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Genetic Testing: Background and Policy Issues

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Summary

Congress has considered, at various points in time, numerous pieces of legislation that relate to genetic and genomic technology and testing. These include bills addressing genetic discrimination in health insurance and employment; precision medicine; the patenting of genetic material; and the oversight of clinical laboratory tests (in vitro diagnostics), including genetic tests. The focus on these issues signals the growing importance of 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 attention. Understanding the basic scientific concepts underlying genetics and genetic testing may help facilitate the development of more effective public policy in this area.

Humans have 23 pairs of chromosomes in the nucleus of most cells in their bodies. Chromosomes are composed of deoxyribonucleic acid (DNA) and protein. DNA is composed of complex chemical substances called bases. Proteins are fundamental components of all living cells, and include enzymes, structural elements, and hormones. A gene is the section of DNA that contains the sequence which corresponds to a specific protein. Though most of the genome is similar between individuals, there can be significant variation in physical appearance or function between individuals due to variations in DNA sequence that may manifest as changes in the protein, which affect the protein's function. 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.

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, as well as its clinical significance, may be large. Experts note that society has recently entered a transition period in which specific genetic knowledge is becoming more integral to the delivery of effective health care. Therefore, the value of and role for genetic testing in clinical medicine is likely to increase in the future.

Policymakers may need to balance concerns about the potential use and misuse of genetic information with the potential of genetics and genetic technology to improve care delivery, for example by personalizing medical care and treatment of disease. In addition, policymakers face decisions about the balance of federal oversight and regulation of genetic tests, patients' safety, and innovation in this area. Finally, the need for and degree of federal support for research to develop a comprehensive evidence base to facilitate the integration of genetic testing into clinical practice (for example, to support coverage decisions by health insurers) may be debated.

Contents

Introduction.....	1
Background.....	1
Policy Issues and Genetic Testing.....	3
Defining “Genetic Test”	3
Policy Issues.....	4
What Type of Information Can Genetic Tests Provide?	5
Policy Issues.....	6
Evaluating Genetic Tests	7
Policy Issues.....	8
The Genetic Test Result.....	11
Policy Issues.....	12

Appendixes

Appendix. Fundamental Concepts in Genetics.....	14
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Contacts

Author Contact Information.....	16
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Introduction

Congress has considered, at various points in time, numerous pieces of legislation that relate to genetic and genomic technology and testing. These include bills addressing genetic discrimination in health insurance and employment; precision and personalized medicine; the patenting of genetic material; the privacy of health information, including genetic information; and the oversight of clinical laboratory tests (in vitro diagnostics), including genetic tests.

The focus on these issues signals the importance of 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 attention. Understanding the basic scientific concepts underlying genetics and genetic testing may help facilitate the development of more effective public policy in this area.

Considering that virtually all disease has a genetic component, the potential public health impact of genetic disease may be significant. Over time, as translational obstacles are addressed, the value of and role for genetic testing in clinical medicine may increase. As the role of genetics in clinical medicine and public health continues to be better understood, the importance of public policy issues raised by genetic technologies is likely to grow.

Limited knowledge of both the appropriate role for genetic information in the clinical management of patients, and the genetic and environmental factors underlying disease, may create a challenging climate for public policymaking. As genetic research continues to advance rapidly, more genetic tests will be developed that provide information with unclear or debated clinical implications as a result of genetic technology outpacing the development of evidence for its application. This situation may create public policy challenges, for example, in terms of decisions about the coverage of genetic testing services and the regulation of such tests.

Policymakers may need to balance concerns about privacy and the potential use and misuse of genetic information with the potential of genetics and genetic technology to improve care delivery, for example by personalizing medical care and treatment of disease. In addition, policymakers face decisions about the balance of federal oversight and regulation of genetic tests, patients' safety, and innovation in this area. Finally, the need for and degree of federal support for research to develop a comprehensive evidence base to facilitate the integration of genetic testing into clinical practice (for example, to improve health care outcomes or to support coverage decisions by health insurers) may be debated.

Background

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, research now shows that many common complex human diseases—including common chronic conditions such as cancer, heart disease, and diabetes—are influenced by

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

several genetic and environmental factors.² For this reason, they could all be said to be “genetic diseases.” For more information about fundamental concepts in genetics—including genes, chromosomes, phenotype, and genotype—see the **Appendix**.

