New Frontiers In Genetic Testing And Screening
NEW FRONTIERS IN GENETIC TESTING AND SCREENING

We often hear that we are witnessing a “genetic revolution” that will profoundly effect our health care in the near future. One of the first fruits of this revolution is the availability of genetic tests able to detect inherited disorders, and even predispositions to develop many diseases that traditionally have not been viewed as genetic in origin. These developments raise a number of questions deserving our careful attention. What forces are driving the growth in genetic testing technology, and what steps are being taken to direct that growth along paths that will be beneficial for patients and for society? What kinds of tests are envisioned, for what kinds of medical conditions? How will genetic tests change the way medicine is practiced? And, perhaps most important, what moral challenges must we confront as we enter an era of genetic medicine? This report addresses these questions to provide a general overview of developments at the center of an emerging public discussion.

During the 1950s the science of genetics developed techniques making it possible to detect chromosomal abnormalities associated with a range of medical problems including malformation, retardation, infertility, and reproductive failure. Some individuals with potentially devastating heritable conditions could now be identified before overt signs and symptoms of disease appeared, and medical researchers could refine their investigations of the mechanisms involved in the development and treatment of such diseases. Advances in molecular biology, especially the discovery of recombinant DNA techniques during the 1970s, further increased our ability to analyze human hereditary material, and the “resolving power” of genetic tests has increased accordingly. Premised on the hope that genetic research will lead to treatments and preventive strategies for common as well as rare genetic disorders, both the private and public sectors have invested major resources to develop genetic technologies.
With the advent of the Human Genome Project (HGP), the growth in our ability to test for specific genetic conditions is now rapidly accelerating. This project, scheduled for completion by the year 2003, represents an international effort to map and sequence the entire human genome. This is a massive undertaking to determine the precise order of about 3 billion nucleotides strung together to form human DNA. Embedded within that sequence are the approximately 80-100,000 genes found in the nucleus of each of our cells. While the ultimate hope is to understand in detail how genes actually function in human development and physiology, the first practical application is to enable us to identify and locate deviations from the “normal” sequence and to link these with specific malfunctions.

This explosion in knowledge and technique confronts us with a variety of ethical, legal, and social issues which require careful consideration by scientists, health care professionals, and the general public. How genetic information is gathered and recorded, and the uses to which it is ultimately put are matters of great importance for individuals and society. There is a sordid history of eugenics movements, both in the U.S. and abroad, which sought to improve society by eliminating “unfit specimens of humanity.” The fear and mistrust with which many view policies and practices that distinguish between individuals on the basis of hereditary traits becomes understandable in light of such historical episodes. The challenge we face is to avoid such abuses while still permitting the use of genetic knowledge for the pursuit of health and other legitimate social goods.

The ELSI Program of the HGP

In the U.S., the HGP is administered by the National Institutes of Health (NIH) through the National Human Genome Research Institute (NHGRI) and the Department of Energy (DOE). The recognition that knowledge derived from genome studies has broader medical and social implications led to the establishment of a program devoted to the ethical, legal, and social implications (ELSI) of mapping
and sequencing the human genome. Initially, 3 percent of the NHGRI extramural budget was devoted to ELSI projects, but since 1991 this figure has increased to 5 percent. This unique effort to prevent foreseeable problems spawned by the growth of biomedical science represents the largest U.S. investment to date in the analysis of the impact of emerging technologies within their ethical, legal and social context.

During its existence, ELSI has identified four high-priority areas for research: (1) privacy and fairness in the use and interpretation of genetic information; (2) clinical integration of new genetic technologies; (3) issues surrounding genetic research; and (4) public and professional education. A large number of extramural projects addressing these priority areas from a variety of perspectives have been sponsored by the ELSI program, and a wide range of ethical, legal, and social issues raised by the HGP have been articulated. Among the questions with which society must grapple are concerns about the balance of benefits and costs associated with particular genetic tests; the indications for performing genetic tests and the purposes for which they are appropriate; who will provide these services, and what standards will be observed; and who will have access to testing services and to test results.

