Congressional Research Service

Report RL33832

Genetic Testing: Scientific Background for Policymakers

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January 30, 2008

Abstract. In the 110th Congress, several pieces of legislation have been introduced that relate to genetic and genomic technology and testing. These include bills addressing genetic discrimination in health insurance and employment, personalized medicine, the patenting of genetic material, and the quality of laboratory tests. The introduction of these bills signals the growing importance of the public policy issues surrounding the clinical and public health implications of new genetic technology. As genetic technologies proliferate and are increasingly used to guide clinical treatment, these public policy issues are likely to continue to garner considerable attention. Understanding the basic scientific concepts underlying genetics and genetic testing may help facilitate the development of more effective public policy in this area.

Order Code RL33832

CRS Report for Congress

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Prepared for Members and
Committees of Congress

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Scientific Background for Policymakers

Summary

In the 110th Congress, several pieces of legislation have been introduced that relate to genetic and genomic technology and testing. These include bills addressing genetic discrimination in health insurance and employment, personalized medicine, the patenting of genetic material, and the quality of laboratory tests. The introduction of these bills signals the growing importance of the public policy issues surrounding the clinical and public health implications of new genetic technology. As genetic technologies proliferate and are increasingly used to guide clinical treatment, these public policy issues are likely to continue to garner considerable attention. Understanding the basic scientific concepts underlying genetics and genetic testing may help facilitate the development of more effective public policy in this area.

Most diseases have a genetic component. Some diseases such as Huntington's Disease are caused by a specific gene. Other diseases, such as heart disease and cancer, are caused by a complex combination of genetic and environmental factors. For this reason, the public health burden of genetic disease is substantial, as is its clinical significance. Experts note that society has recently entered a transition period in which specific genetic knowledge is becoming critical to the delivery of effective health care for everyone. Therefore, the value of and role for genetic testing in clinical medicine is likely to increase significantly in the future.

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Introduction

Virtually all disease has a genetic component.[1] The term "genetic disease" has traditionally been used to refer to rare monogenic (caused by a single gene) inherited disease, for example, cystic fibrosis. However, we now know that all complex diseases, including common chronic conditions such as cancer, heart disease and diabetes, are the product of some combination of genetic and environmental factors. For this reason, they could all be said to be "genetic diseases". Considering this broader definition of genetic disease, the public health burden of genetic disease can be seen to be substantial. In addition, an individual patient's genetic make-up, and the genetic make-up of his disease, will help guide clinical decision making. Experts note that "(w)e have recently entered a transition period in which specific genetic knowledge is becoming critical to the delivery of effective health care for everyone."[2] For this reason, the value of and role for genetic testing in clinical medicine is likely to increase significantly in the future. As the role of genetics in clinical medicine and public health continues to grow, so will the importance of public policy issues raised by genetic technologies.

Science is only beginning to unlock the complex nature of the interaction between genes and the environment in common disease, and their respective contributions to the disease process. The information gleaned from the Human Genome Project will help, and is currently helping, scientists and clinicians to identify common genetic variation that contributes to disease. In addition, research conducted utilizing large population databases that collect health, genetic, and environmental information about entire populations will likely provide more information about the genetic and environmental underpinnings of common diseases. Many countries have established such databases, including Iceland, the United Kingdom, and Estonia. The knowledge of the potential relevance of genetic information to the clinical management of nearly all patients coupled with the lack of complete information about the genetic and environmental factors underlying disease creates a challenging climate for public policymaking.

In many cases, the results of genetic testing may be used to guide clinical management of patients. For example, more frequent screening may be recommended for individuals at increased risk of certain diseases by virtue of their

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[1] Collins, F.S. and V.A. McCusick. (2001) "Implications of the Human Genome Project for Medical Science." *Journal of the American Medical Association* 285:540-544.