The genetic make-up of an individual’s disease—as well as an individual patient’s genetic make-up—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.”³ This sentiment is shared, despite the fact that the translation to practice has perhaps been slower than anticipated. This is due, in part, to the frequent lack of a comprehensive evidence base to inform clinical validity and utility determinations for many genomic technologies.⁴

Researchers have identified a translational gap between genetic discoveries and application in clinical and public health practice and note that “the pace of implementation of genome-based applications in health care and population health has been slow.”⁵ The information provided by the Human Genome Project is helping scientists and clinicians to identify common genetic variation that contributes to disease, primarily through genome-wide association studies (GWAS).⁶ In addition, efforts are underway to close the translational gap, specifically the 2009 establishment of the National Institutes of Health (NIH)-Centers for Disease Control and Prevention (CDC) collaborative Genomic Applications in Practice and Prevention Network (GAPPNet).⁷ Still, evidence is oftentimes lacking, making the assessment of the clinical value of genetic tests challenging.⁸

Experts note that the moderate effect of many common genetic variations, uncovered by GWAS, has helped to highlight the multifactorial nature of complex disease, and that research efforts will be required to detect “missing” genetic influences.⁹ GWAS efforts have identified 1,100 well-validated genetic risk factors for common disease; however, the potential for many of these factors to serve as drug targets is unknown.¹⁰

² Manolio T.A. et al. (2009) “Finding the missing heritability of complex diseases.” *Nature* 461(8): 747-753.

³ Guttmacher A.E. and Collins F.S. (2002). “Genomic Medicine—A Primer.” *New England Journal of Medicine* 347(19): 1512-1520.

⁴ The clinical validity of a genetic test is its ability to accurately diagnose or predict the risk of a particular clinical outcome. 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). See “Evaluating Genetic Tests.”

⁵ Khoury M.J. et al. (2009) “The Genomic Applications in Practice and Prevention Network.” *Genetics in Medicine* 11(7): 488-494.

⁶ Genome-wide association studies (GWAS) are defined by the National Human Genome Research Institute as “an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease.” National Human Genome Research Institute, Glossary of Terms, <http://www.genome.gov/glossary/index.cfm?id=91>.

⁷ For more information about the Genomic Applications in Practice and Prevention Network, see <http://www.cdc.gov/genomics/translation/GAPPNet/index.htm>.

⁸ See, for example, Tier 2 and Tier 3 at CDC, “Genomic Tests and Family History by Levels of Evidence,” <http://www.cdc.gov/genomics/gtesting/tier.htm>.

⁹ Manolio T.A. et al. (2009) “Finding the missing heritability of complex diseases.” *Nature* 461(8): 747-753.

¹⁰ Collins F.S. (2011). “Reengineering Translational Science: The Time Is Right.” *Science Translational Medicine*, 3(90):90cm17.

Research conducted using 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 disease. Many countries have established such databases, including Iceland, the United Kingdom, and Estonia. No similar effort has yet been undertaken in the United States. However, researchers hope to combine genetic, environmental, clinical, behavioral, and other data to facilitate precision medicine. Precision medicine is the idea of providing health care to individuals based on specific patient and disease characteristics, and is a priority in the President's FY2016 budget.¹¹ The President's budget request proposes the development of a national research cohort, composed of 1 million or more volunteers, whose health, genetic, environmental, and other data would be collected and used in research studies to identify novel therapeutics and prevention strategies.¹²

In many cases, the results of genetic testing may be used to guide clinical management of patients, and a particularly prominent role is anticipated in the realm of preventive medicine.¹³ For example, more frequent screening may be recommended for individuals at increased risk of certain diseases by virtue of their genetic make-up, such as colorectal and breast cancer. In some cases, preventive 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 with an identified molecular cause do not have any treatment available; specifically, therapies exist only for approximately 200 of the more than 4,000 conditions with a known molecular cause.¹⁴ In these cases, the benefits of genetic testing lie largely in the information testing provides 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.

Policy Issues and Genetic Testing

Defining "Genetic Test"

Currently, there is no single definition for "genetic test," and the scientific community has not reached a consensus about the best definition. However, one way that a genetic test may be defined scientifically is as follows:

[A]n 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

¹¹ The White House, Office of the Press Secretary, "Fact Sheet: President Obama's Precision Medicine Initiative," January 30, 2015, <http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>.

