

Genetics and Privacy: A Patchwork of Protections

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For additional background information on health privacy, please visit the Health Privacy Project's Web site at www.healthprivacy.org.

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I. Introduction

Rapid advances in the Human Genome Project and the study of human genetics are providing powerful tools for us to understand the instructions in our genetic material. We are daily gaining insights into the mysteries of the human cell, how it works, and why sometimes... it doesn't.

But genetic information and genetic technology can be used in ways that are fundamentally unjust. Genetic information can be used as the basis for insidious discrimination. Already, with but a handful of genetic tests in common use, people have lost their jobs, lost their health insurance, and lost their economic well being because of the misuse of genetic information. It is estimated that all of us carry dozens of glitches in our DNA—so establishing principles of fair use of this information is important for all of us.

— Francis S. Collins
Director of NHGRI
February 8, 2000

IN FEBRUARY 2001 THE NATIONAL HUMAN Genome Research Institute (NHGRI) and Celera Genomics celebrated the sequencing of the human genome. Their celebration resulted in strong public interest in genetics and intense media coverage. With the popular press functioning as both a catalyst and a barometer of the public's interest, it is not surprising that discoveries about genes are now covered frequently in the popular press instead of appearing just in scientific or academic journals. To make these discoveries more accessible, popular news accounts often generalize, oversimplify, or overstate their significance. Some people may believe mistakenly that medicine has reached the point where most people can learn now, through a quick computer analysis of DNA, which serious common diseases they will or will not get in the future. Some people undoubtedly believe that designer pharmaceuticals—targeted to work just on people with specific genetic profiles—will soon be commonplace.

The reality is much more complex. Scientists have much to do before such predictions and treatments are a reality. Indeed, it remains to be seen whether or not those of us alive today will ever see a world where gene-based therapies are common medical treatments.

Genetic Discoveries Offer Great Promise ...

The science of genomics has great promise. Ideally, the more scientists learn about the human genome and its specific genes, the better scientists will understand what causes certain diseases and what can prevent and cure them. Most genetics breakthroughs to date, however, have involved rare single gene disorders. Discoveries involving more common and complex diseases are rare. Furthermore, there is a very long road between the discovery of a particular genetic abnormality and the development of a clinical application to correct it, if any is developed at all.

... And Raise New Concerns

Amidst this uncertainty, one thing is sure. Genetic-related advances in medicine will not occur if individuals are afraid to provide their genetic information to scientists for research purposes. Recent surveys indicate that many people are concerned about how their genetic information will be used (see page 11). It is also clear that, in some cases, genetic information has been used to hurt people rather than help them.

The United States Lacks Needed Policies

The United States lacks a coherent approach to deciding how genetic information should be handled. Currently, it is not possible to assure people that their DNA will not be taken or used against their will or without their knowledge. While certain protections are offered under the new HIPAA provisions, there is no national approach to whether, when, or how genetic testing should be encouraged or discouraged, facilitated or prohibited, and how genetic information should be stored and protected. Instead, the U.S. relies on a patchwork of policies and practices to deal with these issues.

Why are the concerns about inappropriate uses and disclosures of genetic information so intense? Genetic information, which is a subset of medical information, is particularly sensitive because it reveals unique and immutable attributes about an individual. Those attributes are not just unique to the individual, but are shared by his or her family members as well. Sometimes this information has the potential to give individuals and others a frightening, or reassuring, glimpse into the future.

This purpose of this report is to explain the state of the science as it actually is and define some genetic-related common terms; to discuss how the privacy of genetic information is and is not protected (focusing on health care providers, researchers, health plans, and employers); to examine one of the new frontiers in health care—the Internet—and the phenomenon of people entrusting their most sensitive information, including their genetic information, to a largely unregulated cyberspace; and lastly to identify the large gaps in national policy that leave genetic information exposed to misuse.

II. Genetic Testing Primer

AS GENOMIC RESEARCH MOVES FORWARD, emboldened by continually advancing technologies, the potential for discovery is great. The promise of genomic research includes the hope that a better understanding of human genes will translate into the ability to better predict health risks through genetic testing and, ultimately, develop more effective treatments. The current state of genetic testing, however, illustrates the complexity in determining whether genetic testing results are clinically useful. The following is a brief overview of genetics and genetic testing available today (see Appendix A for definition of terms).

Genetics 101

What Is the Human Genome?

- The human genome, a human's complete DNA sequence, contains the genetic instructions for creating a living person. Every human cell (except red blood cells) contains the entire human genome.
- DNA (deoxyribonucleic acid) is a molecule made of four bases, known as A, C, G, and T. DNA is arranged in a double helix, in which a strand of DNA is paired via the bases with another strand of DNA running in the opposite direction. The human genome contains approximately 3.2 billion base pairs.
- In the cell's nucleus, DNA is packaged into units called chromosomes. There are 22 autosomal (non-sex) chromosomes, numbered 1 through 22, and two sex chromosomes, X and Y. Human cells carry two copies of each autosomal chromosome and either XX or XY for a total of 46 chromosomes (23 chromosome pairs).

What Is a Gene?

- A gene is a DNA sequence (a series of bases) that provides the instructions for creating a specific protein. Human Genome Project and scientists at the private company, Celera Genomics, predict the human genome contains about 30,000-40,000 genes.¹

What Are Genotype and Phenotype?

- A genotype is a person's set of genes. A phenotype is the physical manifestation of those genes in the person, or, in other words, whether the person has the physical feature (eye color, for example) or medical condition associated with a gene. Penetrance measures the extent to which having a particular genotype results in a predictable phenotype.

How Are Genes Related to Diseases or Sickness?

- A mutation is a change in the DNA sequence that can cause disease (see Appendix B).
- More than 1,000 genes have been discovered that, when mutated, cause specific diseases.² The vast majority of these diseases are single gene disorders, also known as Mendelian disorders, in which a mutation in one gene causes a certain disease. Single gene disorders are rare, affecting about one percent of the population. Examples include sickle cell anemia, cystic fibrosis, achondroplasia (dwarfism), Huntington's disease, and fragile X syndrome.
- Most common diseases are complex disorders, in which multiple genes and environmental factors contribute. Examples include diabetes type II, depression, and heart disease.

Genetic Testing Basics

What Is Genetic Testing?

A genetic test detects heritable or acquired genotypes...that cause or are likely to cause a specific disease or condition."³ As is true with other laboratory tests, a genetic test is only as good as its accuracy and effectiveness (see Appendix C). The standard terms used to evaluate these factors are analytical validity, clinical validity, and clinical utility.⁴

- *Analytical validity* is a term used to describe how well a test detects what it was designed to detect.
- *Clinical validity* indicates the test's accuracy in identifying or predicting a disease.
- *Clinical utility* is a measure of how useful a test's results are for the individual being tested, whether positive or negative. Factors that affect clinical utility include the availability of effective treatments/preventative measures, the penetrance of the mutation, and the psychological effect of test results on the individual.

In What Situations Is Genetic Testing Used?

Genetic testing is used in numerous situations:

- *Preimplantation diagnosis* is performed after *in vitro* fertilization to detect a genetic condition in an embryo before it is implanted.
- *Prenatal diagnosis* is performed on a developing fetus to diagnose a genetic condition.

- *Newborn screening* tests newborns for those genetic diseases that can be effectively treated or prevented with early detection. Each state mandates newborn screening for certain diseases.
- *Carrier testing* indicates whether an individual possesses one copy of a mutated gene for an autosomal recessive disorder that can be passed on to the individual's child. These disorders require two copies—one from each parent—of the mutated gene to cause disease. If both parents carry the gene, they have a 25 percent risk of producing a child with the disease.
- *Diagnostic genetic testing* is used to diagnose or verify the diagnosis of a disease in an affected individual.
- *Predictive genetic testing* is used to predict the risk of a healthy individual developing a disease, whether or not the individual has a family history of that disease. Because current predictive genetic testing has been developed primarily for rare single gene diseases, such as Huntington's disease, or rare forms of more common diseases, such as certain hereditary breast and colon cancers, it is only recommended for those with a family history of such a disease.⁵

The number of genetic tests performed each year is increasing. Genetic testing laboratories responding to a 1997 survey indicated that in their own labs, the number of genetic tests performed annually rose from almost 100,000 in 1994 to more than 175,000 in 1996.⁶

The diseases for which genetic testing has been developed are primarily rare single gene disorders. As of January 2002, there were approximately 529 diseases for which clinical genetic testing was available, and 374 diseases for which research only genetic testing existed. By comparison, at the end of 1999, those numbers were 361 for clinical and 325 for research only.⁷ (See Appendix D.)