[2] Guttmacher, A.E. and F.S. Collins. (2002) "Genomic Medicine - A Primer." *New England Journal of Medicine* 347(19): 1512-1520.

genetic make-up, such as colorectal and breast cancer. In some cases, prophylactic surgery may even be indicated. Decisions about courses of treatment and dosing may also be guided by genetic testing, as might reproductive decisions (both clinical and personal). However, many diseases do not have any treatment available (for example, Huntington's Disease). In these cases, the benefits of genetic testing lie largely in the information they provide an individual about his or her risk of future disease or current disease status. The value of genetic information in these cases is personal to individuals, who may choose to utilize this information to help guide medical and other life decisions for themselves and their families. The information can affect decisions about reproduction, the types or amount of health, life, or disability insurance to purchase, or career and education choices. As genetic research continues to advance rapidly, it will often be the case that genetic testing may be able to provide information about the probability of a health outcome without an accompanying treatment option. This situation again creates unique public policy challenges, for example, in terms of the financing of genetic testing services and education about the value of testing (see S. 609, 109th Congress, for example).

Concerns about privacy and the use and misuse of genetic information, as well as issues of genetic exceptionalism[3] and genetic determinism[4], may need to be balanced with the potential of genetics and genetic technology to change how care is delivered and to personalize medical care and treatment of disease.

This report will summarize basic scientific concepts in genetics and will provide an overview of genetic tests, their main characteristics, and the key policy issues they raise.

Fundamental Concepts in Genetics

The following section explains key concepts in genetics that are essential for understanding genetic testing and issues associated with testing that are of interest to Congress.

Cells Contain Chromosomes

Humans have 23 pairs of chromosomes in the nucleus of most cells in their bodies. These include 22 pairs of autosomal chromosomes (numbered 1 through 22) and one pair of sex chromosomes (X and Y). One copy of each autosomal chromosome is inherited from the mother and from the father, and each parent contributes one sex chromosome.

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[3] *Genetic exceptionalism* is the concept that genetic information is inherently unique, should receive special consideration, and should be treated differently from other medical information.

[4] *Genetic determinism* is the concept that our genes are our destiny and that they solely determine our behavioral and physical characteristics. This concept has mostly fallen out of favor as the substantial role of the environment in determining characteristics has been recognized.

Many syndromes involving abnormal human development result from abnormal numbers of chromosomes (such as Down Syndrome). Other diseases, such as leukemia, can be caused by breaks in or rearrangements of chromosome pieces.

Chromosomes Contain DNA

Chromosomes are composed of deoxyribonucleic acid (DNA) and protein. DNA is comprised of complex chemical substances called bases. Strands made up of combinations of the four bases (adenine (A), guanine (G), cytosine (C) and thymine (T)) twist together to form a double helix (like a spiral staircase). Chromosomes contain almost 3 billion base pairs of DNA that code for about 20,000-25,000 genes (this is a current estimate, although it may change and has changed several times since the publication of the human genome sequence).[5]

DNA Codes for Protein

Proteins are fundamental components of all living cells. They include enzymes, structural elements, and hormones. Each protein is made up of a specific sequence of amino acids. This sequence of amino acids is determined by the specific order of bases in a section of DNA. A gene is the section of DNA which contains the sequence which corresponds to a specific protein. Changes to the DNA sequence, called mutations, can change the amino acid sequence. Thus, variations in DNA sequence can manifest as variations in the protein which may affect the function of the protein. This may result in, or contribute to the development of, a genetic disease.

Genotype Influences Phenotype

Though most of the genome is very similar between individuals, there can be significant variation in physical appearance or function between individuals. In other words, although we share most of the genetic material we have, we can see that there are significant differences in our physical appearance (height, weight, eye color, etc.). Humans inherit one copy (or allele) of most genes from each parent. The specific alleles that are present on a chromosome pair constitute a person's genotype. The actual observable physical trait is known as the phenotype. For example, having two brown-eye color alleles would be an example of a genotype and having brown eyes would be the phenotype.

