clinical validity and clinical utility should be gathered to determine when a test is ready for clinical application and that validation should occur for each intended use of a test.

*Collection of data.* The Task Force recommended that NIH and the CDC support consortia and other collaborative efforts to facilitate data collection on test safety and effectiveness. It recommended that the CDC play a coordinating role in data gathering and serve as a repository for data submitted by genetic test developers.

*Tests requiring stringent scrutiny.* The Task Force recommended that certain kinds of genetic tests might require a higher level of scrutiny, and it suggested some criteria for determining which kinds of tests these might be. The criteria included whether

- The tests are used for predicting future disease in healthy or apparently healthy people;
- The tests cannot be independently confirmed;
- The tests have low sensitivity and low positive predictive value;
- The tests are for conditions for which an intervention is not available or has not been proven effective in those with positive test results;
- The tests are for disorders of high prevalence;
- The tests are for screening; and
- The tests are likely to be used selectively in ethnocultural groups with higher incidence or prevalence of a disorder.

*Review of genetic tests.* The Task Force recommended that test developers submit their clinical validity and utility data to independent internal and external reviewers and to interested professional organizations. It said that the reviews should ensure that the data are interpreted correctly, that test limitations are described, and that the populations for which the test may or may not be appropriate are defined.

*Enhancing laboratory quality assurance.* The Task Force recommended that CLIA regulations be augmented to strengthen clinical laboratory practices for genetic tests by requiring specific provisions for quality

control, personnel qualifications and responsibilities, patient test management, proficiency testing, quality assurance, confidentiality, and informed consent. The Task Force recommended that clinical laboratories should not offer a genetic test unless its clinical validity has been established or data on its clinical validity are being collected either under an IRB-approved protocol or a conditional premarket approval agreement from the FDA. It also recommended that clinical laboratories pilot a test in order to verify that all steps in the testing process are operating appropriately.

*Ensuring continuity and quality of tests for rare diseases.* The Task Force pointed out that although the vast majority of single-gene diseases are rare, a total of 10 to 20 million Americans are afflicted with rare diseases. The Task Force recommended that laboratories providing genetic testing services for rare diseases should be CLIA-certified, subject to the same internal and external reviews as other clinical laboratories, and required to validate tests used in clinical practice. It further suggested that, because of difficulties in obtaining sufficient data on test validity, consideration should be given to developing less stringent regulations—without sacrificing quality—for genetic testing of rare diseases. The Task Force highlighted the important role of the NIH Office of Rare Diseases in disseminating information about the availability of safe and effective tests for rare diseases.

#### *Progress Since Publication of Task Force Report*

Since receiving the final report of the Task Force on Genetic Testing, DHHS agencies have acted on several of the Task Force recommendations that relate to the oversight of genetic tests. The FDA promulgated the regulation described in Part III for components of tests, thereby introducing a degree of FDA oversight of commercial, laboratory-based testing services. The FDA also has established an advisory panel on genetics to provide expertise needed for the review of genetic test kits.

HCFA and CDC have taken steps to develop recommendations for more specific requirements for the performance of genetic tests under CLIA. After careful review of existing requirements, CLIAC recommended changes to ensure that CLIA specifically addresses genetic testing. The CLIAC recommendations include provisions for the pre- and post-analytical phases of the testing process. The pre-analytical provisions include attention to the need

for informed consent prior to collecting the sample. The informed consent process helps individuals understand the risks and benefits of a specific test so that they can make informed decisions regarding genetic testing. Clinical information, including ethnic background, when appropriate, would need to be submitted to the laboratory performing the test in order to enhance the accuracy of the interpretation of results. This is because although a given test may be likely to predict disease in some populations, it may produce unacceptable false positive results in another ethnic group. To ensure accuracy, samples would have to be transported to the testing laboratory in a manner that would preserve the integrity of the DNA, RNA, protein, or metabolite to be studied. For the post-analytical phase, CLIAC recommended additional requirements for assuring the confidentiality of test results as they are returned to the provider. The security of test information is essential to protecting the privacy of test results, especially when a number of locations require access to the information or results are communicated using computers. To avoid over- or under-interpreting the meaning of test results, CLIAC recommended that they be described clearly, including detailed information about the methods used and the specific factors tested. Counseling must be readily available to help individuals understand the meaning of the specific test that was performed and the significance of the findings to other family members. These and other post-analytical factors require thoughtful design and implementation in order to ensure that the performance of the genetic test maximizes benefits to individuals and families and minimizes socioeconomic risks. The CLIAC recommendations will be published in the **Federal Register** for public comment. Comments will be reviewed and carefully considered before final changes are made to CLIA.