The Complexity of Predictive Genetic Testing

Some of the diseases for which predictive genetic testing is available today include:

- *Huntington's disease* is an adult-onset dementia disorder. There is no cure for Huntington's disease, which limits the clinical utility of the test. But due to the high penetrance of the genotype and the debilitating nature of the disease, prenatal and predictive genetic testing have been available since 1986 for those at risk (those with Huntington's disease in their families).⁸
- About *five percent of breast cancers* are primarily due to inherited factors. Two genes have been discovered that when mutated can cause breast and/or ovarian cancer: *BRCA1* and *BRCA2*. Genetic testing is available for mutations in both genes, but the clinical utility of this test is extremely limited due to the lack of a standard preventative regimen for those who test positive and the large number of mutations with varying penetrance levels that can be found in the genes.⁹

Currently, predictive genetic testing is appropriate for family members of affected individuals, but meaningless at best or harmful at worst for others (e.g. if health decisions are based on a genetic test not meant for the individual). But it is not a straightforward process even for those who might benefit. The clinical utility of the results will depend on a number of factors, including whether the causative mutation in the family has been established and how well the mutation and the gene are understood scientifically. (See Appendix E.)

Factors Influencing Genetic Testing

The success of genetic testing as a clinically useful tool requires the following:

- health care providers who are fully educated in genetics;
- well-trained and readily available genetic counselors;
- the establishment of the validity and utility of genetic tests by scientists;
- accurate results by testing laboratories; and
- the informed consent of patients.

This is a challenging undertaking in the current environment, where genetic testing is available for rare diseases or rare forms of common diseases. If scientists do isolate the hereditary influences behind common diseases, greatly increasing the population of potential test takers, the genetic testing landscape will become far more complicated.

III. How Private Is Genetic Information?

Genetic Testing and Discrimination

The recent case of Terri Seargent illustrates what can happen to an employee after her employer learns that she has a genetically based condition. Ms. Seargent was fired from her job, despite favorable performance appraisals, after she began receiving preventative drug therapy for Alpha-1-antitrypsin deficiency and submitted claims to her employer's health plan.

U.S. Policy Gaps Lead to Confusion, Concern, and Discrimination

While the federal government has spent millions of dollars to promote genetic research, including the sequencing of the human genome, this nation has yet to develop a clear policy about the collection, use, storage, and protection of genetic information. There is no policy or guidance about whether, or under what circumstances, genetic testing should be encouraged, discouraged, facilitated, or prohibited. The lack of such policies has led to an ad hoc approach with results that often vary from one clinician to another, one laboratory to another, one employer to another, one insurer to another, and one state to another.

One clear result of this situation is that individuals cannot be assured that their genetic information will be kept confidential. Concerns abound that genetic information will fall into the wrong hands and lead to disastrous personal consequences:

- A recent *Time/CNN* poll found that 75 percent of people would not want their health insurer to have information about their genetic profile.¹⁰
- A 1997 survey about genetic discrimination showed that 63 percent would not take genetic tests if health insurers or employers could obtain the results. Eighty-five percent believe that employers should be prohibited from obtaining information about their employees' genetic conditions, risks, and predispositions.¹¹
- A recent study involving genetic counselors documents that concern about discrimination is a significant factor affecting willingness to undergo testing and to seek reimbursement from health insurers.¹²

The repercussions of genetic information falling into the wrong hands can be far ranging and include the loss of insurance or employment, having a mortgage called in or denied, or having genetic information used in child custody disputes or personal injury lawsuits.

Concerns about repercussions combined with complex medical questions result in an arduous decision-making process for those considering genetic testing or participating in a clinical trial in which genetic information will be gathered. People often are faced with risking their privacy or promoting their health or the health of the larger society.

Legal Protections for Genetic Information

There is no comprehensive federal law that safeguards the privacy of health information, including genetic information. Instead, a patchwork of federal and state laws protects health information based on the entity that collects or creates the information.

In practical terms, to determine whether a particular use or disclosure of information is legal or illegal, one needs to know which law applies (federal, state or both), who or what entity is involved and, in some cases, where or how the information was obtained.

Drawbacks of the HIPAA Privacy Regulation

The HIPAA regulation, which has a limited scope:

- does not directly regulate many entities that create or receive health information, including:
 - pharmaceutical companies
 - workers' compensation insurers
 - life or disability insurers
 - employers
 - many researchers; and
- reaches only indirectly some of the entities to which a regulated entity is permitted to disclose the information.

The Federal HIPAA Privacy Regulation and Genetic Information

HIPAA Privacy Basics

The federal Health Insurance Portability and Accountability Act (HIPAA), passed in 1996, required the federal government to implement a privacy law that covered health information created or received by private health care providers and health plans. The HIPAA privacy regulation, which took effect in April 2001, protects identifiable health information at the location where it usually begins to wind its way through the health care system—with a health care provider or health plan (see Figure 1). It is the first federal law to protect health information created or received by private health care providers and health plans. Most entities that must comply with it have until April 14, 2003 to do so.

Who Must Comply with the HIPAA Privacy Regulation?

The following entities are required to comply with this new federal law:

- health care providers (doctors, hospitals, clinics, pharmacies, laboratories) that transmit claims-type information electronically;
- health plans, broadly defined to include employer-sponsored health plans, private health insurance companies, and HMOs, as well as a number of health programs sponsored by the federal and state governments; and
- health care clearinghouses, which act as claims processing intermediaries between health care providers and health plans.

Some Genetic Information Will Be Protected by HIPAA Privacy Regulation

Genetic information will be protected by the HIPAA regulation if it meets the definition of “protected health information.” Protected health information is defined broadly and includes information about the past, present, or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present, or future payment for the provision of health care to an individual. According to the U.S. Department of Health and Human Services (HHS), “the definition of protected health information includes genetic information that otherwise meets the statutory definition.”¹³

Under this definition, information about genetic tests, services, or counseling will clearly be protected, as will information about an individual’s family history - an important component of genetic information. Although the definition of protected health information does not explicitly refer to family history, HHS made clear that medical information about a family member contained within an individual’s medical record is information about the individual.¹⁴

Health care providers that provide general medical services and create or receive genetic information, as well as specialists that provide genetics services, perform genetic tests, or interpret genetic test results, will have to comply with the HIPAA privacy regulation if they otherwise meet the definition of a covered provider. The essential prerequisite for providers to be “covered” is that they transmit claims-type information electronically using HHS-prescribed standard formats.¹⁵ (See Figure 1.)

Interestingly, the HIPAA privacy regulation will not protect the actual tissue or blood sample that generated the genetic information.

Genetic Information Treated the Same as Other Protected Information

Falling within the scope of the HIPAA privacy regulation means that genetic information will be protected to the same extent as other health information. Thus, once a health care provider obtains an individual’s written consent, the provider can use and disclose that information for treatment, payment, and many other health care purposes (the law refers to “health care operations” purposes and defines it rather broadly). A health plan does not need to obtain the individual’s consent before using and disclosing health information, including genetic information, for these health-related purposes.

HIPAA Protections in the Research Setting

Genetic information compiled, or genetic testing performed, in a research context may not be protected by the HIPAA regulation. Protection of genetic information in this context will depend on whether the researcher is functioning as a health care “provider” and, if so, whether the researcher (or the institute that employs him or her) bills insurance companies for health care services.

Research involving genetic information will be impacted by the privacy regulation to the extent that researchers attempt to obtain protected health information from an entity that must comply with the regulation. Before covered entities can disclose patient identifiable information to researchers, certain requirements must be met.

Figure 1. Is the Information Covered by HIPAA?

Determining if a piece of health information—including genetic information—is covered by the HIPAA privacy regulation requires reviewing all of the following criteria.

Does the information meet the definition of “protected health information?”

Protected health information includes information about the past, present, or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present, or future payment for the provision of health care to an individual. The definition of protected health information includes genetic information that otherwise meets the statutory definition. This includes genetic tests, services, or counseling, as well as an individual’s family medical history.



Is the information holder covered by the regulation?

The information holder must be a health care provider, health plan, or health care clearinghouse as defined in the regulation. “Health care provider” covers most of the people and organizations consumers traditionally think of as providers. It includes any person who furnishes, bills, or is paid for health care in the normal course of business. Thus, doctors, nurses, counselors, clinics, hospitals, pharmacies, and similar persons and organizations are health care providers under the regulation. As for those who furnish health-related supplies, the regulation applies only to those who sell or dispense these items pursuant to a prescription. The term “health plan” covers just about any organization that provides or pays the cost of medical care, including fee-for-service insurers, HMOs, Medicare and Medicaid programs, issuers of long-term care policies, group health plans, and others.