¹² For more information on this initiative, see CRS Report IN10227, *The Precision Medicine Initiative*, by Amanda K. Sarata and Judith A. Johnson.

¹³ Collins F.S. (2010). "Opportunities for Research and NIH." *Science* 327: 36-37.

¹⁴ Collins F.S. (2011). "Reengineering Translational Science: The Time Is Right." *Science Translational Medicine*, 3(90):90cm17.

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.¹⁵

Once the sequence of a gene is known, looking for specific changes is relatively straightforward using modern techniques of molecular biology. Using microarray technology, hundreds or thousands of genetic variations can be detected simultaneously.¹⁶ In addition, new advances in sequencing technology, termed next generation sequencing, have allowed for the rapid sequencing of large portions of DNA, including whole genomes or subsets of genes of interest.¹⁷

How Many Genetic Tests Are Available?

In February of 2012, the National Institutes of Health (NIH) established an online registry of genetic tests. This registry includes information voluntarily submitted by genetic test providers about their genetic tests. Submissions include basic test information, such as the test's purpose and whether it is for research or clinical use, and more complex test information, such as details about the test's analytical and clinical validity and about its clinical utility.

In February of 2015, the NIH Gene Testing Registry reports that over 25,500 genetic tests have been registered by over 400 laboratories.

Sources: GTR: Genetic Testing Registry, <http://www.ncbi.nlm.nih.gov/gtr/>; NIH, "Confused by genetic tests? NIH's new online tool may help," February 29, 2012, <http://www.nih.gov/news/health/feb2012/od-29.htm>; <http://www.ncbi.nlm.nih.gov/gtr/all/?term=%22src+gtr%22%5BProperties%5D>.

Policy Issues

The way genetic test is defined can be important to the development of genetics-related public policy. For example, the above scientific definition is broad, including both predictive and diagnostic tests and analyses on a broad range of material (nucleic acid, protein, and metabolites), 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 because predictive tests may raise public policy concerns that diagnostic tests do not (see "What Type of Information Can Genetic Tests Provide?"). On the other hand, policymakers wishing to avoid raising potentially controversial issues associated with predictive genetic testing may instead choose a definition limited to diagnostic testing. In still 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, for example, to help avoid capturing certain types of tests, such as some newborn screening tests, in the scope of a proposed law.

Policies extending protection against discrimination—for example, the Genetic Information Nondiscrimination Act (GINA, P.L. 110-233)—may aim to be broader (e.g., including predictive tests, not limiting the definition to tests analyzing only certain materials). On the other hand, policies addressing the stringency of oversight of clinical laboratory or in vitro diagnostic tests, of

¹⁵ Report of the Secretary's Advisory Committee on Genetic Testing (SACGT), "Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT," July 2000.

¹⁶ Microarray technology is defined as "a developing technology used to study the expression of many genes at once. It involves placing thousands of gene sequences in known locations on a glass slide called a gene chip. A sample containing DNA or RNA is placed in contact with the gene chip. Complementary base pairing between the sample and the gene sequences on the chip produces light that is measured. Areas on the chip producing light identify genes that are expressed in the sample." See <http://ghr.nlm.nih.gov/glossary=microarraytechnology>.

¹⁷ Behjati S. and Tarpey P.S. "What is next generation sequencing?," *Archives of Disease in Childhood*, vol. 98, no. 6, pp. 236-238, August 2013.

which genetic tests are a subset, may aim to be more limited (e.g., only those tests that are considered to be higher risk).

In certain cases, the lack of an accepted definition for “genetic test” may affect policymaking. For example, in discussions about whether to add a genetic testing specialty under the Clinical Laboratory Improvement Amendments of 1988 (CLIA, P.L. 100-578), the law regulating clinical laboratories, it was decided not to do so, partially based on the fact that there is “no widely accepted definition of a ‘genetic test.’”¹⁸

What Type of Information Can Genetic Tests Provide?