CDC has established the Human Genome Epidemiology Network to advance the collection, analysis, dissemination, and use of peer-reviewed epidemiologic information on human genes. The Network promotes the use of this knowledge base for making decisions involving the use of genetic tests and services for disease prevention and health promotion by health care providers, researchers, members of industry and government, and the public.

CDC is 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. Such data collection through a consortium approach is important for several reasons. In addition to the increasing number of predictive tests for common chronic diseases and potential for commercialization and premature use of genetic tests, there is a need for making consistent information available to providers, consumers, and policymakers. Also, the evaluation of tests may require longitudinal clinical and epidemiologic data, data that are generated from both public and private sources. The goals of the public/private partnership include identifying data elements needed for the evaluation of genetic tests, exploring a framework for data collection and dissemination, and facilitating the review of data for a smoother transition from gene discovery to clinical and public health. Two pilot data collection efforts for cystic fibrosis and hereditary hemochromatosis are in the preliminary stages.

The CDC, NIH, the Health Resources and Services Administration (HRSA), and the Agency for Health Care Policy and Research (AHCPR) are beginning to collaborate more closely to promote and support the development of genetic knowledge and technology and to ensure that this knowledge and technology is used appropriately to improve the health and well being of the Nation. The goal of this collaboration is to enhance agency programs involving technical assistance, professional and public education, data collection and surveillance, applied genetic research and assessment, policy development, and quality assurance.

#### Part V: Critical Issues To Be Addressed

SACGT has been asked to assess, in consultation with the public, whether current programs for assuring the accuracy and effectiveness of genetic tests are satisfactory or whether other oversight measures are needed for some or possibly all genetic tests. This assessment requires consideration of the potential benefits and risks (including socioeconomic, 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. If, after public consultation and analysis, SACGT finds that other oversight measures are warranted, it has been asked to recommend options for such oversight. The advantages and disadvantages of each option must be

considered carefully before a final determination is made.

SACGT has been asked to address these five specific issues.

*Issue 1:* What criteria should be 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?

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

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

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

These five issues are discussed in more detail below. This discussion is provided in order to foster public discussion and deliberation. Following the discussion of each major issue, SACGT presents a number of related questions. SACGT encourages public comment on all or any one of the major issues and approaches and on the related questions. SACGT presents a sixth set of other related questions relevant to genetic testing and encourages public input on these as well.

#### *Issue 1: What Criteria Should Be Used To Assess the Benefits and Risks of Genetic Tests?*

Assessing the benefits and risks of genetic tests 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. The second step in assessing the benefits and risks of genetic tests is to evaluate how well tests perform in the clinical environment, which is the principal focus of discussion for this issue.

In considering this issue, SACGT identified three primary criteria that could be used to assess the benefits and risks of a genetic test. One criterion is clinical validity, which refers to the accuracy of the test in diagnosing or predicting risk for a health condition. Clinical validity is measured by the sensitivity, specificity, and predictive value of the test. The second criterion is clinical utility, which involves identifying the outcomes associated with positive and negative test results. Because 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. The third criterion relates to the social context within which genetic testing is performed.

#### Factors To Be Considered in Assessing Clinical Validity

Because clinical validity considers many aspects of genetics that make genetic testing complex, it is a measure that is essential to the assessment of the benefits and risks of genetic tests. A test's clinical validity is influenced by a number of factors beyond the laboratory, including the purpose of the test, the prevalence of the disease or condition tested for, and the adequacy of relevant information.

*Purpose of test.* Genetic tests have a number of purposes, and some are used for more than one purpose. The acceptable level of a predictive value of a genetic test may vary depending on the purpose for which the test is used (for example, for diagnosing or predicting a future health risk). In addition, a higher predictive value may be required of a stand-alone test than of a test that is used to confirm other laboratory or clinical findings.

*Prevalence.* 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.