If the information holder is a provider, does the provider transmit the regulated health information electronically?

The regulation applies only to those providers that conduct insurance-related transactions. Some of the transactions that require a health care provider to comply include: submitting health claims or equivalent encounter information; determining eligibility for a health plan; receiving health care payment and remittance advice; and receiving referral certification and authorization. In a very general sense, if the provider accepts health insurance (including Medicaid) or participates in an HMO, then the provider likely engages in the type of electronic transactions necessary to bring him or her within the scope of the HIPAA privacy regulation. If a provider transmits health information electronically in relation to any of these transactions, HIPAA requires the provider to use a standard format. October 2003 is the deadline for compliance with this requirement. Only providers who use the required formats are covered by the privacy regulation. (However, a law enacted in December 2001 requires that between April 2003 and October 2003, providers still have to comply with the privacy regulation even if they do not engage in these transactions using the standard formats.) This requirement does not apply to health plans; they are covered regardless of the format or means they use to transmit protected information.

Opt-outs or Specific Authorization

Some uses and disclosures of protected information will require the opportunity for an opt-out in advance, some will require specific individual authorization, and other uses and disclosures can proceed without notice, authorization, or consent.

Plans Can Ask for Genetic Information

Unlike some federal legislative proposals and some state laws, the HIPAA privacy regulation will *not* prevent covered health plans from requesting that individual plan members provide genetic information to the plan or from requiring applicants for insurance to provide genetic information or undergo genetic tests as part of the insurance underwriting process.

The regulation will, however, impact health plan or health insurer requests to a covered health care provider for a patient's genetic information. How the law will impact those requests depends upon the purpose of the request. For example, an insurer seeking genetic information about an insurance applicant from a covered health care provider would need to provide the health care provider with an authorization signed by the applicant. Also, the regulation's "minimum necessary" standard should prevent a health plan from insisting that the covered health care provider disclose the results of a genetic test involving a plan member when the results of that test are not necessary for the health plan to reimburse the provider for conducting the test.¹⁶

Some Marketing Is Permissible

One of the more controversial aspects of the HIPAA privacy regulation is that it permits health care providers and plans to use and disclose protected health information for certain marketing and fundraising activities provided specific safeguards are met.

The Impact of the HIPAA Privacy Regulation on State Privacy Laws That Protect Genetic Information

Many states have passed laws that protect the privacy of health information. Some of these laws target genetic information, but like the federal regulation, the approach is often limited to certain entities that hold that information, such as health care professionals, hospitals, or health insurance companies. Many of the laws that specifically target genetic information apply to health insurers, HMOs, or employers.

Stronger State Laws Add to HIPAA Protections

The HIPAA privacy regulation sets a federal floor of privacy protections. It does not preempt (or trump) state laws that conflict with it if those state laws provide stronger privacy protections. State laws that provide weaker privacy protections are preempted. Thus, for example, a state law that requires specific patient consent or authorization before any disclosure of genetic information would not be preempted and would still apply to entities covered by that state's law even if those entities also must comply with the federal regulation.

Many states have passed genetic nondiscrimination and privacy laws that apply to the insurers and HMOs covered by the HIPAA privacy regulation. According to the National Conference of State Legislatures (NCSL), 26 states have laws that require informed consent prior to disclosure of genetic information (often limited to results of genetic tests) by health insurers.¹⁷ These laws may provide individuals with greater control over disclosures of their genetic information than the HIPAA privacy regulation. In addition, state laws that regulate people or entities that are not reached by the HIPAA privacy regulation would not be impacted by the HIPAA privacy regulation, and people in those states would have additional privacy protections for their genetic information. For example, laws in 14 states require informed consent before a third party can perform or require a genetic test or obtain genetic information.¹⁸

HIPAA and Employers

A noteworthy feature of the HIPAA privacy regulation is its limits on disclosures of protected health information, including genetic information, by group health plans and insurers to employers that sponsor group health plans. Most people with private insurance get their insurance through their employer or the employer of a parent or partner. As a result, many people have concerns about their employers having access to private medical information.

The HIPAA privacy regulation goes to great length to protect workers and their dependents from inappropriate disclosures to employers and from inappropriate uses by employers, but because the employer has established the health plan, the regulation cannot completely shut down the flow of all information.

The HIPAA privacy regulation permits group health plans and insurers to share protected health information with the employer/plan sponsor only in limited circumstances and only when certain requirements are met. The regulation does this by reconciling the employer/plan sponsor's need for access to some information with the need to ensure that protected health information is not used for employment-related purposes or purposes unrelated to the employer's management of the group health plan.

Employee Health Claims

Employers obtain employee (and dependent) health information through health claims submitted to employer-sponsored health plans. How much protected health information the HIPAA privacy regulation will permit the employer to obtain from the group health plan will depend on how involved the employer is in administering the health plan.

Most people (nearly 60 percent) with private employer-sponsored health insurance work for employers that arrange with a health insurance company or HMO to provide or pay for health care services. In return for premiums, the insurance company or the HMO bears the risk of medical claims and manages the plan. In that case, the employer has no need for personally identifiable health information about its employees.

Just over 40 percent of people with private employer-sponsored health insurance work for employers that “self-insure.” These employers bear the risk of medical claims even though they may contract with an outside administrator to manage the plan on a day-to-day basis. Some self-insured employers, however, administer these health plans inhouse and have direct access to health information from claims submitted by plan participants or by health care providers.

Will An Employer Learn of an Employee’s Genetic Test?

Would the HIPAA privacy regulation keep an employer from learning through its health plan that one of its workers had just undergone genetic testing to assess predisposition to a certain type of hereditary colon cancer? It depends on how the employer manages the group health plan. If the employee submits a claim for reimbursement to the health insurance plan and if the employer handles payment of the medical claims, the employer may learn that the worker had undergone the genetic test. The best practice would be for the employer to hire an outside administrator to handle all the claims so the employer does not need to review any patient-identifiable information, but the HIPAA privacy regulation does not require that. The HIPAA privacy regulation should prevent the employer (or any other entity that pays the claim) from learning the result of that genetic test (positive or negative) because that information is not necessary to process and pay for that claim.

Required “Firewalls” Aim to Protect Information

Of particular importance are the provisions that require the use of firewalls to separate the group health plan functions of the employer/plan sponsor from the rest of the employer/plan sponsor. Under the regulation, only employees involved in health plan administration would have access to protected health information. Employees wearing multiple “hats” could legitimately use other employees’ protected health information *to administer the group health plan*, but they could not use this information for any other purpose.

Employer as Provider

The HIPAA privacy regulation may impact the way that employers obtain protected health information about their employees in one other way. An employer that actually provides health care services to its employees, such as through an on-site medical clinic or employee assistance program, may, with respect to the provision of such care, be a health care provider that is required to comply with the HIPAA privacy regulation. As with all other health care providers, the provider would have to engage in standard electronic HIPAA transactions in order to be a “covered” provider under the privacy regulation. (See Figure 1.) In general, providers will meet this electronic transmission prerequisite by engaging in electronic transactions with insurers, such as submitting claims for services to insurers. Since it is hard to imagine an employer’s on-site clinic engaging in such transactions, the health information created or received in these programs will generally not be protected by the privacy regulation.

Genetic Information Obtained by Private Employers¹⁹

Employers learn about the health status and medical conditions of their employees (and in some cases, employees' dependents) in various ways (other than through the group health plan). Some of this information concerns work-related illnesses and injuries, but much of the information available to employers concerns conditions, illnesses, and injuries that do not happen *at work* or *because* of work. These conditions, illnesses, and injuries might be considered "work-related" only in situations where they prevent the employee from coming to work or performing some of the routine functions of the job for some period of time. Following is a brief overview of some ways that employers collect and use medical information, including genetic information. It is beyond the scope of this report to provide a thorough discussion of all the federal laws that allow employers to collect and use such information.

Testing Not Required for Employer to Gather Genetic Information

In order for employers to obtain genetic information about newly hired employees, employers do not need to require employees to undergo genetic tests. All the employer needs to do is ask or require new hires to divulge genetic information, or ask or require them to sign a release authorizing someone else, such as a health care provider or health plan, to disclose it to the employer.

Employer-required Medical Examinations

Many employers, indeed most large employers, require that new hires take medical examinations. According to a 2001 survey by the American Management Association (AMA), 65 percent of major U.S. firms require medical examinations of new hires.²⁰ About 34 percent of major U.S. firms require medical examinations of current employees. Drug testing is the most common type of medical examination, followed by fitness-for-duty examinations, which assess the ability of an applicant or employee to perform job functions. Medical examinations required by employers can be quite far reaching, and the AMA survey confirms that employers use the results when they make decisions about hiring, placement, retention, and dismissal.