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 paternity, forensic purposes, such as “DNA fingerprinting,” or for ancestry), there are two general types of genetic testing: (1) diagnostic and (2) predictive. Diagnostic genetic tests can be utilized to identify the presence or absence of a disease. Predictive genetic tests can be used to predict if an individual will definitely get a disease in the future or to predict the *risk* of an individual getting a disease in the future (predispositional).¹⁹

For example, testing for mutations in the BRCA1 and/or BRCA2 genes provides probabilistic information about how likely an individual is to develop breast or ovarian 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. 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, including (1) reproductive genetic testing, (2) newborn screening, and (3) pharmacogenomic testing.

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 (preimplantation genetic diagnosis). Reproductive genetic testing, such as prenatal testing, may be either diagnostic or predictive in nature.

Newborn screening is a type of testing that helps to identify newborns with certain metabolic or inherited conditions. Some, but not all, newborn screening tests are genetic tests. Newborn screening tests identify children who might have a disorder and who require confirmatory diagnostic testing, and conditions tested for are selected based on availability of a treatment, among other things. Many states have chosen to add certain genetic tests to their newborn

¹⁸ See Department of Health and Human Services, Secretary’s Advisory Committee on Genetics, Health, and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, Washington, DC, April 2008, p. 31.

¹⁹ Ross L.F., Saal H.M., Davis K.L. et al. “Technical report: ethical and policy issues in genetic testing and screening of children,” *Genetics in Medicine*, vol. 15, no. 3, pp. 234-245, 2013.

screening panels (for example, all states now include a test for Sickle Cell Disease as well as for Cystic Fibrosis).²⁰

Pharmacogenomic testing is testing used to help determine the best course of treatment for an individual patient based either on the patient's own genotype or on the genetic characteristics of his specific disease or condition. It may be used before administration of a medication to determine potential effectiveness, dosing levels, or potential adverse interactions or events, or it may be used after administration and manifestation of a clinical event, for use in determining the basis of the specific event or outcome in the particular patient. This type of testing is considered to be a key component of personalized, or precision, medicine.

Policy Issues

The type of information generated by a genetic test—whether predictive or diagnostic—is relevant to certain policy issues. Specifically, it bears on coverage decisions by health insurers, and it was an important consideration in the development of GINA.

Coverage of Genetic Tests. Decisions about health insurance coverage and reimbursement for genetic tests that provide predictive information—especially if there is no treatment available—are oftentimes more complex than decisions about coverage of diagnostic genetic tests. A private health insurer may determine 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.

Genetic Discrimination. Considerations relating to genetic discrimination may be different with predictive testing than they are with diagnostic testing.²¹ Title I of GINA addressed potential discriminatory action based on predictive testing and the possibility of something happening in the future in the context of health insurance. This is due to the fact that, with predictive genetic testing, the health outcome at issue may never manifest, or if it is certain to, may not manifest for decades into the future. For this reason, policymakers believed that action taken by health insurers based on such information was unfair to the individual. To limit this protection to predictive test information, the definition of “genetic test” in Title I of GINA specifically excluded tests that are “an analysis of proteins or metabolites that [are] directly related to a manifested disease, disorder, or pathological condition that could reasonably be detected by a health care professional with appropriate training and expertise in the field of medicine involved.”²²

An individual's concern about the privacy of her genetic information may be heightened if the information is predictive as opposed to diagnostic. For example, an individual who tests positive for being at increased risk of developing breast cancer in the future might believe unfavorable insurance or employment decisions based on this information in the present (when she does not have breast cancer) would be more unfair than a decision based on manifested disease. In this

²⁰ Screening, Technology and Research in Genetics, “Expanded Newborn Screening Using New Technologies, Financial, Ethical, Legal and Social Issues,” <http://www.newbornscreening.info/Parents/otherdisorders/SCD.html> and <http://www.newbornscreening.info/Parents/otherdisorders/CF.htm>.

²¹ Genetic discrimination may be defined as differential treatment of a similarly situated individual in either health insurance coverage or employment based upon that individual's genetic information.

²² Genetic Information Nondiscrimination Act of 2008 (P.L. 110-233). See for example GINA §101(d), 29 U.S.C. §1191b(d).

case, this individual may have increased concern with keeping this information private from health insurers or employers, even in the context of GINA's nondiscrimination protections.