*Adequacy of information.* For many genetic tests, particularly those used for predicting risk, 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 is the second criterion that is critical to assessing the benefits and risks of genetic tests. 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 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, of the degree of certainty with which a diagnosis can be made, and of the potential for adverse socioeconomic effects versus beneficial treatment if a diagnosis is made. Factors affecting clinical utility include the potential benefits and risks of test results, the nature of the health condition and its potential outcomes, the purpose of the test, uncertainties of genetic test results, the provision of information concerning other family members, and the quality of evidence for assessing outcomes.

*Potential benefits and risks of genetic test results.* There are a number of potential benefits and risks of genetic testing. The benefits and risks of true positive and negative test results must be considered, as must the risks of false positive and negative results (see list of benefits and risks below). A true positive result means that the test result is positive, and the condition or predisposition is actually present. A true negative result means that the test result is negative, and the condition or predisposition is not present. False results can also be both positive and negative. A false positive occurs when the test indicates a positive result when in fact the condition or predisposition is not present. A false negative occurs when the test indicates a negative result but the condition or predisposition is present.

Potential benefits of a positive test result:

- May provide knowledge of diagnosis or risk status.
- May allow preventive steps or treatment interventions to be taken.
- May identify information about risk status in other family members (also a potential harm).

Potential benefits of a negative test result:

- May rule out specific genetic diagnosis or risk.

May eliminate the need for unnecessary screening or treatment.

Potential risks of a positive test result:

- May expose individuals to unproven treatments.
- May cause social, psychological and economic harms, including stigmatization and potential exclusion from health insurance and employment.
- May identify information about risk status in other family members (also a potential benefit).

• For false positive test results, individuals may be exposed to unnecessary screening and treatment.

Potential risks of a negative test result:

- May give false reassurance regarding risk due to nongenetic causes.

May have psychological effects, such as "survivor guilt."

- For false negative test results, may delay diagnosis, screening, and treatment.

• *Nature of health condition and health outcomes.* The nature (severity, degree of associated disability, or potentially stigmatizing characteristics) of the health condition being tested for 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. 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. As uncertainties increase about the health outcomes associated with a test result, so do 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.

*Purpose of the genetic test.* The purpose of the test is an important factor in assessing clinical utility. Genetic tests used to predict a disease or condition will have different risks and uncertainties associated with it as compared to a diagnostic test. For example, the use of a test 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 possesses a BRCA1 or BRCA2 mutation. Tests used for diagnostic purposes will most likely be conducted as part of a clinical evaluation to diagnose a specific disease or will be used for clearly inherited diseases or conditions.

Genetic tests used for predictive purposes in healthy persons are associated with greater uncertainties and risks. Currently, tests used for predictive purposes will give an estimate of the risk a person may have of developing a particular disease or condition. Due to incomplete knowledge, 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. Predictive genetic tests may have profound effects on the

lives of otherwise healthy individuals. Even though degree of risk is uncertain, a positive test result for breast cancer may affect treatment, reproductive, and lifestyle plans. A negative test result for a BRCA1 mutation does not eliminate the risk of breast cancer, because BRCA1 mutations account for only a small percentage of breast cancer cases overall. A woman with a negative test result still carries, at minimum, the breast cancer risk of the average woman and she should still continue with preventive screening measures.

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. The higher the prevalence of the genetic condition, the greater the number of people who will be subjected to false positive and false negative results. On the other hand, if treatment options are available, screening for highly prevalent diseases may have significant public health value.

*Uncertainties of genetic test results.* The assessment of a test's clinical utility is affected by the accuracy of test results. 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. If a woman is from a family in which multiple cases of early breast cancer have occurred, she is likely to be at risk for an inherited susceptibility to breast cancer even if genetic testing has failed to identify a specific cancer-associated mutation in her family.

*Information about family members.* Because genetic information may have implications for family members, the potential of the test to reveal information about family members is another factor 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 a woman with breast cancer tests positive for a BRCA1 mutation, her 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.

*Quality of evidence for outcomes assessment.* The quality of evidence for assessing outcomes of genetic test results is a factor in the clinical utility of a genetic test. Often, evidence to assess relevant factors, especially those related to potential social or economic harms, is limited or lacking. In assessing potential risks under these circumstances, incomplete information and the potential for harms that have not yet been documented must be considered. Established methods for evaluating the quality of the evidence should be used to assess outcomes.