Other important avenues for collection of medical information are:

- workers' compensation claims;
- medical examinations required or performed for occupational health and safety purposes;
- requests to accommodate a disability;
- requests for paid or unpaid sick leave; and
- requests for family or medical leave.

All of these ways in which employers may obtain health information could result in employers obtaining *genetic* information.

Genetic Testing by Employers

There is no solid source of empirical evidence to document how often or for what purpose employers currently obtain genetic information about job applicants or employees or require them to undergo genetic testing. For decades, some employers have performed genetic testing on their employees (or obtained test results) and used that information for employment purposes, but such practices have never been widespread.²¹ What little evidence there is—the 2001 AMA survey—it is far from authoritative. Nonetheless, it reveals that some major U.S. firms acknowledge conducting genetic testing of employees. According to the survey, one percent of major U.S. firms test new hires or employees for sickle cell anemia, .4 percent conduct genetic testing for Huntington’s Disease, and 14 percent conduct medical examinations to detect susceptibility to workplace hazards, which the surveyors acknowledge might involve genetic testing. The three percent of major U.S. firms that perform testing for breast and colon cancer appear to be conducting genetic testing to assess predisposition to breast and colon cancer, rather than testing for presence of actual disease, but the summary of the survey is not entirely clear.

Gathering Employees’ Family Medical History

Most striking, 20 percent of major U.S. firms collect information about family medical history, a rich and important source of genetic information. Employers may be just as likely not to hire someone whose mother and sisters died of breast cancer in their 40s as they are to not hire someone who has actually undergone testing for the known genetic mutations that may indicate an elevated risk of developing breast cancer.

Call for Federal Legislative Limits

The Burlington Northern controversy (see sidebar) led to immediate calls on Capitol Hill for passage of legislation that would prohibit genetic testing by employers except in limited circumstances. As of the end of February 2002, Congress had held a number of hearings on such legislation. If enacted, the legislation would limit employer acquisition of, use of, and disclosure of genetic information. In the absence of targeted federal legislation, employees must turn to state laws.

Linking Genetic Test Results to On-the-job Injuries

Burlington Northern Santa Fe Railroad’s genetic testing policy recently made front page news and resulted in lawsuits brought by the U.S. Equal Employment Opportunity Commission and a union representing affected workers. The company required employees who developed carpal tunnel syndrome to undergo genetic testing—testing that the employer seemed to believe would show whether the employee was predisposed to carpal tunnel syndrome. This testing was done without the employees’ knowledge. Presumably, the employer intended to argue that the injuries of such “predisposed” employees were not sufficiently “work-related” to be eligible for workers’ compensation. Respected leaders in the scientific community soundly denounced the genetic testing done by Burlington Northern as “junk science.” As a result of the publicity and lawsuits, the company stopped the testing and entered into a quick settlement. As a result, the complex legal issues raised by this type of testing were not thoroughly hashed out in the courts.

State-level Restrictions

According to the National Conference of State Legislatures (NCSL), 28 states have enacted laws that limit the ability of employers to collect, use, and disclose genetic information. The scope and content of these laws vary considerably.²²

Employers Generally Required to Keep Medical Information Confidential

As a general matter, federal laws, such as the Americans with Disabilities Act, that allow private employers to collect medical information (including genetic information) about employees require that medical information be kept in confidential medical files. As a result, an employer who disclosed such information outside the company would probably violate federal law, unless the law explicitly permitted the disclosure (for example, to government authorities investigating compliance with the law). Unfortunately, there is a fair amount of on-the-ground confusion about who within the employer entity is permitted to see these confidential medical files. When non-medical personnel ask to see actual employee medical files, they put occupational health professionals in a bind. By asking them to disclose the requested medical information and violate patient/worker privacy, quite possibly in violation of the law, occupational health professionals risk being reprimanded, disciplined, or fired. In companies that do not employ or retain medical professionals, and thus rely directly on medical opinions provided by an employee's own health care professional, management personnel may have direct access to substantial amounts of medical information without the buffer provided by corporate medical personnel.

IV. Genetics and Internet Health

The Growing Role of the Internet in Health Care

Often touted as the future of health care, the Internet promises to transform the way health care entities conduct business and the way patients obtain health care information and services.

This transformation is reflected in the migration of traditional “bricks-and-mortar” health care entities to the Web and the creation of thousands of solely Internet-based health care entities. There are thousands of health-related Web sites and they are proving popular.²³ Each year, millions of people access health information online, and while there are various estimates of the precise number, all agree that the number has increased dramatically in recent years.

The Internet makes efficient online communication possible and facilitates the collection, storage, and transfer of vast amounts of consumer health information. While these services can be valuable to patients and providers, they also mean that highly sensitive information can be collected and distributed in new ways, leaving such information vulnerable to security breaches. And the development of privacy protective policies and practices for health information on the Internet lags far behind the technology.

Genetic Information on the Web

Not surprisingly, the exponential growth of the Internet has led to the creation of Web sites devoted to genetic information, though it is impossible to know with certainty the number of Web sites that collect genetic information or provide other genetics-related services.

A search on the Google search engine using just the term “paternity testing” brings up more than 33,000 hits. A 2000 survey of 157 patients referred to general genetics clinics showed that nearly half searched the Internet for genetics-related information prior to their clinic visit, leading the authors to conclude that Internet use among people referred to genetics clinics is widespread.²⁴

Some sites sell kits that allow individuals to preserve their own DNA samples, while others collect genetic information and “bank” it. Site owners may use this information for their own internal research or sell it to others for use in research or marketing. Some sites provide genetic services, including counseling about specific genetic tests or diseases and some offer paternity testing, testing to establish other familial relationships, or services that allow people to be identified through their DNA profile. As interest in the human genome increases, these sites undoubtedly will proliferate.

Privacy Policies on Genetics Web Sites

Privacy policies and practices vary widely at health sites—if they exist at all—and most sites are not currently regulated by federal privacy laws.²⁵ Here are a few sites that illustrate the variety of services available online and their privacy policies:²⁶

DNA.com

This site, operated by DNA Services, Inc., provides information about genetics, from DNA basics to live audio chats with genetics experts and a searchable database about genetically based diseases. It also operates the Gene Trust, which recruits volunteers to help study the link between genetics and disease. Its goal is: “to speed up the rate of medical discovery in order to develop better diagnostics and more effective treatments.” Health information, including the genetic information DNA Sciences derives from participants’ DNA (through a blood sample sent to DNA Sciences), is stored in off-line databases.

The site’s privacy policies are extensive. It is a licensee of the TRUSTe Privacy Program and subscribes to the HONcode principles of the Health On the Net Foundation.



www.dna.com

Genescene.com

This site, operated by Global TeleGenetics, Inc., also provides general information about genes and genetically based diseases. Visitors can complete a computerized questionnaire and get an “immediate automated result assessing an individual’s genetic health risks for a specific medical concern.” Visitors can also obtain information and support from a “professional genetic counselor” or get a consultation “with the assistance of your local primary care doctor and provided by a licensed medical doctor at GeneScene.Com who is board-certified in medical genetics.”

The site has a privacy policy as well as extensive legal disclaimer and informed consent forms. The site subscribes to the HONcode principles of the Health On the Net Foundation.

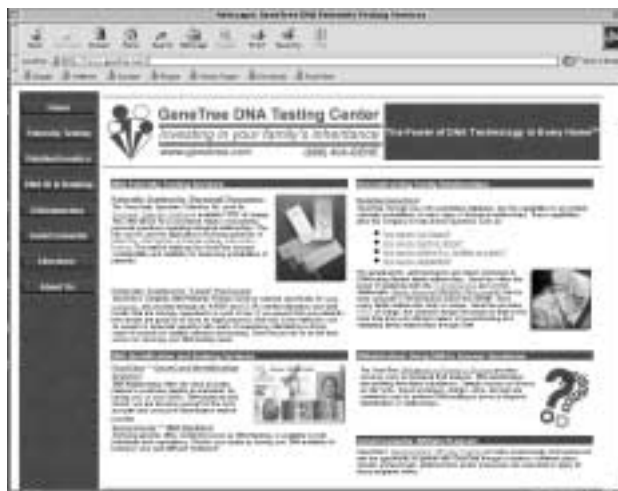
Genetree.com

This site, operated by GeneTree Inc., offers a variety of services including: paternity testing, validation of family relationships, DNA identification cards, DNA banking, DNA identification from various bodily substances, and telephone and email consultations with genetic counselors.