Specifically, research has demonstrated that this concern persists, despite the passage of GINA. A 2008 survey on personalized medicine found that few consumers are readily willing to share the results of genetic tests with current employers (2%), health insurers (3%), or a prospective employer (1%).²³ This finding is supported by another survey conducted by Cogent Research at almost the same time (late May to early June of 2008). This survey found that compared with attitudes in 2006, Americans are less interested in sharing the results of their genetic tests with their health insurer (decrease of 3%), the lab that conducted the genetic test (decrease of 9%), and even with their doctor (decrease of 9%).²⁴ Cogent carried out a survey again in 2010, and found that Americans are increasingly concerned about access to their genetic information; specifically, the 2010 Cogent survey found that 71% of Americans are concerned about storage of and access to their information, with the same percentage concerned specifically about access by health insurers.²⁵

In some cases, people feel differently about genetic information than they do about other medical information (a position termed genetic exceptionalism).²⁶ This viewpoint may be based on actual differences between genetic testing and other medical testing, for example, that genetic tests can reveal predictive and probabilistic information. It also may be based on a personal belief that genetic information is inherently different than other medical information. For example, genetic information about an individual may reveal things about family members, and therefore decisions by an individual to share her own genetic information can potentially also affect her family.

Congress passed GINA, partially as a result of these considerations, and many states, beginning in the early 1990s, enacted laws addressing genetic discrimination in health insurance, employment, and life insurance. Since GINA was enacted, the genetics community and others have considered and weighed possible expansions to the law. These potential changes have included extending the law to additional types of insurance (e.g., life insurance, disability insurance) or to additional health systems (e.g., Indian Health Service [IHS] or the Military Health Service [MHS]). Congress has not taken up any of these proposed modifications to the law.

Evaluating 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. These characteristics evaluate the performance of a genetic test from the viewpoint of both

²³ Burrill & Company/Change Wave Research, "Personalized Medicine and Wellness Survey," 2008, http://www.burrillandco.com/content/CWSurvey_61708.pdf.

²⁴ Cogent Research, "Cogent Genomics Attitudes and Trends: 2008," http://oba.od.nih.gov/oba/SACGHS/meetings/March2009/White_slides.pdf.

²⁵ Cogent Research, "Americans' Concern about the Privacy of Their Genetic Information Reaches New High," <http://www.businesswire.com/news/home/20110110006242/en/Americans%E2%80%9999-Concern-Privacy-Genetic-Information-Reaches-High>.

²⁶ For more information about characteristics of genetic information that may be viewed as unique and public perspectives on the differences between genetic and other medical information, see CRS Report RL34376, *Genetic Exceptionalism: Genetic Information and Public Policy*, by Amanda K. Sarata.

the laboratory and the clinical perspectives. Analytical validity evaluates the test's ability to do what it is intended to do; clinical validity evaluates the test result's link to a relevant clinical outcome; and clinical utility evaluates the test result's link to effective clinical treatment and management options.

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.²⁷ 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 above-mentioned characteristics of genetic tests—analytical validity, clinical validity, and clinical utility—have ties to public policy issues. Specifically, these characteristics are relevant to (1) the federal regulation of genetic tests, and (2) coverage decisions by payers.

Oversight of Genetic Tests. Genetic tests are regulated by the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS), through the Clinical Laboratory Improvement Amendments (CLIA).²⁸ FDA regulates genetic tests that are

²⁷ An analyte is a substance or chemical constituent undergoing analysis.

²⁸ For more detailed information about the regulation of IVDs, see CRS Report R43438, *Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests*, by Amanda K. Sarata and Judith A. Johnson.

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 ensure that the test detects what the manufacturer says it will, in the intended patient population. 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, the manufacturer must determine that the genetic test is safe and effective, or that it is substantially equivalent to something that is already on the market that has the same intended use.

Most genetic tests, however, are performed not with test kits, but rather as laboratory testing services (referred to as either laboratory-developed 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. Laboratory-developed tests (LDTs) are not currently regulated by the FDA in the way that test kits are and, therefore, the clinical validity of the majority of genetic tests is not regulated. The FDA does currently regulate certain components used in LDTs, known as Analyte Specific Reagents (ASRs), but only if the ASR is commercially available. If the ASR is made in-house by a laboratory performing the LDT, the test is not regulated at all by the FDA. This type of test is sometimes referred to informally as a “homebrew-homebrew” test.