#### 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, e.g., conditions associated with mental illness or dementia. Thus, the social context of a disease may be an important factor for an individual to consider prior to taking a genetic test. In addition to affecting the individual, these special risks may affect entire populations. In particular, special consideration should be given to genetic stigmatization and discrimination, genetic testing in specific U.S. populations, and the possible development and use of genetic tests for non-health related conditions.

*Genetic stigmatization.* Genetic test results can change how people are viewed by their family, friends, and society, and how they 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.

*Genetic discrimination.* Diagnostic or predictive genetic information about an individual may lead to discrimination in health insurance, life insurance, and education and employment. The potential for discrimination may be particularly acute for people with, or at risk for, diseases or conditions that are chronic, severely disabling, and lack effective or affordable treatments. Educational opportunities may be restricted, further limiting future life possibilities. Fears of genetic

discrimination have made the establishment of Federal privacy and confidentiality protections a high priority for many.

As important as legal protections are, however, they cannot prevent all adverse consequences of genetic information. For example, the stigma associated with certain genetic diseases or conditions can affect personal choices, such as marriage and child bearing.

*Special considerations for U.S. populations.* Significant social concerns have grown out of the strong memories of the American eugenics movement and the painful history of programs that tested minority populations for conditions such as sickle cell disease. In some cases, these programs heightened discrimination against those tested. Given this history, tests developed for use in particular population groups, whose incidence of a condition may be higher, or in circumstances where the meaning of the test could be interpreted only within a certain population, may carry higher risks. This issue is of great concern in the United States because of the exceptional diversity of the population. Specific genetic diseases or conditions occur with different frequencies in different populations. As genetic testing becomes more common, the potential for stigmatization of groups increases. Educational programs, legal protections, and the involvement of ethnocultural group representatives in assessing the risks and benefits of genetic tests are needed to reduce the risk of stigmatization of groups.

In addition, social categories used to classify ethnocultural differences often do not accurately reflect actual genetic variation within a population. For example, since the categories "Hispanic" and "Asian" encompass populations from different parts of the world, genetic variations are likely to exist within these populations. Thus, care should be taken in determining the ethnocultural background of individuals in order to ensure accurate interpretation of genetic test results. A further note of caution is also necessary. In developing genetic tests, it will be important to assure their accuracy when used in different populations. In so doing, however, the erroneous assumption that there is a straightforward, one-to-one relationship between one's genes and one's ethnocultural identity may be inadvertently reinforced. This could result in stigmatization because even accurate tests could reinforce misguided cultural notions about genetic determinism.

*Tests for conditions not commonly regarded as medical or health-related.*

In the future, it may be possible to develop genetic tests that could be used to identify predispositions to certain patterns of behavior, such as risk-taking, shyness, or other complex features of personality. Although the assumption that single genes, or even many genes, can predict complex human actions is simplistic, the possibility of such tests raises profound ethical questions and concerns because their potential psychological and socioeconomic harms are so significant and the potential misuse of such information is so great. The boundaries between "health-related" and "non-health related" are not clear cut, and they may shift over time. It will, therefore, be difficult to avoid harm from genetic tests simply by limiting their use to situations of diagnosing or predicting disease. For example, genetic tests might be used to predict susceptibility to conditions that are health-related but where a strong behavioral component exists, such as obesity, alcohol abuse, or nicotine addiction. Individuals identified as at risk for stigmatized conditions such as these may suffer special harms.

#### Questions Related to Issue 1:

1.1 What are the benefits/risks of having a genetic test?

1.2 What are the major concerns regarding the different genetic tests that are currently available?

1.3 What expectations do individuals have about genetic tests, such as whether they have a high level of accuracy and can be used to help make health or important personal decisions?

1.4 In deciding whether to have a genetic test, does it matter whether a treatment exists for the condition or disease being tested for? Is the information provided by the test important or useful by itself?

1.5 Do concerns about the ability to keep genetic test results confidential influence an individual's decision to have a genetic test?

1.6 Are genetic tests different from other medical tests, such as blood tests for diabetes or cholesterol? Should genetic test results be treated more carefully with more confidentiality than other medical records?