In addition to funding extramural research, ELSI has established a joint NIH-DOE Working Group to provide overall guidance to the ELSI program and to develop policy options and recommendations. The Working Group in its turn created two task forces, one to examine issues regarding the use of genetic information by health insurers, and the other to explore options for the effective regulation of commercially available genetic tests. Drawing largely on the research base represented by the extramural ELSI projects to date, the task forces have issued their final reports on these topics. These reports contain extended discussions of challenges generated by the dramatic increase in predictive genetic information, and offer clear policy recommendations. Although the ELSI program carries no authority to directly make
public policy, the strategy of forming working groups to address key areas of concern may prove to be an effective way to influence the public officials who do have such authority.\textsuperscript{9}

**Forms of Genetic Testing**

Most genetic tests attempt to detect the presence of genes that are associated with disease or predispose those who inherit the genes to disease. In the case of recessive disorders, we might test for “carriers” of the gene who do not themselves develop the disease, but whose children might be at increased risk. There are also tests that can identify genes which are not correlated with known medical disorders. Such tests can be useful in laboratory research, or to determine the genetic composition of populations, or to identify individuals for legal purposes. Here, however, we will limit discussion to the use of genetic tests within the framework of health care. While some of the issues we raise are common to all forms of genetic testing, others are specific to, or more pronounced with, particular types of testing.

**Carrier Testing** — Carriers are people with one normal and one abnormal copy of a gene. Since one normal gene is present, carriers typically do not exhibit clinical symptoms, although in some circumstances relatively mild symptoms might appear. It is estimated that, on average, each of us is a carrier for 3 to 5 abnormal genes. There are two broad categories of carriers. First, carriers of autosomal recessive disorders, such as cystic fibrosis, sickle-cell anemia, and Tay-Sachs disease, can be either males or females. When two carriers mate there is a 1 in 4 chance that their child will inherit the abnormal gene from both parents and so develop the associated disease. Second, carriers of X-linked (or sex-linked) disorders, such as hemophilia A and Duchenne muscular dystrophy, are females one of whose two X chromosomes contains an abnormal gene. Males have only one X chromosome, which is always inherited from their mothers, so there is a 1 in 2 chance that male children of a carrier will inherit the abnormal gene and develop the disorder.
In the context of clinical genetics, the traditional purpose of carrier testing is to provide prospective parents information about risks to their offspring so they can make informed reproductive decisions. From a public health perspective, the purpose of carrier screening is to avoid the births of children with serious, costly, or untreatable disorders. For either purpose, however, the results of testing might be misleading. For a disease like sickle-cell anemia, which involves a single, well characterized mutation in the gene for hemoglobin, a negative test effectively eliminates any risk of the disease. In contrast, more than 700 mutations of the gene implicated in cystic fibrosis have now been identified, though not all of these mutations actually result in the disease. Approximately 1 in 25 Americans are carriers for cystic fibrosis, and a test for 70 of the most common mutations will identify 90% of carriers in the white population and 97% of carriers in the Ashkenazi Jewish population. However, this test detects considerably fewer of the mutations responsible for cystic fibrosis in African Americans and Asian Americans. Averaging over the whole population of actual cystic fibrosis carriers, then, a negative test has a more than 1 in 10 chance of being a “false negative.”

The primary ethical issues raised by carrier screening include the question of whether it is ever justified to coerce people to have the tests, either through government mandate or by more subtle psychological pressures. Protecting the confidentiality of test results is also important since it is not only prospective parents who have an interest in information about carrier status. Both employers and health insurers might find this information useful to limit the costs of providing health care to dependents. If carrier status itself was viewed as a form of disability, the Americans with Disabilities Act (ADA) might provide some protection against employment or insurance discrimination, but proving that one’s access to health care or employment opportunities has been restricted on the basis of genetic information would be very difficult.
Prenatal and Preimplantation Diagnosis – A couple might suspect they are at high risk for having a child with a genetic disease, perhaps because they already have had an affected child, or because of a family history. In such circumstances they might seek a genetic test to determine whether the disorder is present in their offspring before birth. The information they gain from a positive test result could be used to help them plan ahead for raising a child with special needs. More controversially, it enables them to abort an affected fetus or, if they are using artificial reproductive technologies, to discard gametes or zygotes that would result in a child with a genetic disorder. In a very direct way, then, prenatal and preimplantation genetic testing raises the question of what kinds of infants will be born.\textsuperscript{17}