Many complex factors affect how a genotype (DNA) translates to a phenotype (observable trait) in ways that are not yet clear for many traits or conditions. Study of a person's genotype may determine if a person has a mutation associated with a disease, but only observation of the phenotype can determine if that person actually has physical characteristics or symptoms of the disease. Generally, the risk of developing a disease caused by a single mutation can be more easily predicted than the risk of developing a complex disease caused by multiple mutations in multiple

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[5] National Research Council, Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health. Washington, DC: National Academies Press (2006); p. 19.

genes and environmental factors. Complex diseases, such as heart disease, cancer, immune disorders, or mental illness, for example, have both inherited and environmental components that are very difficult to separate. Thus, it can be difficult to determine whether an individual will develop symptoms, how severe the symptoms may be, or when they may appear.

Genetic Tests

What is a Genetic Test?

Scientifically, a genetic test is defined as

> an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes.[6]

Once the sequence of a gene is known, looking for specific changes is relatively straightforward using the modern techniques of molecular biology. In fact, these methods have become so advanced that hundreds or thousands of genetic variations can be detected simultaneously using a technology called a microarray.

Policy Issues. The way genetic test is defined is extremely important to the development of genetics-related public policy. For example, the above scientific definition is very broad and inclusive, but this may not be the best way to achieve certain policy goals. It may sometimes be desirable to limit the definition only to predictive, and not diagnostic, genetic testing (see "What are the different Types of Genetic Tests?"). In other cases, it may be desirable to limit the definition to only analysis of specific material, such as DNA, RNA, and chromosomes, but not metabolites or proteins. Considerable variation in the definition of genetic test may be found in the many state genetic nondiscrimination laws. Policies extending protection against discrimination may aim to be as broad as possible, whereas policies addressing coverage of genetic tests may aim to be more limited.

How Many Genetic Tests are Available?

As of January 2008, genetic tests are available for 1,513 diseases. Of those tests, 1,225 are available for clinical diagnosis, while 288 are available for research only.[7] The majority of these tests are for single-gene rare diseases. Asked about the

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[6] Report of the Secretary's Advisory Committee on Genetic Testing (SACGT), "*Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT,*" July 2000, at [http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf].

[7] See [http://www.genetests.org] for information on disease reviews, an international directory of genetic testing laboratories, an international directory of genetics and prenatal

(continued...)

realistic promise of genetic technology, Francis Collins, the Director of the National Human Genome Research Institute predicted,

> I think we can count on the availability within the next decade of a panel of genetic tests that are going to be offered to all of us to determine our risk of common illnesses, focused particularly on those diseases for which there is some intervention available for those found to be at high risk.[8]

What are the Different Types of Genetic Tests?

Most clinical genetic tests are for rare disorders, but increasingly, tests are becoming available to determine susceptibility to common, complex diseases and to predict response to medication.

With respect to health-related tests (i.e., excluding tests used for forensic purposes, such as "DNA fingerprinting"), there are two general types of genetic testing: diagnostic and predictive. Genetic tests can be utilized to identify the presence or absence of a disease (diagnostic). Predictive genetic tests can be used to predict if an individual will definitely get a disease in the future (predictive-presymptomatic) or to predict the risk of an individual getting a disease in the future (predictive-predispositional). For example, testing for mutations in the BRCA1 and/or BRCA2 genes provides probabilistic information about how likely an individual is to develop breast cancer in his or her lifetime (predispositional). The genetic test for Huntington's Disease provides genetic information that is predictive in that it allows a physician to predict with certainty whether an individual will develop the disease, but does not allow the physician to determine when the onset of symptoms will actually occur (presymptomatic). In both of these examples, the individual does not have the clinical disease at the time of genetic testing, as they would with diagnostic genetic testing.