*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?*

In attempting to address this issue, SACGT considered whether the criteria

of clinical validity and clinical utility could be used to characterize the potential risks associated with a given test, which would allow tests to be grouped according to the risks that are associated with them. Using this information, tests might be organized into categories such as "high risk" and "low risk." Such a categorization would not be simple or straightforward, however, because it would depend upon 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. For example, a test of high predictive value that identifies a nonstigmatizing condition with a safe and effective treatment might fall into a low-risk category, while a test that has high predictive value and that identifies a genetic risk for a serious condition for which treatment is unproven might fall into a high-risk category.

As these general examples illustrate, categorizing tests will require the weighing of several different aspects of the test and of the disease that the test is used to diagnose or predict. Developing an appropriate mechanism for this process poses a challenge, and it is likely that such a mechanism will involve at least three steps. In the first step, data concerning the test would be collected perhaps using a standardized format to ensure that all of the required data are reported. In the second step, the data would be analyzed to determine risk category. One possible approach would be to initially sort tests into a readily identifiable low-risk category (possibly tests with well-defined characteristics that meet a previously defined low-risk threshold). For tests not falling within the low-risk category (possibly tests for rare diseases or complex, common diseases), a third step involving a more detailed evaluation of available data would be required to make a final determination of risk category.

Thus, determining the risk category of a test will involve evaluating the data available regarding the analytical and clinical validity of the test and the outcomes of positive and negative test results. This evaluation should consider socioeconomic factors, such as the potential for stigmatization and other social risks, including the likelihood that a test would be used in particular population groups. For tests that are determined to be high risk or potentially high risk, the analysis likely will require a diverse range of technical expertise and input.

*Questions Related to Issue 2:*

2.1 Do some genetic tests raise more ethical, legal, medical, and social concerns than others and should they be in a special category and require some special oversight? If so, what tests or types of tests would fall into such a category?

2.2 Are there some genetic tests that raise no special concerns and therefore need no special oversight? If so, what tests or types of tests would fall into this category?

*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. Some of these data are publicly available; others are not. It appears that in the future, a laboratory that develops a particular test will need to continuously collect data regarding its analytical validity, and at a minimum, a summary of the results of the evaluation should become available as part of the information on analytical validity contained in the test labeling.

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. One option is to continue to rely 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. A second option is to make each laboratory that offers a test responsible for collecting and analyzing the information that is required to support its claims for the test according to national standards. A third choice would be for a Government agency, possibly the CDC, to coordinate the creation and collection of information on clinical applications of tests that detect particular mutations and perhaps to define appropriate claims for tests as well. (See Part IV for a discussion of CDC's current efforts in this area.) A fourth option, discussed as part of Issue 4, would be to form a consortium of government, professional associations, and industry that would create, collect, and analyze information about clinical applications. More than likely, data on any genetic test will be incomplete and must be collected on a continuous basis. If the data available at the time of the initial evaluation suggest benefit of the test in clinical practice, the test may be approved on the condition that data will continue to be collected and will be reviewed again at a future date.

Another approach to data collection on validity and utility of genetic tests could be modeled after tumor registries. Tumor registries document and store information about a patient's history, diagnostic findings, treatment, and outcome. Information within a tumor registry may be used to generate a variety of reports on topics such as patient quality of care and long-term results of specific treatments.

Regardless of the option chosen for data collection, once the data have been collected and evaluated, they must be disseminated to health care practitioners and the public. This must include not only data generated prior to offering the test for clinical use, but also data generated as part of any postmarket evaluation. One option 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.

*Questions Related to Issue 3:*

3.1 Given that collection of data is an ongoing process, what type of system or process should be established to collect, evaluate, and disseminate data about the analytical validity, clinical validity and clinical utility of genetic tests?

3.2 How can the system or process for data collection, evaluation, and dissemination be structured in such a way as to protect the privacy and confidentiality of the data that is collected?

*Issue 4: What Are the Options for Oversight of Genetic Tests and the Advantages and Disadvantages of Each Option?*

SACGT has been asked to focus on oversight of the accuracy and effectiveness of genetic tests—especially, the development, use, and marketing of genetic tests developed by clinical laboratories. SACGT recognizes that there are many areas beyond test development, use, and marketing that might have an equally important impact in assuring the safety and effectiveness of a genetic test. For example, the

training and education of health care providers who prescribe genetic tests and use their results for clinical decision making is a critical issue, in particular as it relates to their ability to stay abreast of new information on the uses, capabilities, and limitations of these tests. The effect that gene patenting is having on the cost, accessibility, and quality assurance of genetic tests is another critical issue, as is the potential for workplace and insurance discrimination that could result from genetic testing. Oversight of genetic tests that provide non-health related information is another area of inquiry. SAGCT will focus its attention on these other high priority oversight issues once it completes its current work.