This site also has a privacy policy, but, nowhere in the policy does it state what GeneTree Inc. does with the genetic information it compiles about individuals. The policy does assure individuals, however, that their email address, mail address, and phone number will not be shared with other companies. The page on DNA ID and Banking states: “DNA profiles are maintained in a confidential database,” but does not explain how GeneTree will use one’s genetic information or to whom it will disclose this information. The same page indicates that the DNA identification cards are produced through a joint partnership with another company, so at least that company will have access to a person’s genetic profile.



www.genescene.com



www.genetree.com

Federal Privacy Protections Online and Genetic Information

HIPAA Privacy Regulation and Federal Trade Commission Protections

The only federal health privacy law that may have some application to these Web sites is the HIPAA privacy regulation. The HIPAA privacy regulation makes no distinction between health care online and offline, so some health Web sites *will* be covered by the regulation, and consumers may benefit from the new privacy protections required of these sites. Most parties that engage in online health activities, however, will fall outside the scope of the regulation.

For online activity *not* covered by the HIPAA privacy regulation, a consumer's only federal legal protection will come from the Federal Trade Commission (FTC). The FTC has the authority to prosecute Web sites that engage in unfair or deceptive practices, such as noncompliance with their own privacy policies. However, the FTC has no authority to challenge sites that say nothing about privacy or post poorly conceived or drafted privacy policies.²⁷ Nor is the FTC likely to seek new authority from Congress any time soon.²⁸

How the HIPAA Privacy Regulation Protects Online Genetic Information

As discussed earlier, the HIPAA privacy regulation covers health care providers that transmit health information electronically in a standard format and health plans. Once an entity is a "covered entity," it is subject to the new regulation whether it is conducting business online or off.

As covered entities migrate to the Web and establish an online presence, their online collection and transmission of protected health information will generally be reached by the privacy regulation. None of the genetics-oriented Web sites highlighted above is a covered entity subject to the privacy regulation.

Determining if an Online Health Plan Is Covered

It should be fairly easy to determine if a health plan that offers genetic services over the Web is a covered entity. The term "health plan" is broadly defined in the regulation and covers just about anyone that provides or pays the cost of medical care, including fee-for-service insurers, HMOs, Medicare and Medicaid programs, issuers of long-term care policies, group health plans, and others. Given this broad definition, it is fairly likely that a Web site hosted by a health insurer or HMO will be a covered health plan under the regulation.

Determining if an Online Health Care Provider Is Covered

It will be more difficult for consumers to tell whether any given *provider* is subject to the regulation, since not all health care providers fall under the regulation's definition of "covered entity." For example, it is difficult to know if the genetics counselors at GeneScene are covered providers. One of the sites (www.dna.com) goes to great lengths to tell visitors that no physician-patient relationship is established. This should be a tip that the site doesn't want the responsibility—professional or regulatory—that comes with the establishment of a bona fide physician-patient relationship.

To determine whether a person or organization is a covered provider under the privacy regulation, a consumer would need to answer the three key questions listed below. A provider is only covered by the privacy regulation if the answer to *all* of these questions is yes. (See also Figure 1.) Answering even the simplest of these questions, however, may not be as easy as it appears:

1. Is the person or organization a health care provider as defined by the rule?

- As defined in the regulation, the term “health care provider” covers most of the people and organizations that consumers traditionally think of as providers. It includes any person who furnishes, bills, or is paid for health care in the normal course of business. Thus, doctors, nurses, counselors, clinics, hospitals, pharmacies, and similar persons and organizations are health care providers under the regulation.
- As for those who furnish health-related supplies, the regulation applies *only* to those who sell or dispense these items pursuant to a *prescription*.²⁹ Under this requirement, a pharmacist is a health care provider, while a Web site that sells vitamins or books and tapes on losing weight is not. Similarly, a pharmaceutical company is not a “health care provider” since it does not sell or dispense drugs pursuant to a prescription.
- Many Web sites merely offer information, not health care services. A site that merely offers information on genetic conditions and tests is not considered to be providing health care, as defined in the federal regulation.

2. Does the provider transmit health information electronically in connection with one of the financial or administrative “transactions” listed in HIPAA?

- If a person or an organization is a “health care provider” under the regulation, the next question to ask is whether it engages in the type of “transactions” that will bring it within the scope of the privacy regulation. Since the intent of the relevant part of HIPAA (including the privacy regulation) is to simplify the processing of health insurance claims, the *privacy regulation applies only to providers who conduct insurance-related transactions*. Some of the transactions that trigger application of HIPAA to a provider include: submitting health claims or equivalent encounter information; determining eligibility for a health plan; receiving health care payment and remittance advice; and receiving referral certification and authorization. All of these transactions are related to health insurance-type transactions.
- In a very general sense, this question can be boiled down to: “Does the provider accept health insurance (including Medicaid) or participate in an HMO?” If the answer to this question is yes, it is likely that the provider engages in the type of electronic transactions necessary to bring him or her within the scope of the privacy regulation.

3. Does the provider transmit health information electronically and in the required standard format?

- If a provider transmits health information electronically in relation to any of these transactions, such as verifying insurance coverage or filing a health claim, HIPAA requires the provider to use a standard format. October 2003 is the new deadline for compliance with the requirement for adopting the standard formats. HHS has taken the position that only providers who use the required formats are covered by the privacy regulation. (To make matters more complicated, a law enacted in December 2001 states that between April 2003 and October 2003, providers still have to comply with the privacy regulation even if they do not engage in these electronic transactions *using the standard formats*.³⁰)
- If a provider has an online presence and accepts insurance, it probably will be safe to assume that he or she transmits the required type of information electronically. But it is problematic for a consumer to determine whether a provider uses the standard format.

Covered Entities Must Provide Notice and Obtain Consent

Legally, beginning in April 2003, any health care provider that must comply with the HIPAA privacy regulation must provide patients with a notice of privacy practices and obtain the individual's written consent before using or disclosing protected health information even for treatment purposes. The failure to see such a notice posted should alert a Web site visitor that the provider does not think it is required to comply with the privacy regulation or is unaware of it. Moreover, actually seeing a HIPAA-compliant privacy notice posted on a Web site might lull a Web surfer into a false sense of security since only some, but not all, of a Web site's health-related activities may actually constitute health care services that are protected by the regulation. In either case, the individual submits genetic information or other protected health information at his or her peril.

Desire for Anonymity May Lead to Dangerous Results

People often believe they are invisible and anonymous online, but they are often exposing their most sensitive health information to Web sites that are not required by law to protect the information or keep it confidential. It is ironic that a person's desire for anonymity may leave him or her especially vulnerable to exposure. The potential for abuse here is enormous, and threatens to act as a barrier to the fullest advances in genetic science and medicine.

V. Closing the Privacy Gaps

THERE ARE FIVE PRIMARY GAPS IN NATIONAL policy that leave genetic information exposed.

1. Genetic Source Materials Need Protections

The HIPAA privacy regulation does not protect tissue, blood, or any other bodily source of a person's genetic information. A person's genetic information is relatively easy to obtain. All one needs to do is swipe a glass the person has been drinking from or take a strand of hair that has fallen out.

2. Reach of HIPAA Privacy Regulation Too Limited

Many key entities that obtain and use health information are not directly reached by the HIPAA privacy regulation. These entities include:

- employers
- pharmaceutical companies
- pharmacy benefit managers
- workers' compensation insurers
- life insurers
- disability income insurers
- many researchers

The Department of Health and Human Services (HHS) did not have the option of including these entities in the privacy regulation because of limits in the underlying HIPAA statute. Congress would have to act to fill these HIPAA gaps. Filling these gaps would require starting with a dialogue about whether and under what circumstances each of these entities should have access to genetic information and, if so, how they should be permitted to and prohibited from using such information.

3. Certain HIPAA Privacy Regulation Provisions Too Permissive

HHS made certain policy judgments in the privacy regulation that should be reconsidered. These include the regulation's inappropriately permissive approach to:

- health-related marketing using protected health information
- access to protected health information by law enforcement officials

HHS has shown no inclination to revisit these issues. Congress could, of course, intervene.

4. Private Right of Action Needed

The HIPAA privacy regulation does not include meaningful enforcement rights. Someone who believes the regulation has been violated can complain to the violator and/or to HHS, but few believe that HHS will ever have the resources needed to fully investigate individual complaints. HHS did not believe it had the authority to include a new federal private right of action for individuals whose rights are violated. Thus, Congress would have to act to remedy this enforcement gap.