Any clinical laboratory test that is performed for health-related reasons on a human specimen 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.²⁹ FDA determines the category of complexity of the test so the laboratories know which requirements 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 or 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. Supporters of the CLIA regulatory process argue that regulation of the testing process gives 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.

Although the analytical validity of genetic tests is regulated by CMS through CLIA (P.L. 100-578), as noted, the majority of genetic tests are not regulated based on (in any part) an assessment of their clinical validity. Given that the majority of genetic tests are LDTs, advocates for increased regulation of genetic tests have expressed concern that the majority of genetic tests are not assured to be clinically valid and that, therefore, the results of the tests could be either misleading or not useful to the individual.³⁰ This has also raised concerns about direct-to-consumer marketing of genetic tests—as most of these tests are also LDTs and not test kits—where the connection between a DNA variant and a clinical outcome (clinical validity) has not been clearly established. Because clinical validity is not part of the regulatory regime for LDTs currently, tests with unproven clinical validity are allowed to be marketed to consumers. 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 or outcomes when in fact there is no

²⁹ See <http://www.cms.hhs.gov/CLIA/>.

³⁰ Center for Genetics and Public Policy. “Genetic Testing Quality Initiative.” <http://www.dnapolicy.org/policy.gt.php>.

scientific basis—or inadequate evidence—underlying such an assertion. This issue was the subject of a July 2006 hearing by the Senate Special Committee on Aging,³¹ as well as two reports by the U.S. Government Accountability Office (GAO), in 2006 and 2010.³²

Coverage of Genetic Tests. While insurers generally require that, where applicable, a test be approved by the Food and Drug Administration, 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.³³ This 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 long time to collect. Although payers are beginning to cover companion diagnostics and other genetic tests, they may require stringent evidence of improved health outcomes.

Clinical utility and clinical validity both figure prominently into coverage decisions by payers, by both private health insurers and public programs, and in particular, “clinical utility data are necessary for reimbursement decisions.”³⁴ There are many genomics-based tests where the evidence of clinical utility is limited, and therefore, “[a] critical challenge to genomic medicine is how we bridge the evidence gap necessary to pave the way for coverage and reimbursement of genetic tests.”³⁵ While a lack of such data can hinder or complicate coverage and reimbursement decisions, potentially leaving patients without coverage for these tests, the lack of data also may leave payers unable to comprehensively evaluate the effectiveness of a test.

Payers, both private and public, have implemented approaches to covering genomic technologies concomitant with the collection of clinical utility data. For example, United HealthCare covers the OncotypeDX test for breast cancer³⁶ for patients meeting specific criteria, and requires data collection on the subsequent course of clinical treatment. In this way, the payer covers the test as the relevant clinical utility data are being collected.³⁷ In addition, CMS issued a national coverage determination (NCD) for Pharmacogenomic Testing for Warfarin Response; this allows for

³¹ Senate Special Committee on Aging, “At Home DNA Tests: Marketing Scam or Medical Breakthrough?,” July 27, 2006, <http://www.aging.senate.gov/hearings/at-home-dna-tests-marketing-scam-or-medical-breakthrough>.

³² GAO, “Direct-To-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices,” GAO-10-847T, July 22, 2010; and, GAO, “Nutrigenetic Testing: Tests Purchased from Four Web Sites Mislead Consumers,” GAO-06-977T, July 27, 2006, <http://www.gao.gov/assets/120/114612.pdf>.

³³ The concepts of medical necessity and clinical utility share some similarities; as noted previously in the report, 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).

³⁴ McCormack R.T. et al. “Codevelopment of Genome-Based Therapeutics and Companion Diagnostics,” *Journal of the American Medical Association*, published online February 12, 2014.

³⁵ National Human Genome Research Institute, “Reimbursement Models to Promote Evidence Generation and Innovation for Genomic Tests,” October 24, 2012, <http://www.genome.gov/27552210>.

³⁶ For more information on this test, see <http://www.oncotypedx.com/>.