#### Current Oversight of Genetic Tests

As a starting point, it is important to recognize that some oversight of the development, manufacturing, use, and marketing of genetic tests is already in place. Currently, genetic and nongenetic tests receive the same level of oversight from governmental agencies. These oversight provisions are discussed in Part III and reiterated here briefly. All laboratory tests, including genetic tests, performed for the purpose of providing information for the health of an individual must be conducted in laboratories certified under CLIA. The CLIA program provides oversight through inspections conducted by HCFA using its own scientific surveyors or surveyors of deemed organizations or State-operated CLIA programs that have been approved for this purpose. The oversight provided includes a comprehensive evaluation of the laboratory's operating environment, personnel, proficiency testing, quality control, and quality assurance. To date, CLIA oversight has emphasized intra-laboratory processes. As discussed in Part IV, HCFA and CDC have taken steps to develop recommendations for more specific requirements for the performance of genetic tests under CLIA.

Under the medical device regulations, the FDA requires that genetic tests packaged and sold as kits to laboratories require premarket approval or clearance by the FDA. The premarket review would evaluate the test's accuracy and analytical validity. For devices in which the link between clinical performance and analytical performance has not been well established, the FDA requires that additional analyses be conducted to determine the test's clinical characteristics, or its clinical sensitivity and specificity. In some cases, the FDA requires that the predictive value of the

test be analyzed for positive and negative results. The FDA has not attempted to extend its authority to regulate home brew tests (tests developed by laboratories for their own use). All of the genetic tests described in Part II are home brew tests. FDA has implemented regulation of the active ingredients of genetic tests, or analyte-specific reagents (ASRs). Manufacturers of ASRs are required to comply with good manufacturing practices, restriction of sales to laboratories capable of performing complex tests, and requirements that certain information accompany both the reagents and the test results.

Additional oversight protections are provided by professional organizations and state health departments. Organizations such as CAP, ACMG, and NCCLS have developed guidelines and standards for the development and use of genetic tests. State health departments may require laboratory facilities and personnel that perform genetic tests be licensed.

#### Possible Areas of Oversight

In considering areas of oversight, SAGCT has focused on several key issues. While these are not the only areas in which additional oversight might be considered, and public comment on other issues would be welcome, SAGCT expects to consider at least the following issues.

*Introducing Laboratory-Developed Tests into Clinical Practice. Analytical Validity.* It seems clear that a genetic test should not be used in clinical practice (i.e., for other than research purposes) unless it has been shown to detect reliably the mutation that it is intended to detect. CLIA now 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 audited during a CLIA inspection. Most believe that the current system needs review. Some have suggested that voluntary or mandatory standards should be enhanced to assist laboratories in deciding when a test's analytical validity has been determined and is acceptable, or that laboratories should be required to obtain the concurrence of an independent third party before a test is offered for use in clinical practice.

*Clinical Validity.* Similar questions arise with respect to the appropriate level of knowledge 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 and usually long term process (often requiring decades of work). At the same time, many people want to see gene discoveries 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 laboratory decision making with respect to 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.

*Clinical Utility.* Also important is the degree to which benefits are provided by positive and negative test results. Some have argued that genetic tests should not be available unless they can provide information useful in making health-related decisions and that consumers are likely to 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 if it 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 some observers have suggested that additional oversight is needed to ensure greater awareness of the utility of the test.

*Changes in Test Methodology.* When test manufacturing methods and materials change, either deliberately or inadvertently, the performance characteristics of a test can change as well, which can change the analytical validity, clinical validity, and clinical utility of the test. Some have suggested that stronger incentives should be created to re-qualify tests when methods and materials change.

*Patient Safeguards.* Informed consent in the research phase of development. In some cases, laboratories that are developing genetic tests for eventual use in clinical practice conduct studies using identifiable patient samples. 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.

