A Public Consultation on Oversight of Genetic Tests

December 1, 1999 - January 31, 2000

SUMMARY

Secretary's Advisory Committee on Genetic Testing
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SUMMARY

Introduction

New genes and genetic tests are being discovered and developed at an increasing pace. Scientists are making more rapid progress in understanding the role of genetics in many common complex diseases and conditions—such as heart disease, cancer, and diabetes—and are gaining 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.

Genetic tests can be used in many ways. The most straightforward use is to diagnose disease or confirm a diagnosis in a symptomatic individual. Additionally, some tests can provide predictive information about the course of disease, that is, its severity or age of onset. Still other tests can be used to 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. In all cases, these tests are used only to detect or predict disease. They are not designed as treatments for disease, such as gene therapy, although their results can sometimes suggest treatment options.

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. 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 information obtained from this project is likely to lead to a rapid expansion in the number of tests available and ultimately will guide the development of new approaches to therapy.

In the meantime, however, questions have been raised about the speed and manner by which we adopt these tests for use in the delivery of medical care. For tests that are well established and have been proven over time to be reliable indicators of the presence of disease or potential for disease, there is less concern. Concerns increase, however, for newer tests that have not been widely evaluated, and for which the clinical usefulness is not well established.

The U.S. Department of Health and Human Services (DHHS) recognizes how important it is for the public to understand that while genetic tests can be extremely beneficial, they also can pose medical and psychological risks to individuals and families as well as socioeconomic risks that may affect entire groups and their individual members. As the diagnostic and predictive uses of genetic testing continue to increase, and as the effects of testing on society become clearer, its impact will become broader and ultimately will affect all of our lives. Because the use and ramifications of these tests are not yet fully realized, additional consideration is needed regarding whether current programs for assuring the safety and effectiveness of genetic tests are satisfactory or whether additional oversight measures are needed before such tests are introduced for wide-scale use.

The DHHS established the **Secretary's Advisory Committee on Genetic Testing (SACGT)** to help the Nation prepare for some of the revolutionary changes in clinical and public health practice resulting from the continued and increasing use of genetic testing. At SACGT's first meeting in June 1999, the U.S. Assistant Secretary for Health and Surgeon General asked the Committee to assess, in consultation with the American public, whether current programs for assuring the accuracy and effectiveness of genetic tests are adequate or whether other or additional oversight measures are needed. 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. If, after public consultation and analysis, SACGT finds that other or additional oversight measures are warranted, it has been asked to recommend appropriate options in a final report to the Surgeon General, due March 15, 2000.

Genes and Disease

The human genome is vast. It is estimated to contain 100,000 to 140,000 genes made up of 3 billion to 4 billion chemical elements, all residing on 23 pairs of chromosomes. Genes are made up of DNA and provide instructions for the body's manufacture and use of essential proteins and enzymes. Proteins are required for the structure, function, and regulation of all cells, tissues, and organs in the body.

Mutations in genes are responsible for an estimated 3,000 to 4,000 clearly hereditary diseases and conditions. Some of them–including Huntington disease, cystic fibrosis, neurofibromatosis, and 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 common and chronic diseases, although the development of these diseases is unlikely to be due to a single genetic mutation. Genetic alterations can increase a person's risk of developing one of these disorders, but the disease will develop from the cumulative interactions of genetic and environmental factors, such as diet and smoking.

There are many ways by which genetic alterations can cause disease, and just as many ways to detect these changes, with some approaches more direct than others. Moreover, when several genes are responsible for disease or predisposition to disease—and environmental factors are also at play—understanding the significance of any particular gene or set of genes in the development of disease becomes even more complex. Although genetic changes are often inherited, they can also develop during an individual's lifetime (an acquired mutation). Thus, genetic damage that occurs during a person's lifetime would not be detected early in life.

Genetic Testing

Genetic testing involves the analysis of chromosomes, genes, and/or gene products (e.g., proteins or enzymes) to determine whether a genetic alteration related to a specific disease or condition is present in an individual. Genetic tests are performed for a number of purposes, including:

- to diagnose a genetic disorder or condition in a developing fetus (prenatal diagnosis);
- to detect certain genetic diseases in newborns (newborn screening);
- to determine whether an individual carries one 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) in order to assess a person's risk of passing the mutation on to his or her children (carrier testing);
- to identify or confirm the diagnosis of a disease or condition in an affected individual (diagnostic/prognostic testing);
- to determine whether individuals who

have a family history of a disease, but no current symptoms, have the gene mutation (presymptomatic testing); and

- to determine the probability that a healthy individual with or without a family history of a certain disease might develop that disease (predictive testing).

Genetic tests can also be used for the purpose of genetic screening. In genetic screening, groups or populations may be offered testing because it is believed that the group has a greater chance of carrying a gene that increases the risk of disease to them or to their children.