³⁷ Carlson B. “Payers Try New Approaches to Manage Molecular Diagnostics,” *Biotechnology Healthcare*, vol. 7, no. 3, pp. 26-30, Fall 2010. “In its contract with United Healthcare, Genomic Health agreed to screen all physician orders for Oncotype DX to make sure patients met test criteria. United has the right to audit Genomic Health records and is entitled to a refund for tests performed on United patients who did not meet the criteria. United also audits Oncotype DX test results annually and matches those results with claims for chemotherapy. A low recurrence score suggests low benefit from chemotherapy. A high percentage of patients with a low score but who still received chemotherapy allows United to open and renegotiate the contract.”

Coverage with Evidence Development (CED) for pharmacogenomic testing with the use of warfarin.³⁸ In this way, CMS will cover testing for specified Medicare beneficiaries and in so doing will generate data on the clinical utility of the test.³⁹

Coverage of genetic tests and services—that are preventive clinical services—may be negatively affected by a lack of high-quality evidence to support their clinical utility. The Patient Protection and Affordable Care Act of 2010 (ACA, P.L. 111-148) in some cases requires and in some allows private health insurers, Medicare, and Medicaid to cover clinical preventive services (as specified in the law) and outlines cost-sharing requirements in some cases for these services.⁴⁰ However, the ACA provisions in some cases tie coverage of clinical preventive services to determinations by the U.S. Preventive Services Task Force (USPSTF, located in the Agency for Healthcare Research and Quality [AHRQ]), and these determinations are based on the quality of the evidence available to support a given clinical preventive service.

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 variations are not inherited, but rather are acquired in DNA due to replication errors or exposure to mutagenic chemicals and radiation (e.g., UV rays). In contrast to most other medical tests, genetic tests can be performed on material from a body, and may continue to provide information after the individual has died, as a result of the stability of the DNA molecule.

DNA-based testing of inherited genetic variations differs from other medical testing in several ways. These test results can have exceptionally long-range predictive powers over the lifespan of an individual; can predict disease or increased risk for disease in the absence of clinical signs or symptoms; can reveal the sharing of genetic variants within families at precise and calculable rates; and, at least theoretically, have the potential to generate a unique identifier profile for individuals.

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

³⁸ CMS, "National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1)," <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&bc=BAAAgAAAAAA&>.

³⁹ CMS, "Draft Guidance for the Public, Industry, and CMS Staff Coverage with Evidence Development in the Context of Coverage Decisions," November 29, 2012. "Fundamentally, CED is a determination that an item or service is reasonable and necessary, based on the best available evidence, under an explicit condition that patients be enrolled in a research study that evaluates outcomes, effectiveness, and appropriateness of the item or service in question. The reasonable and necessary standard and its subparts are found in Section 1862(a)(1) of the Social Security Act (the Act)."

⁴⁰ For more information about requirements relating to the coverage of clinical preventive services under the ACA, see CRS Report R41278, *Public Health, Workforce, Quality, and Related Provisions in ACA: Summary and Timeline*, coordinated by C. Stephen Redhead and Elayne J. Heisler.

Pharmacogenomic testing may be used to determine *both* 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 genetic variations in disease tissue, a tumor may have acquired genetic variations that render the tumor susceptible or resistant to chemotherapy.

A companion diagnostic (CoDx) test—a type of pharmacogenomic test—is a test that can be used to determine and guide the appropriate use of companion pharmaceuticals. Companion diagnostics may be co-developed with respective drugs (in a process utilizing FDA review for both the test and the drug) or they may be developed in-house by laboratories as LDTs. With respect to inherited genetic variation in drug metabolizing enzymes, a pharmacogenomic test may determine that an individual, for example, is a slow metabolizer of a certain type of drug (e.g., statins) and this information can be used to guide both drug choice and dosing.

Policy Issues

Personalized medicine—increasingly referred to as precision medicine—is health care based on individualized diagnosis and treatment for each patient determined by information specific to the individual or his disease, including information at the genomic level. Advocates maintain that pharmacogenomic testing and companion diagnostics are important because they are a key component in the success of precision medicine; “[g]enome-based, targeted therapeutics and codeveloped CoDx tests are the foundation of personalized medicine and have potential for contributing to high-value health care.”⁴¹ This is due to the fact that “[c]ompanion diagnostic tests define the subset of patients who are most likely to benefit from a therapy or who should not receive the therapy because of ineffectiveness or predicted adverse effects.”⁴² Policy issues that will be important to precision medicine include coverage of genetic tests, and specifically companion diagnostics, and privacy concerns with respect to large-scale research efforts to uncover relationships between genetics, environment, behavior, and clinical factors in disease.