Informed consent for tests used in clinical practice. Even after a test has been accepted into clinical practice, some observers have suggested that due to the predictive power of genetic tests and the impact test results may have on the individual 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 obtained. There is currently no requirement for such an informed consent.

Availability of genetic education and counseling. 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 individuals.

*Post Market Data Collection.* Many tests are put into clinical use before full information about their validity and utility has been obtained. Virtually everyone agrees that it is critical that data continue to be collected after such tests reach the market. Yet, no comprehensive method for data collection now exists. Many observers believe that ongoing mechanisms to collect data need to be put in place. A number of potential mechanisms to accomplish data collection are outlined in the discussion of Issue 3.

*Information Disclosure and Marketing.* Data disclosure. There is no current requirement that data about a test's analytical validity, clinical validity, or clinical utility, or lack thereof, be disclosed to health care providers or patients. Some observers believe that laboratories should be encouraged or required to make such information available and to ensure that the data is accurate and complete.

*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 that promotion and advertising of genetic tests may be permitted, but emphasis should be placed on taking action against false or deceptive claims.

Possible Directions and Implications of Further Oversight

SACGT welcomes public input on whether further oversight measures are needed, and if so, how additional oversight might be addressed. If, from its deliberations and public consultation, SACGT determines that further oversight is needed, possible directions that could be taken include the strengthening and expansion of current CLIA or FDA regulations or voluntary standards and guidelines, the formation of interagency review boards, or the formation of a consortium of representatives from government, industry, and professional organizations.

In assessing whether further oversight is warranted, it is important to consider the implications that further oversight may have on the current system and all parties involved. Among other issues, any new proposals to provide additional oversight of this rapidly growing technology should take into consideration the trade-offs involved as well as the evolving nature of genetic research and technology.

*Trade-offs.* In considering whether additional oversight is 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 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 resource implications that may affect the costs of genetic tests and public access to them.

Evolving nature of genetic research and technology. New information on genetics and human diseases and conditions are published on an almost daily basis, and new technologies are emerging rapidly. Due to this pace of discovery and technological change, the assessment of the analytic validity, clinical validity, and clinical utility of a genetic test is likely to change in light of new findings. For example, data from population studies or the identification of additional genes or mutations will change and, in most cases, improve knowledge about a specific genetic disease or condition in a specific population. Observers have suggested

that laboratories will need to be able to access and assimilate new information continuously in order to update the clinical validity and utility of their tests and that oversight methods will need to monitor, guide, and sample the flow of new information rather than take snapshots of what is known at a given moment in time. According to this view, health care providers and oversight groups will need to recognize and adapt their methods to the conditions created by continuous knowledge generation.

#### *Questions Related to Issue 4:*

4.1 Information about the accuracy, validity, and usefulness of genetic tests is being gathered through research studies. At what point should an experimental test be considered ready for general use? Is it important for a test to be immediately available even if its validity has not been fully established? Might the point at which a test is considered ready for general use be different for different types of genetic tests? Since data on the validity of tests for rare diseases are especially difficult to collect, should special considerations be given to rare disease testing to ensure access to these tests and, if so, what should the considerations be?

4.2 What level of confidence should individuals have, or might they want to have, in the information they receive about a genetic test? Would the level of confidence change depending on the type of disease (e.g., cancer versus gum disease) or the type of testing being done (e.g., predictive versus diagnostic testing)?

4.3 Is making information available to the consumer about a genetic test, such as information about its accuracy, predictive power, and available therapy, a sufficient form of oversight?

4.4 Would one form of oversight be to review or inspect promotional material directed to consumers (such as commercials, billboards, or Internet marketing) and health care providers (such as package inserts) to make sure that claims made are accurate? Is this sufficient oversight?

4.5 Should genetic education/counseling provided by an individual with special training always be available when genetic tests are offered? Should this apply for every genetic test or only for some kinds of genetic tests?

4.6 Certain trade-offs may be necessary in order to ensure that genetic tests are safe and effective. Are consumers willing to pay for the cost of additional oversight of genetic tests (in the form of higher prices, health insurance premiums, or taxes)? Are consumers willing to wait for the effectiveness of genetic tests to be

demonstrated before having access to a new genetic test?