At present, genetic testing for more than 300 diseases or conditions is available in more than 200 laboratories in the United States, and investigators are exploring the development of tests for an additional 325 diseases or conditions. Recently, concerns have been raised about the impact that patenting human genes may be having on genetic testing, as 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.

Terminology Used to Evaluate Genetic Tests

In order to understand the oversight issues that SACGT is considering, it is important to be familiar with some basics about the terminology used by laboratories and health care providers when assessing the effectiveness and usefulness of genetic tests.

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

A test could be analytically valid, that is, it detects what it is supposed to detect, but that information alone has no meaning if it does not help diagnose or predict disease. Therefore, a test also must be clinically valid. *Clinical validity* refers to the accuracy with which a test predicts a clinical condition. Thus, a test would be clinically valid if it successfully detects the disease or predisposition. When a test is under development and its success rate is still being determined, it should be conducted only on individuals who are known to have the condition (as well as those who are known not to have the condition to serve as comparisons).

Clinical utility refers to the usefulness of the test and the value of the information to the person being tested. If a test has utility, it means that the results—positive or negative—provide information that is of value to the person being tested because he or she can use that information to seek an effective treatment or preventive strategy. Even if no interventions are available to treat or prevent the disease or condition, there may be benefits associated with knowledge of a result.

The validity and utility of genetic tests, both in laboratory and clinical terms, are important considerations when deciding the risks and benefits of such tests as well as in considering procedures by which to ensure their appropriate use.

A more in-depth discussion of these terms and others and of the process of genetic testing can be found in the Committee's full public consultation document. In addition, a good source of background information regarding genes, gene mutations, genetic research, and genetic testing is *Understanding Gene Testing*, a booklet produced

by the National Cancer Institute and the National Human Genome Research Institute, available at http://www.accessexcellence.org/AE/AEPC/NIH/index.html).

Current Oversight Mechanisms for Diagnostic Tests

At present, most genetic tests are regulated in some way at the Federal level. One set of regulations was created in 1988 through the Clinical Laboratory Improvement Amendments (CLIA), administered by the Health Care Financing Administration (HCFA), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). In addition, FDA regulates test components and test kits under the Federal Food, Drug, and Cosmetic Act. Finally, all federally sponsored research is subject to Federal regulations protecting human subjects in research. Private sector organizations provide oversight in partnership with HCFA and CDC by serving as agents for the government as accrediting bodies and by developing professional and laboratory guidelines and standards. Some States also play a role in the oversight of genetic testing.

Regarding current oversight measures, it is important to note that tests that are packaged and sold as kits to other laboratories are considered to be diagnostic devices and require approval or clearance by the FDA before wide-scale distribution. In contrast, FDA does not require such approval or clearance of tests developed by laboratories and provided as services, often called "home brews." FDA has stated that it has the authority to regulate home brews, but to date has not attempted to extend that authority to regulate home brew tests. The agency has taken steps to establish a measure of regulation of the home brew tests by instituting controls over the active ingredients (or reagents) used by laboratories to perform genetic tests. This regulation requires reagent manufacturers to follow certain general controls, such as good manufacturing practices, but usually does not require an in-depth review of reagents prior to their use.

SACGT's Task

In its review of current oversight of genetic tests, SACGT has been asked to consider the potential benefits and risks (including socioeconomic, psychological, and medical) of genetic tests to individuals, families, and society. The Committee also has been asked to consider 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 five major issues that SACGT has been asked to address are outlined in bold below. Under each major issue is a brief discussion of a possible approach to the issue followed by several related questions. SACGT encourages public comment on the major issues and approaches and on the related questions. A sixth set of questions is presented to provide the public with an opportunity to comment on other issues relevant to genetic testing.

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

In considering this issue, SACGT has identified three primary criteria that could be used to assess the benefits and risks of a genetic test: 1) clinical validity, which refers to the accuracy of the test in diagnosing or predicting risk for a health condition; 2) clinical utility, which involves identifying the outcomes associated with positive and negative test results; and 3) the social implications of genetic testing. 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.

Related Questions

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 he 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?

SACGT has considered whether clinical validity, clinical utility, and social issues could be used to characterize the potential risks associated with a given test. 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.

Related Questions

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?

Data on tests 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 to coordinate the creation and collection of information and to define appropriate claims for tests. A fourth option would be to form a consortium of government, professional associations, and industry that would create, collect, and analyze information about clinical applications.

Related Questions

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 safety 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, such as the training and education of health care providers, public understanding of genetics, and gene patents, that might have an equally important impact on assuring the safety and effectiveness of a genetic test. 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.

SACGT welcomes public input on whether further oversight measures are needed, and if so, how they 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.

Related Questions

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 gene*tic 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.

Related Question

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?*

Process for Public Consultation and Input

SACGT is endeavoring to encourage broad public participation in the consideration of these issues. Such public involvement in the 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.

In order to be considered by SACGT, public comments need to be received by January 31, 2000. Please send comments to SACGT as follows:

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