To differentiate themselves from eugenicists and demonstrate respect for parental autonomy in reproductive decision making, genetic counselors have been guided by an ethic of non-directiveness when disclosing genetic risk information to clients.\textsuperscript{18,19} Now the increasing number of diagnosable disorders is prompting discussion of what limits on autonomy might be appropriate, and whether there might not even be a duty to avoid the birth of children with severe genetic disorders.\textsuperscript{20,21} In addition to raising profound concerns about stigmatization and discrimination against those with heritable disabilities,\textsuperscript{22,23} a wealth of new information will emerge about the genetic bases of benign traits with no connection to disease and disability. Such information will make it possible to use genetic testing to ensure that children will have traits that most commentators think should be irrelevant in an egalitarian society.\textsuperscript{24} Selection of the sex of a child, when there is no reason to suspect the presence of a sex-linked disorder like hemophilia, is only the most obvious example. While there might be some circumstances where sex selection could be justified, most commentators view it as a dangerous practice because of its likely negative social impact on the status of women.
Newborn Screening - Genetic screening of newborns is most common, and least controversial, when it is done to detect conditions that would consistently result in serious harm to the child, but for which early treatment can be initiated to prevent death, mental retardation, or permanent disability. \(^{25}\) Conditions such as phenylketonuria (PKU), hypothyroidism and sickle-cell anemia are familiar targets of routine screening programs. In the case of PKU, which can be controlled by a special diet, virtually all the states mandate routine screening of newborns, though parental refusal might be allowed on religious or other grounds. Unlike PKU testing, which is conducted on virtually all newborns in the U.S., screening programs for sickle-cell have been targeted primarily toward African-Americans. Initially, the focus on this minority population aroused mistrust because of our nation’s long history of racial discrimination. Problems were exacerbated because tests identified infants who were carriers as well as those with a disease producing “double dose” of the gene, and many were misled into believing that these infant carriers would themselves develop sickle-cell anemia. \(^{26,27}\)

Experience with sickle-cell screening programs raises the question whether information about carrier status should be reported, and if so, to whom, when it becomes available as an “artifact” of a test for a recessive disorder. The mandatory nature of some programs leads to questions about the appropriate role of government in providing genetic testing. While some commentators believe mandatory screening can be justified on the basis of the benefits provided to even a relatively small number of affected children, \(^{28}\) others argue that voluntary programs with adequate informed consent procedures are likely to be just as effective as mandatory programs. \(^{29}\) An additional set of problems surrounds the samples collected for newborn screening. Potentially, these samples provide a “bank” of genetic material for virtually all newborns in the U.S. The information in such a genetic bank would have great value for public health initiatives as well as for both epidemiological and laboratory research. But the individuals who
provided the samples might not want this information to be available, or at least to restrict its availability. What uses should be permitted for such samples, and what safeguards should be established to ensure confidentiality? These questions are acquiring a new urgency with the accelerating growth in new possibilities for genetic testing.30

Late-onset Disorders and Susceptibility Testing - Some genetic diseases have no early signs or symptoms or only manifest later in life. A classic example of such a late-onset genetic disease is Huntington disease or chorea, a dominant disorder that typically appears during the fourth decade of life.31 Presymptomatic testing can be most useful in identifying conditions like Huntington disease which are caused by mutations of a single gene with a high degree of “penetrance,” that is, the gene is virtually always expressed regardless of other external influences.32 Knowing whether one has inherited the gene for Huntington disease permits a glimpse of the future which can be invaluable as a person formulates long-term goals and plans, and some who receive positive test results even find that this heightens their sense of living in the present.33 Information about one’s future is not, however, an unqualified good. Until preventive measures or effective treatments are developed to forestall or prolong the time until the onset of symptoms, the information that one will develop a devastating condition like Huntington disease might be viewed more as an added burden than as a benefit.34,35

In contrast to relatively rare single gene disorders with high penetrance, however, many of the late-onset diseases for which genetic tests are becoming available occur much more commonly in the general population, and cannot be predicted with a high degree of certainty. Examples include such familiar disorders as various forms of heart disease, breast cancer, ovarian cancer, colon cancer, and Alzheimer disease.36 For these common disorders, a positive genetic test result cannot establish that the individual tested will develop the disease, but only indicates an increased susceptibility or predisposition for a specific disease. This
might be the case because the disease is multi-factorial, requiring the presence of several genes, or the presence of environmental conditions in combination with the genetic trait being assessed, or because the gene is not fully penetrant so that there is significant variation in the degree to which it is expressed. In any case, susceptibility testing only provides the information that the individual tested has a certain probability of developing the disease, relative to the general population. Such information can still be very useful, especially when other risk factors are known and can be avoided with reasonable effort. But the many uncertainties associated with these tests mean that great care must be exercised in conveying information about test results. In addition, as with other kinds of genetic information, there is deep concern that employers and health insurers will use information about positive test results to limit their own risks at the expense of those who have undergone the tests.