Coverage of Genetic Tests. Health insurers are playing an increasingly large role in determining the availability of genetic tests by deciding which tests they will pay for as part of their covered benefit packages; however, there is some uncertainty as to how health insurers will assess and choose to cover genetic tests as they become available. 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, and specifically, the success of personalized medicine will be determined at least partially by coverage decisions. Medicare coverage determinations are often closely monitored by private health insurance plans, and many private plans will follow Medicare's decisions. Therefore, a decision by CMS to cover a new test through a favorable NCD will often result in more rapid diffusion and adoption of a test in the health care system.⁴³ Many aspects of genetic tests, including their clinical validity and utility, may complicate the coverage decision-making process for insurers.

Test manufacturers' decisions to develop a given test are affected, among other things, by both the likelihood of gaining favorable coverage decisions and by the likelihood of gaining

⁴¹ McCormack R.T. et al. “Codevelopment of Genome-Based Therapeutics and Companion Diagnostics,” *Journal of the American Medical Association*, published online February 12, 2014.

⁴² Ibid.

⁴³ 75 *Federal Register* 57046, September 17, 2010.

reimbursement that accurately reflects the costs of developing and carrying out the test. One issue with respect to gaining favorable coverage decisions has been the length of time required to do so. Manufacturers have stated that they will often focus their efforts on gaining FDA approval, without realizing that upon receiving such approval, Medicare coverage of the test is not automatic.⁴⁴ Medicare NCDs have traditionally been done serially with FDA pre-market review. To attempt to address this issue, FDA and CMS began a parallel review process whereby FDA approval is underway at the same time as is the CMS coverage determination. This pilot program, initiated in 2011 for a period of two years, was recently extended until 2015.⁴⁵

Genetic Research and Privacy. To facilitate the translation of precision medicine into health care, the President's FY2016 budget request proposes the development of a national research cohort, composed of 1 million or more volunteers, whose health, genetic, environmental, and other data would be collected and used in research studies to identify novel therapeutics and prevention strategies. Privacy concerns with respect to participation in such a cohort may be affected by the relatively recent demonstration that research subjects can be re-identified using de-identified sequence data in conjunction with other publicly available data sources.⁴⁶ Re-identification of research subjects in this manner could provide access to information about genetic test results, gene expression data, and phenotypic information (see the **Appendix** for a discussion of genotype and phenotype). Given this ability to re-identify research subjects, Congress might consider reevaluating and possibly modifying relevant current law, including GINA, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, or the Freedom of Information Act (FOIA).

⁴⁴ 76 *Federal Register* 62808, October 11, 2011.

⁴⁵ 78 *Federal Register* 76629, December 18, 2013.

⁴⁶ Gymrek M., McGuire A.L., Golan D., Halperin E., and Erlich Y. "Identifying Personal Genomes by Surname Inference," *Science*, vol. 339, pp. 321-324, 18 January 2013.

Appendix. Fundamental Concepts in Genetics

The following section explains some 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.

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 composed 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).⁴⁷

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 that 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 similar between individuals, there can be significant variation in physical appearance or function between individuals. In other words, although individuals share most of the genetic material other individuals have, there are significant differences in 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, or measurable, physical trait is known as the phenotype. For

⁴⁷ The National Human Genome Research Institute at the National Institutes of Health reports that the estimated number of human genes is between 20,000 and 25,000. See <http://www.genome.gov/11508982>.

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 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 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.

Glossary⁴⁸

Allele: An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent.

Amino acid: Amino acids are a set of 20 different molecules used to build proteins.

Autosomal chromosome: An autosome is any of the numbered chromosomes, as opposed to the sex chromosomes.

DNA: DNA is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix.

Genotype: A genotype is an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene.

Karyotype: A karyotype is an individual's collection of chromosomes.

Metabolite: A product of metabolism.

Phenotype: A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype.

RNA: Ribonucleic acid (RNA) is a molecule similar to DNA. Unlike DNA, RNA is single-stranded.

⁴⁸ Definitions for terms are taken from the "Talking Glossary of Genetic Terms," National Human Genome Research Institute, <http://www.genome.gov/glossary/index.cfm?id=180>.

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