5. Web-based Information Vulnerable

A significant gap in protection exists due to the ever-expanding use of the Internet, where genetic information is collected, used, and disclosed in ways that are largely unchecked by policy and practice. This report merely touched upon a few of the genetics-related Web sites. The brewing ethical and policy debates over genetic privacy and the ongoing dialogue about Internet privacy would be advanced considerably through a better understanding of how genetic information is collected via the Web and how it is subsequently used and disclosed.

Appendices

Appendix A: Understanding the Lingo of Basic Genetics

Appendix B: Gene Discovery:
Identifying Genes that Cause Disease

Appendix C: Genetic Testing in General

Appendix D: The Uses of Genetic Tests

Appendix E: The Complexity of Predictive and Carrier
Genetic Testing

Appendix A: Understanding the Lingo of Basic Genetics

Chromosomes—In the cell’s nucleus, DNA is packaged into units called chromosomes. There are twenty-two autosomal (non-sex) chromosomes, numbered 1 through 22 based on their decreasing size, and two sex chromosomes, X and Y. Human cells carry two copies of each autosomal chromosome and either XX or XY for a total of 46 chromosomes (23 chromosome pairs). Egg and sperm cells contain one of each chromosome rather than a pair.

DNA—Every human cell (except red blood cells) contains the entire human genome. A genome is an organism’s complete DNA sequence. DNA (deoxyribonucleic acid) is a long molecule made of four nucleotide components—adenine, cytosine, guanine and thymine, known as A, C, G and T. DNA is arranged in a double helix, in which a strand of DNA is paired via the nucleotides with another strand of DNA running in the opposite direction. The nucleotides pair in a uniform manner—adenine always pairs with thymine, and cytosine with guanine. These pairs of nucleotides are commonly referred to as base pairs, and this is the unit in which the length of DNA is described. The human genome contains approximately 3,200,000,000 base pairs.

Genes—A gene is a DNA sequence (a series of nucleotides) that provides the instructions for creating a specific protein. Because one chromosome of each pair is inherited from the mother and the other from the father, the chromosome pairs have corresponding genes, but each may have a slightly different version of the gene. These different forms of the same gene are referred to as alleles. Often these differences are due to single nucleotide polymorphisms, or SNPs (pronounced “snips”), which are single base pair variations that occur frequently in a population. All human genomes are 99.9% identical—the variability of the remaining 0.1% accounts for the differences between humans.

Genotype, Phenotype, and Penetrance—A genotype is a person’s set of genes. A phenotype is the physical manifestation of those genes in the person. Penetrance is a measure for correlating genotype with phenotype. Complete penetrance occurs when a given genotype always results in a particular phenotype. When this does not happen, the genotype is incompletely penetrant. Factors that affect the penetrance of a genotype include environmental influences, the functional importance of the gene’s protein product, and the influence of other genes.

Mutations—A mutation is a change in the DNA sequence that can cause disease. There are different kinds of mutations, including a single base pair change, the deletion of a segment of DNA, and the insertion of part of one chromosome into a different chromosome.

Sequencing—The process of sequencing the human genome determines the precise order of base pairs along each chromosome. Knowing the order of the A’s, C’s, G’s and T’s is useful for many applications, including gene discovery and the location of additional targets for medicines. However, having the sequence of the human genome does not explain the complex biology of human beings—instead, the sequence is an important source of additional clues.

Transcription and Translation—Cells produce proteins from genes by engaging in two cellular processes: transcription and translation. Transcription occurs first, and involves the transcribing (or copying) of DNA into a molecule called RNA. RNA is made of the same nucleotides as DNA except for uracil, or U, which RNA uses instead of thymine, or T. The next step is translation, in which the RNA, known as messenger RNA (mRNA), is translated into a protein. The cell’s protein manufacturing machinery “reads” the mRNA in sets of three nucleotides, which are referred to as codons. Each codon corresponds to a certain amino acid, and the cell builds a protein by joining together the amino acids called for by the mRNA.

Appendix B: Gene Discovery: Identifying Genes that Cause Disease

The Human Genome Project has accomplished what would have been unthinkable before this past decade—the sequencing and analysis of over ninety percent of the human genome. An international consortium of research teams, headed by the National Human Genome Research Institute, is responsible for the publicly funded Human Genome Project.³¹ The sequence data generated from this project are freely available on the Internet. A private company, Celera Genomics, simultaneously conducted its own human sequencing project.³² Human Genome Project scientists plan on completing the sequence of the human genome by 2003.

The sequencing and analysis of the human genome has shed new light on the estimated number of human genes. Human Genome Project and Celera scientists predict the human genome contains about 30,000-40,000 genes.³⁴

Scientists use a technique called positional cloning to identify genes involved in disease. This technique compares the genomes of affected individuals (those with the disease) with family members that are not affected to locate the gene and characterize the mutation(s) that result in the disease.

More than 1,000 genes have been discovered that, when mutated, cause specific diseases.³⁵ The vast majority of these diseases are single gene disorders, also known as Mendelian disorders, in which a mutation in one gene causes a certain disease. With a single gene disorder, it is relatively easier to elucidate the protein function and understand the ramifications of the mutated gene—there is one gene and one protein to focus on. However, single gene disorders are rare, affecting about one percent of the population. Some examples of single gene disorders include sickle cell anemia, cystic fibrosis, achondroplasia (dwarfism), Huntington's disease, and fragile X syndrome.

Most common diseases are complex disorders, in which many genes contribute. The resulting proteins interact in a cascade of events and are influenced by environmental factors, such as diet. Examples include diabetes type II, depression, and heart disease. With complex disorders, it is necessary to sort out the many genetic and environmental contributions, a process that adds layer upon layer of complexity.

Appendix C: Genetic Testing in General

What is a Genetic Test?

The Department of Health and Human Services Secretary’s Advisory Committee on Genetic Testing (SACGT), created in 1998 to “advise the Department of Health and Human Services on the medical, scientific, ethical, legal, and social issues raised by the development of genetic tests,” defines genetic testing as follows (bracketed material added):³⁶

“A genetic test is an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, 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.”

[Karyotype: an individual’s complete set of chromosomes; metabolite: a chemical intermediate in the reactions of metabolism; metabolism: the chemical reactions involved in breaking down nutrient molecules.]

“Tests that are used primarily for other purposes, but that may contribute to diagnosing a genetic disease (e.g., blood smear, certain serum chemistries), would not be covered by this definition.”

Determining the Accuracy of Genetic Tests

As is true with other laboratory tests, a genetic test is only as good as its accuracy and effectiveness. The standard terms used to evaluate these factors are *analytical validity*, *clinical validity*, and *clinical utility*.³⁷

- *Analytical validity* is a term used to describe how well a test detects what it was designed to detect. To be analytically valid, a genetic test must produce a positive result when the relevant mutation is present (called analytical sensitivity), and a negative result when that mutation is absent (called analytical specificity). In other words, a test must be sensitive enough to detect the mutation when it is present, and specific enough to correctly determine when the mutation is absent. Another requirement of analytical validity is the consistency of test results from sample to sample.
- *Clinical validity* indicates the test’s accuracy in identifying or predicting a disease. A genetic test would be clinically valid if it produces a positive test result for an individual that has the disease or is predisposed to it (clinical sensitivity) and a negative test result for an individual without the disease or predisposition (clinical specificity). Included in an assessment of a genetic test’s clinical validity is predictive value—positive predictive value indicates the individual has or will get the disease, and negative predictive value indicates the individual does not have or will not get the disease.
- *Clinical utility* is a measure of how useful a test’s results are for the individual being tested, whether positive or negative. Some of the issues considered in determining the clinical utility of a genetic test include the availability of effective treatments or preventative measures for the disease implicated by the mutation, the penetrance of the mutation, and the psychological effect the test results may have on the individual.

Appendix D: The Uses of Genetic Tests

Genetic testing is used in numerous situations: preimplantation diagnosis, prenatal diagnosis, newborn screening, carrier testing, diagnosis, and predictive testing.³⁸

- **Preimplantation** diagnosis is performed after in vitro fertilization to detect a genetic condition in an embryo before it is implanted.
- **Prenatal diagnosis** is performed on a developing fetus to diagnose a genetic condition.
- **Newborn screening** tests newborns for those genetic diseases that can be effectively treated or prevented with early detection. Each state mandates newborn screening for certain diseases.
- **Carrier testing** indicates whether an individual possesses one copy of a mutated gene for an autosomal recessive disorder. These disorders require two copies of the mutated gene to cause disease, and two carriers have a 25% risk of producing an affected child.
- **Diagnostic** genetic testing is used to diagnose or verify the diagnosis of a disease in an affected individual.
- **Predictive** genetic testing is used to predict the risk of a healthy individual developing a disease, whether or not the individual has a family history of that disease. Since current predictive genetic testing has primarily been developed for rare diseases or rare forms of more common diseases like breast and colon cancer, the testing is only recommendable for those with a family history of such a disease.