Within this broader framework of diagnostic and predictive genetic tests, several distinct types of genetic testing can be considered. Reproductive genetic testing can identify carriers of genetic disorders, establish prenatal diagnoses or prognoses, or identify genetic variation in embryos before they are used in in vitro fertilization. Reproductive testing, such as prenatal testing, may be either diagnostic or predictive in nature. Newborn screening is a type of genetic testing that identifies newborns with certain metabolic or inherited conditions (although not all newborn screening tests are genetic tests). Traditionally, most newborn screening has been diagnostic, but recently several states have added some predictive genetic testing to their panels of newborn screening (for example, Maryland includes testing for cystic fibrosis).[9] Finally, pharmacogenomic testing, or testing to determine a patient's likely response

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[7] (...continued)
diagnosis clinics, and a glossary of medical genetics terms.

[8] E. Rabinowitz, "Genetics in Medicine: Hype or Real Promise?" *Health plan*, January/February 2003.

[9] Newborn Screening Programs, Family Health Administration, Maryland Department of Health and Mental Hygiene. [http://www.fha.state.md.us/genetics/pdf/Pamphlet_NBS.pdf].

to a medication, may be considered either diagnostic or predictive, depending on the context in which it is being utilized.

Policy Issues. Generally, predictive genetic testing (both presymptomatic and predispositional), rather than diagnostic testing, raises more complex ethical, legal and social issues. For example, issues surrounding insurance coverage and reimbursement for this type of test, especially if no treatment is available, are far more complex than with diagnostic genetic testing. A private insurer may feel that paying for a test that predicts the onset of a disease with no treatment is not cost-effective. Even more complicated are cases where the test only shows an increased probability of getting a disease. In addition, Medicare's screening exclusion means that this type of test generally will not be covered for the elderly population.[10]

Another issue is the oversight of genetic tests. Strong oversight of genetic tests may be more important where the information is probabilistic rather than diagnostic and when a treatment is not available. Finally, issues of genetic discrimination may be different with predictive testing than they are with diagnostic testing. Genetic discrimination may be defined as differential treatment in either health insurance coverage or employment based upon an individual's genotype. Discriminatory action based on the possibility of something happening in the future, or even the certainty of it happening in the future, might raise more concern than would action taken based upon diagnostic information. With probabilistic genetic information, the health outcome of concern may never manifest, or if it is certain to, may not manifest for decades into the future.

The Genetic Test Result

Genetic tests can provide information about both inherited genetic variations, that is, the individual's genes that were inherited from their mother and father, as well as about acquired genetic variations, such as those that cause some tumors. Acquired mutations are not inherited, but rather are acquired in DNA due to replication errors or exposure to mutagenic chemicals and radiation (e.g., UV rays).

DNA-based testing of inherited genetic variants differs from other medical testing in important ways: it can have exceptionally long-range predictive powers over the lifespan of an individual; it can predict disease or increased risk for disease in the absence of clinical signs or symptoms; it can reveal the sharing of genetic variants within families at precise and calculable rates; and, at least theoretically, it has the potential to generate a unique identifier profile for individuals. Also, unlike most other medical tests, the stability of DNA means that most genetic tests can be performed on material from a body and continue to provide information after the individual has died.

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[10] Secretary's Advisory Committee on Genetics, Health, and Society. "Coverage and Reimbursement of Genetic Tests and Services." February 2006. [http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf]. CMS has interpreted the Medicare statute to exclude coverage of preventive care unless specifically authorized by Congress.

Genetic changes to inherited genes can be acquired throughout a person's life. Tests that are performed for acquired genetic markers that occur with a disease have implications only for individuals with the disease, and not family members. Tests for acquired genetic changes are also usually diagnostic rather than predictive, since these tests are generally performed after symptoms present.

Pharmacogenomic testing may be used to determine acquired genetic variations in disease tissue (i.e., acquired variations in a tumor) or may be used to determine inherited variations in an individual's drug metabolizing enzymes. For example, with respect to determining acquired variation in disease tissue, a tumor may have acquired genetic changes that make it different from normal tissue that may also render that tumor susceptible or resistant to chemotherapy. With respect to inherited variation in drug metabolizing enzymes, an individual may be found to be a slow metabolizer of a certain type of drug (statins, for example) and this information can be used to guide both drug choice and dosing.