*Issue 5: What Is an Appropriate Level of Oversight for Each Category of Genetic Test?*

Different levels of oversight may be appropriate for tests that present different or unknown levels of risk, have different purposes, and are at different stages of development. Until SACGT has had an opportunity to consider public comment, it is premature for SACGT to formulate or offer any views on whether additional oversight is needed, and if so, what form it should take. SACGT welcomes public comment on this subject.

*Question Related to Issue 5:*

5.1 How can oversight be made flexible enough to incorporate and respond to rapid advances in knowledge of genetics?

*Issue 6: Are There Other Issues in Genetic Testing of Concern to the Public?*

6.1 Is the public willing to share, for research purposes, genetic test results and individually identifiable information from their medical records in order to increase understanding of genetic tests? For example, tumors removed during surgery are often stored and used by researchers to increase understanding of cancer. Should samples from individuals with genetic disorders or conditions be managed in a manner similar to cancer specimens? Or does the public feel that this could cause confidentiality problems? If so, are there special informed consent procedures that should be used?

6.2 Research studies involving human subjects or identifiable human tissue samples that are funded by the Government or are subject to regulations of the FDA must be reviewed by an Institutional Review Board (IRB). (An IRB is a specially constituted review body established or designated by an organization to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.) Some studies involving genetic tests do not fall into either of these categories and, therefore, are not required to be reviewed by an IRB. For example, a private laboratory developing a test for its own use would not be required to obtain IRB review. Should all experimental genetic tests be required to be reviewed by an IRB?

6.3 When some medical tests (e.g., routine blood counts) are performed, patients do not sign a written consent to have the test performed. Should health care providers be required to obtain written informed consent before

proceeding with a genetic test? Should this apply to all tests or only certain tests? Should testing laboratories be required to obtain an assurance that informed consent has been obtained before providing test services?

6.4 Does the public support the option of being able to obtain a genetic test directly from a laboratory without having a referral from a health care provider? Why or why not?

6.5 Should any additional questions or issues be considered regarding genetic testing?

**Part VI. Conclusion**

SACGT was chartered to advise the DHHS on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests. At SACGT's first meeting in June 1999, the Assistant Secretary for Health and Surgeon General asked the Committee to assess, in consultation with the public, 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 socioeconomic, 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.

The question of whether more oversight of genetic tests is needed has significant medical, social, ethical, legal, economic, and public policy implications. The issues may 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 is endeavoring to encourage broad public participation in the consideration of the issues. Such public involvement in this process will enhance SACGT's analysis of the issues and the advice it provides to DHHS. SACGT looks forward to receiving public comments and to being informed by the public's perspectives on oversight of genetic testing.

*Comment Period and Submission of Comments*

In order to be considered by SACGT, public comments need to be received by January 31, 2000. Comments can be submitted by mail or facsimile. Members of the public with Internet access can submit comments through

email or participate in the SACGT website consultation.

Secretary's Advisory Committee on Genetic Testing, National Institutes of Health, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892, 301-496-9839 (facsimile), sc112c@nih.gov (email), <http://www4.od.nih.gov/oba/sacgt.htm> (website).

Dated: November 24, 1999.

**Sarah Carr,**

*Executive Secretary, SACGT.*

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket Nos. 91N-0101, 91N-0098, 91N-0103, and 91N-100H]

**Food Labeling: Health Claims and Label Statements for Dietary Supplements; Strategy for Implementation of *Pearson Court Decision***

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is informing the public of its strategy to implement a recent court decision in *Pearson v. Shalala (Pearson)*. The agency is taking this action to ensure that interested persons are aware of the steps it plans to follow to carry out the decision. FDA is also announcing how it plans to process petitions for dietary supplement health claims during the interim implementation period.

**FOR FURTHER INFORMATION CONTACT:** Marquita B. Steadman, Center for Food Safety and Applied Nutrition (HFS-007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, 301-827-6733.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

On January 15, 1999, the U.S. Court of Appeals for the D.C. Circuit issued its decision in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999). In *Pearson*, the plaintiffs had challenged FDA's health claim regulations for dietary supplements and FDA's decision not to authorize health claims for four specific nutrient-disease relationships: Dietary fiber and cancer, antioxidant vitamins and cancer, omega-3 fatty acids and coronary heart disease, and the claim that 0.8 mg of folic acid in dietary supplement form is more effective in