Although the number of available genetic tests continues to grow, the diseases for which genetic testing has been developed are primarily rare single gene disorders. There are approximately 529 diseases for which clinical genetic testing is available, and 374 diseases for which research only genetic testing exists (as of January 23, 2002).³⁹ At the end of 1999, those numbers were 361 for clinical and 325 for research only. The number of genetic tests performed each year is increasing. Genetic testing laboratories responding to a 1997 survey indicated that in their own labs, the number of genetic tests performed annually rose from almost 100,000 in 1994 to over 175,000 in 1996.⁴⁰

The rapid pace of genetic testing advances has occurred along with a growing debate on what oversight the development of genetic tests requires. The National Institutes of Health and the Department of Energy established the Task Force on Genetic Testing in 1995 to provide recommendations for the development of safe and effective genetic tests. This task force was one of many initiatives the Human Genome Project instigated to ensure the detailed examination of ethical, legal and social issues surrounding the sequencing of the human genome. The task force's final report led to the creation of the SACGT. Last year the SACGT released its first report, in which it recommended that the Food and Drug Administration review all new genetic tests before they are used for clinical care or public health purposes.⁴¹ Currently, the FDA exercises its oversight authority on those tests developed by manufacturers to be sold as kits to various laboratories, but does not regulate the development of tests by individual laboratories for their own use (which includes offering their on-site testing services clinically). The FDA has chosen not to exercise its oversight authority over these "in-house" tests because their numbers are believed to exceed the agency's current review capabilities.⁴²

Appendix E: The Complexity of Predictive and Carrier Genetic Testing

Predictive Testing

To illustrate the great complexity that can underlie the assessment of whether a predictive genetic test is clinically useful, and to highlight the concerns surrounding predictive testing, some examples of diseases for which this kind of testing is available today are helpful. Although each situation is unique, the examples are broadly ordered on a scale of decreasing utility.

1. *Multiple endocrine neoplasia type 2* is a rare disorder caused by mutations in the *RET* proto-oncogene. It is an autosomal dominant syndrome, which means it only requires one copy of a mutated version of the responsible gene to cause disease. Without intervention, patients with this disorder are highly likely to develop medullary thyroid carcinoma, a type of cancer that can be fatal. Removal of the thyroid gland before cancer develops has been shown to be an effective preventative measure. The *RET* proto-oncogene mutations that cause multiple endocrine neoplasia type 2 have been well characterized, including the establishment of genotype-phenotype correlations, and genetic testing is currently used to identify those patients who will benefit from preventative thyroidectomy. The availability of an effective intervention and data on the penetrance of the various mutations contribute to the test's high clinical utility.⁴³
2. *Huntington's disease* is an adult-onset autosomal dominant disorder characterized by progressive neurological degeneration leading to dementia. The causative mutation in the Huntington's disease gene is a trinucleotide-repeat of cytosine, adenine, and guanine (CAG) that occurs more than 35 times. Generally, the number of CAG repeats inversely relates to the age of onset for the disease—the more repeats a patient has, the sooner that patient will begin to experience symptoms. There is no cure for Huntington's disease, a major limiting factor when determining the clinical utility of genetic testing for this disease. But due to the high penetrance of the genotype and the debilitating nature of the disease, prenatal and predictive genetic testing have been available since 1986 for those at risk (those with Huntington's disease in their families). The accepted standard of care includes pre-test counseling and the availability of post-test counseling.⁴⁴

3. *Hereditary non-polyposis colorectal cancer* (HNPCC) accounts for less than five percent of colon cancers. It is an autosomal dominant disorder caused by an inherited mutation in one of five DNA-mismatch-repair genes whose protein products are involved in repairing mistakes when DNA undergoes replication in a dividing cell. Affected individuals face an 80 percent risk of developing colon cancer in their lifetimes.

Genetic testing is available for at risk members of HNPCC affected families. Current genetic tests can only identify the mutations found in about 60 percent of such families, so only after an individual with colon cancer has tested positive for a known mutation would testing be recommended for that person's family. Only in this situation can a negative result be meaningful—if a person tests negative for the mutation known to be responsible for the HNPCC that has been diagnosed in other family members, that person's risk is reduced significantly. Without the framework of an established mutation within a family, a negative result would be inconclusive, as it cannot distinguish between two possibilities: there is no mutation, or there is a mutation that the test has not been designed to detect.

The benefit of identifying those with the mutated gene within an affected family is the existence of an effective preventative strategy. Screening the colon for tumors during a procedure called a colonoscopy has been found to reduce the risk of developing colon cancer by 56 to 62 percent and can prevent colon cancer deaths, since tumors that are detected early can potentially be treated. The recommended screening interval is once every three years.

Although there is an effective preventative course of action to reduce the risk of colon cancer in HNPCC families, HNPCC mutations also predispose an affected individual to a number of other cancers. This presents an especially difficult situation for women. Although the risk for colon cancer for an individual with an HNPCC mutation is more than 80 percent, calculating the risk for HNPCC affected men only and HNPCC affected women only finds a much higher risk of colon cancer for men. For women, the risk of developing endometrial cancer, a cancer of the lining of the uterus, is actually higher than that of colon cancer: 60 percent compared to 56 percent. There is currently no standard procedure to screen for endometrial cancer—further research to establish the efficacy of various methods is needed. Although it is worthwhile to screen for colon cancer in both men and women, women are left with an additional high cancer risk for which there is no preventative measure, an issue that must be carefully explained with genetic counseling. Those with HNPCC mutations are also at risk for stomach and ovarian cancers (13 percent and 12 percent, respectively), but as these risks are relatively minimal, this information is mainly of use when assessing a patient's symptoms.⁴⁵

4. About 5 percent of *breast cancers* are primarily due to inherited factors. Studies of affected families show an autosomal dominant pattern of inheritance. Two genes have been discovered that when mutated follow this pattern: *BRCA1* and *BRCA2*. Genetic testing is available for mutations in both genes, but the clinical utility of this test is extremely limited. Those women who have mutations in *BRCA1* or *BRCA2* face a lifetime risk of 55 to 85 percent for breast cancer, and a 15 to 65 percent risk for ovarian cancer. The inexact range given for these increased risks highlights the inability to know with certainty if and when breast or ovarian or both cancers will develop. For those who test positively, there is no one standard preventative regimen. Women and their doctors must weigh the pros and cons of whether to manage their risk with increased medical surveillance, try chemoprevention with the drug tamoxifen, or elect to surgically remove breast and/or ovarian tissue before cancer develops. More research is needed on the outcome of each method to establish which if any is the most effective in reducing risk.

Deciding who would benefit from testing involves creating an extensive family pedigree for an individual with a family history of breast cancer, including information on the age affected relatives first developed cancer and age of cancer-related death. Certain features of the pedigree can provide clues that *BRCA1* or *BRCA2* mutations may be responsible for the inheritance pattern in that family.

Even with this information, deciding whether to undergo genetic testing remains difficult. If a woman tests positive for a *BRCA1* or *BRCA2* mutation, she faces another difficult decision: which treatment plan to follow. If a woman tests negative, this could very well be a false negative. In a family in which a mutation has not been established due to the deaths of affected individuals, a member desiring predictive testing would not have the reference needed to understand the results—*BRCA1* and *BRCA2* do not account for all hereditary breast cancers, so a negative result for mutations in these genes does not preclude the existence of a different predisposing gene that has not yet been characterized. These factors make testing for *BRCA1* and *BRCA2* mutations a particularly personal decision for those with a family history of breast cancer, depending on an informed decision-making process that includes an explanation of what the results will mean for the individual by a genetic counselor or a physician with expertise in genetics.⁴⁶

These examples present the current reach of predictive genetic testing—appropriate for family members of affected individuals, but meaningless at best or harmful at worst (if health decisions are based on a genetic test not meant for the individual) for others. Those who can benefit from genetic testing are a small group, as the diseases involved are rare or are rare forms of more common diseases. Whether predictive genetic testing remains a clinical tool for the few or becomes a standard screen for the many is a subject of debate. Dr. Francis Collins, the director of the National Human Genome Research Institute, predicts that the next five to seven years will bring the discoveries of the multiple genes behind many common diseases.⁴⁷ He foresees a revolution in medical care, as predicting genetic risks becomes the focus of an increasingly individualized and prevention-based medical practice. Dr. Neil Holtzman, co-editor of the Task Force on Genetic Testing's final report and a faculty member at the Johns Hopkins Medical Institutions, takes a more skeptical view, maintaining that the very complexity of common diseases greatly reduces the ability to establish the penetrance of genotype on phenotype in these diseases, thereby preventing meaningful predictive genetic risk assessment for common diseases.⁴⁸

Carrier Testing

Although the outcome for predictive testing in a large population remains to be seen, there is a kind of genetic testing that can be appropriate on a population-wide scale: carrier testing. Carrier testing identifies those individuals who have one copy of a mutated gene for a recessive disorder, and if the carrier rate in the population is high enough, an argument can be made to offer screening to the general population. However, the complexity of developing a test that can be meaningful for large numbers of different people is not to be underestimated. The arduous road to population-wide carrier testing for the autosomal recessive disorder cystic fibrosis is a fitting example.⁴⁹

The *CFTR* gene, which when mutated causes cystic fibrosis, produces a protein that sits at a cell's membrane and creates a channel through which chlorine leaves the cell. When the *CFTR* gene is mutated, the protein it makes is deformed, and cannot function properly. Chlorine builds up inside the cell, a situation that negatively affects the whole body but is especially detrimental to the lungs, which become dry and mucous-filled.