Policy Issues. In some cases, people feel differently about their genetic information than they do about other medical information, a sentiment embodied by the concept of genetic exceptionalism. This may be based on the stated differences between genetic testing and other medical testing, but also may be based on personal belief that genetic information is powerful and different than other medical information. For this reason, public policies around genetic discrimination in health insurance, employment and sometimes life insurance proliferated at the state level in the 1990s, and genetic nondiscrimination legislation has been considered by Congress for nearly a decade. Whether genetic information is somehow different from other medical information; whether it can be separated logically from other medical information; and whether it deserves special protection are all important public policy issues.

Pharmacogenomic testing is important because it will help provide the foundation for personalized medicine. Personalized medicine is healthcare based on individualized diagnosis and treatment for each patient determined by information at the genomic level. Many public policy issues are associated with personalized medicine. For example, there is some uncertainty currently as to how health insurers will assess and choose to cover pharmacogenomic testing as it becomes available. In addition, there are issues surrounding the regulation of pharmacogenomic testing. The Genomics and Personalized Medicine Act of 2007 (S. 976) considers many of these issues.

Characteristics of Genetic Tests

Genetic tests function in two environments: the laboratory and the clinic. Genetic tests are evaluated based primarily on three characteristics: analytical validity, clinical validity, and clinical utility.

Analytical Validity. Analytical validity is defined as the ability of a test to detect or measure the analyte it is intended to detect or measure.[11] This characteristic is critical for all clinical laboratory testing, not only genetic testing, as it provides information about the ability of the test to perform reliably at its most basic level. This characteristic is relevant to how well a test performs in a laboratory.

Clinical Validity. The clinical validity of a genetic test is its ability to accurately diagnose or predict the risk of a particular clinical outcome. A genetic test's clinical validity relies on an established connection between the DNA variant being tested for and a specific health outcome. Clinical validity is a measure of how well a test performs in a clinical rather than laboratory setting. Many measures are used to assess clinical validity, but the two of key importance are clinical sensitivity and positive predictive value. Genetic tests can be either diagnostic or predictive and, therefore, the measures used to assess the clinical validity of a genetic test must take this into consideration. For the purposes of a genetic test, positive predictive value can be defined as the probability that a person with a positive test result (i.e., the DNA variant tested for is present) either has or will develop the disease the test is designed to detect. Positive predictive value is the test measure most commonly used by physicians to gauge the usefulness of a test to clinical management of patients. Determining the positive predictive value of a predictive genetic test may be difficult because there are many different DNA variants and environmental modifiers that may affect the development of a disease. In other words, a DNA variant may have a known association with a specific health outcome, but it may not always be causal. Clinical sensitivity may be defined as the probability that people who have, or will develop a disease, are detected by the test.

Clinical Utility. Clinical utility takes into account the impact and usefulness of the test results to the individual and family and primarily considers the implications that the test results have for health outcomes (for example, is treatment or preventive care available for the disease). It also includes the utility of the test more broadly for society, and can encompass considerations of the psychological, social and economic consequences of testing.

Policy Issues. These three characteristics of genetic tests have important ties to public policy issues. For example, although the analytical validity of genetic tests is regulated by the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (P.L. 100-578), the clinical validity of the majority of genetic tests is not regulated at all. This has raised concerns about direct-to-consumer marketing of genetic tests where the connection between a DNA variant and a clinical outcome has not been clearly established. Marketing of such tests to consumers directly may mislead consumers into believing that the advice given them based on the results of such tests could improve their health status/outcomes when in fact there is no scientific basis underlying such an assertion. This issue was the subject of a July 2006 hearing by the Senate Special Committee on Aging. In addition, clinical utility and clinical validity both figure prominently into coverage decisions by payers, but a lack of data often hinders coverage decisions, leaving patients without coverage for these expensive tests.