Approximately 1 in 25-30 Caucasians are carriers of a cystic fibrosis mutation—they have one functioning copy of the *CFTR* gene, and one mutated copy. Two copies of the mutated gene are needed to cause disease, so these individuals are healthy. But if two carriers have a child, there is a 25 percent chance that the child will inherit each parent's mutated copy of *CFTR*. Often, the first indication of the each parent's carrier status is the birth of an affected child.

The 1989 study that first described the relationship between a mutated copy of *CFTR* and cystic fibrosis fostered anticipation that screening programs might soon be available for those contemplating pregnancy, since the carrier rate is so high. In the end it took 12 years for a workable and ethical model for population-wide cystic fibrosis screening to be developed.

Many complex issues needed to be addressed, including the following. First, the *CFTR* gene has one of the highest known numbers of possible mutations, with over 900 having been discovered thus far. Deciding which mutations to test for would have huge consequences for the efficacy of population-wide screening, as this would define what a positive or negative test result actually means. The fact that the frequency of certain *CFTR* mutations varies between ethnic groups would also be an important consideration. Second, although cystic fibrosis is severe and fatal for many affected individuals, there are those who develop very mild symptoms and some who are asymptomatic. It is not known which mutations will lead to the severest forms of the disease. Third, although there are many treatments for cystic fibrosis, and the prognosis will continue to change as scientific research into new drugs and gene therapies continues, there is currently no cure.

Even with these limitations, the general consensus in the scientific community was that screening should be developed. The challenge was to address the complex nature of cystic fibrosis in order to create a meaningful screening program. To meet this challenge, the National Institutes of Health convened two conferences. The first, a consensus conference held in 1997, recommended that screening for cystic fibrosis be offered to those with a family history of the disease, those with a partner who has the disease, and those planning a pregnancy or currently pregnant. In 1998, the second conference devised implementation strategies for the first conference's recommendations. Thereafter, a steering committee was formed to develop implementation guidelines for doctors and laboratories. The committee established a standard screening panel of 25 mutations, all of which occur at a frequency of $\geq 0.1\%$ in the general population. The guidelines also include provisions on the quality assurance procedures to be followed by laboratories wishing to perform this testing, examples of genetic testing reports that indicate clearly what test results mean and the implications based on the tester's ethnicity, and the vital role of genetic counseling before and after cystic fibrosis testing to ensure that those testing are truly informed about the procedure and the options available depending on the results.

Inappropriate Genetic Testing

Current experiences with genetic testing will be an important guide for future developments in genetic testing. This is not only true for the necessities, such as rigorous research and skillful counseling, but also for the pitfalls that should be avoided. One such pitfall occurred with the initial discovery of a potential genetic link for late-onset Alzheimer's disease, when a biotechnology company rushed to develop a test and bring it to market before enough research had been done.⁵⁰

Alzheimer's disease (AD) is the most frequent cause of dementia during old age. Individuals with AD initially experience a short-term memory deficit that gradually progresses to loss of cognitive ability and an altered personality. Risk factors for the disease include head trauma, exposure to toxins and age. It also has been discovered that a certain version of the *APOE* gene, the $\epsilon 4$ allele, confers an increased risk and an earlier age of onset for the disease, especially in those with two copies of this allele (those who are homozygous for the allele). However, estimates of this risk vary, with the highest reported risk of developing AD by the age of 80 for an individual homozygous for $\epsilon 4$ at 50%. Also, the correlation between *APOE* $\epsilon 4$ and risk of AD is stronger for whites and weaker for African Americans and Hispanics. Half of all Alzheimer's disease patients have no copies of the $\epsilon 4$ allele. All of these factors have led to a broad consensus that *APOE* predictive testing of asymptomatic individuals for AD is unwarranted, as this testing cannot currently lead to a meaningful assessment of risk for AD. Additionally, the use of *APOE* genetic testing alone as a diagnostic tool to confirm AD in a patient exhibiting memory problems is not supported by current research.

Studies showing a link between the *APOE* $\epsilon 4$ allele and AD were first reported in 1993. Although these findings were preliminary, the *APOE* Genotype Report was introduced by Genica Pharmaceuticals in 1994. In 1996, Athena Neurosciences, having acquired Genica, reintroduced the test as the ApoE Genetic Test, to be used as a diagnostic tool for those already suffering dementia.

There is great potential for harm when an "in-house" test is offered before a consensus has been reached on the appropriateness of its use. Without a scientifically supported context within which predictive value and genotype-phenotype correlation have been assessed, a genetic test has little meaning. An *APOE* test will divulge whether an individual has two $\epsilon 4$ alleles, one, or none, but cannot provide sufficient information to clarify the risk of future disease. Marketing a genetic test for *APOE* as an indicator of risk for AD gives the test an aura of legitimacy that is premature. An individual who does not understand the test's low predictive value would do themselves more harm than good by taking the test: a positive result could be equated with a certain future diagnosis of AD, a weighty and unnecessary psychological burden, whereas a negative result could provide the misguided belief that one will never get AD. Anecdotal evidence of clinicians offering AD genetic testing to demanding patients willing to pay for it does exist—it is disturbing to consider what health and lifestyle choices these patients may have made based on the results of this test.

Endnotes

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16. Another part of the HIPAA statute, separate from the part of the statute that led to issuance of the HIPAA privacy regulation, prevents health plans and insurers, in the group market, from refusing to enroll an individual due to that individual's (or a dependent's) genetic information. It also prohibits charging one individual (or family) in a group more than others in the group on the basis of the individual's (or a dependent's) genetic information. This law also prohibits insurers in the individual insurance market from refusing to enroll, for any health-related reason, a subset of individuals who are leaving the group market and meet other prerequisites. More comprehensive non-discrimination legislation pending in Congress (S 318/HR 602; S. 382; S. 1995) would build on these HIPAA protections and further limit health plan and insurer *access* to genetic information as well as *uses* of genetic information by health plans and insurers in medical underwriting. According to the National Conference of State Legislatures (NCSL), laws in 25 states limit insurer access to genetic information, while laws in 33 states strictly prohibit the use of genetic information for risk selection and risk classification purposes. For a list and brief description of these laws, visit www.ncsl.org/programs/health/genetics/ndishlth.htm (accessed 1/18/02).
17. For a list and brief description of these laws, visit www.ncsl.org/programs/health/genetics/ndishlth.htm (accessed 1/18/02).
18. For a list and brief description of these laws, visit www.ncsl.org/programs/health/genetics/prt.htm (accessed 1/18/02).
19. This section of the report focuses on genetic information in the hands of private employers. Federal government workers have special protections as a result of an executive order issued by President William Jefferson Clinton in February 2000. See Questions and Answers: Executive Order 13145 to Prohibit Discrimination in Federal Employment Based on Genetic Information, available at www.eeoc.gov/federal/genetic/qanda.html (accessed 1/18/02).
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28. Last fall, FTC Chairman Timothy J. Muris stated that the FTC plans to abandon pursuit of new online privacy legislation but will increase funds for agency enforcement of existing laws. See “FTC Chairman Announces Aggressive, Pro-Consumer Privacy Agenda,” FTC Press Release, October 4, 2001, available at www.ftc.gov/opa/2001/10/privacy.htm (accessed 2/1/02).
29. The privacy regulation applies to providers of health care. The regulation defines “health care” as including the sale or dispensing of a drug, device or other equipment, or item in accordance with a prescription. 45 CFR § 160.103. “Health care” therefore does not include over-the-counter drugs.
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