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[11] An analyte is defined as a substance or chemical constituent undergoing analysis.

Coverage by Health Insurers

Health insurers are playing an increasingly large role in determining which medical tests are available by deciding which tests they will pay for as part of patient benefit packages. Many aspects of genetic tests, including their clinical validity and utility, may complicate the coverage decision-making process for insurers. While insurers require that a test be approved by the Food and Drug Administration (when required), they also want evidence that it is "medically necessary;" that is, evidence demonstrating that a test will affect a patient's health outcome in a positive way. This additional requirement of evidence of improved health outcomes underscores the importance of patient participation in long-term research in genetic medicine. Particularly for genetic tests, data on health outcomes may take a very long time to collect.

Policy Issues. Decisions by insurers to cover new genetic tests have a significant impact on the utilization of such tests and their eventual integration into the health care system. The integration of personalized medicine into the health care system will be significantly affected by coverage decisions. Although insurers are beginning to cover pharmacogenomic tests and treatments, the high cost of such tests and treatments often means that insurers require very stringent evidence that they will improve health outcomes. In addition, the fact that Medicare does not routinely cover preventive services (unless authorized specifically by Congress) means that coverage for many genetic tests and services, which may be considered preventive, may not be granted under Medicare. As Medicare coverage decisions are often looked to by private insurers as a guide for their own coverage decisions, it is difficult to predict what effect this might have on the uptake and utilization of genetic tests more broadly.

Regulation of Genetic Tests by the Federal Government

Genetic tests are regulated by the FDA and CMS through CLIA. FDA regulates genetic tests that are manufactured by industry and sold for clinical diagnostic use. These test kits usually come prepackaged with all of the reagents and instructions that a laboratory needs to perform the test and are considered to be products by the FDA. FDA requires manufacturers of the kits to make sure that the test detects what they say it will, in the patient population in which they intend the test to be used. With respect to the characteristics of a genetic test, this process requires manufacturers to prove that their test is clinically valid. Depending on the perceived risk associated with the intended use promoted by the manufacturer, genetic tests must either prove that they are safe and effective, or that they are substantially equivalent to something that is already on the market that has the same intended use.

Most genetic tests are performed, not with test kits, but rather as laboratory testing services (or "homebrew" tests), meaning that clinical laboratories themselves perform the test in-house and make most or all of the reagents used in the tests. Homebrew tests are not currently regulated by the FDA in the way kits are and, therefore, the clinical validity of the vast majority of genetic tests is not regulated. The FDA does regulate certain components used in homebrew tests, known as Analyte Specific Reagents (ASRs), if the ASR is commercially available. If the ASR is made in-house by a laboratory performing a homebrew test, the test is not regulated at all by the FDA. This type of test is known as a "homebrew-homebrew" test.

Any clinical test that is performed with results returned to the patient must be performed in a CLIA-certified laboratory. CLIA is primarily administered by CMS in conjunction with the Centers for Disease Control and Prevention (CDC) and the FDA.[12] FDA determines the category of complexity of the test so that laboratories know which parts of CLIA they must follow. As previously noted, CLIA regulates the analytical validity of a clinical laboratory test only. It generally establishes requirements for laboratory processes, such as personnel training and quality control/quality assurance programs. CLIA requires laboratories to prove that their tests work properly, to maintain the appropriate documentation, and to show that tests are interpreted by laboratory professionals with the appropriate training. However, CLIA does not require that tests made by laboratories undergo any review by an outside agency to see if they work properly. Proponents of CLIA argue that regulation of the testing process gives the laboratories optimal flexibility to modify tests as new information becomes available. Critics argue that CLIA does not go far enough to assure the accuracy of genetic tests since it only addresses analytical validity and not clinical validity.

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[12] See [http://www.cms.hhs.gov/CLIA/].