An example of some of the complexities arising with genetic testing for late-onset diseases is provided by our early experience with testing for the BRCA1 gene associated with one form of hereditary breast cancer. Several hundred mutations of the BRCA1 gene have been identified to date, but not all of these increase susceptibility for breast cancer. It is estimated that the proportion of breast cancers in the general population associated with the BRCA1 gene is only 5-7% of those diagnosed before age 40, and only 1-4% of those diagnosed over age 40. Studies of individuals at particularly high risk in light of family histories of breast cancer estimated that for women in this group with BRCA1 mutations, 51-73% will develop breast cancer by age 50, and 82-87% by age 70. Finally, BRCA1 mutations are thought to be present in considerably less than 1% of the U.S. population. Given such statistics, it is clear that relatively few of the women who actually develop breast cancer would have benefited from being tested for BRCA1 mutations. And even for those who are believed to be at high risk, the personal and social
meaning of test results might remain ambiguous. In light of such uncertainties, commentators generally recommend that extensive education and genetic counseling be provided both before and after any tests are conducted for late-onset disorders.42

Clinical Integration of Genetic Testing

Until recently, most clinical genetic services were found in obstetric and pediatric settings, with relatively few specialized clinics for adults affected by late-onset genetic disorders.43 With the knowledge gained from the HGP, genetic testing will be possible for a multitude of disorders affecting people of all ages. While there will be rapid growth in the number of genetic tests available, a smaller percentage of those tests will be sought for their relevance to reproductive decisions. Increasingly, people will confront their doctors wanting to know whether they possess particular genetic traits that will influence their health, and what, if anything, they can do to prevent the onset of diseases to which they are susceptible. The availability of predisposition and presymptomatic testing for disorders that are not evident at birth or in childhood is necessitating the integration of genetics into the primary care setting in our health care delivery system.44

As genetic technologies become more prevalent in health care, key features of the clinical relationship will change. Traditionally, people came to the doctor with a “presenting complaint,”45 and clinical efforts were directed to determining the causes and controlling the symptoms of the patient’s condition. With presymptomatic and susceptibility testing, however, an individual with no present medical complaints can become the focus of attention. An important feature of current genetic medicine is the lack of effective treatment for many diagnosable conditions, the so-called “therapeutic gap.”46 Where this gap between diagnosis and therapy is present, the clinical relationship will take the form of surveillance and watchful waiting for the first signs that a disease process has begun. The people who will have
such an ongoing relationship to the medical world, but without manifest disease, have been referred to as a new class of “unpatients.” This new relationship challenges our everyday notions of health, disease, and the goals of genetic medicine. Should we view those identified by presymptomatic and susceptibility testing as already diseased, even in the absence of any morbidity? Do carriers who are not themselves affected have genetic disorders?

Physicians attempting to provide information and advice to their patients will need to be able to translate complicated statistical relationships into everyday language. And patients will need to familiarize themselves with a variety of concepts from the science of genetics if they are to make informed decisions about being tested. An adequate informed consent process will also have to include discussion of the psychological and social impact of genetic testing, including both the potential for stigmatization and discrimination, and the meaning of test results for the families of patients. A significant effort to educate both health care professionals and the general public about the new realities of genetic medicine must accompany the widespread introduction of genetic testing into the medical mainstream.

The proliferation of genetic tests also raises a variety of more “technical” concerns about how to assure that available tests satisfy high standards of quality. The Task Force on Genetic Testing formed as part of the ELSI program has made specific recommendations regarding methods for validating genetic tests and for assessing the clinical value of the information they provide before new tests are made generally available. The Task Force also addressed the process of research and data collection on which the development of genetic tests depends. Recommendations include providing for external review of research protocols and the pooling of data on the safety and effectiveness of new genetic tests. Finally, suggestions are offered for a system of formal oversight to establish and enforce strict quality assurance standards for laboratories performing genetic tests.
Issues of Privacy and Fairness

The information revealed by genetic tests is directly relevant to persons who are biologically related to the individual who undergoes testing, since “blood relatives” have many genetic traits in common. For example, if a person is discovered to be a carrier of a gene for a recessive condition like cystic fibrosis or sickle-cell anemia, or a gene that increases susceptibility to breast cancer or Alzheimer disease then, barring the unlikely event that this represents a new mutation, at least one of their parents also has this gene, and any siblings of the person tested might also have inherited the gene in question. This raises the question of whether physicians and genetic counselors should disclose genetic test information to relatives who might be at increased risk of an inherited disorder despite the general presumption in favor of maintaining the confidentiality of medical information. Although legal obligations in this regard remain undefined, in 1983 the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research argued that it is ethically permissible to warn a relative about such risks when (1) reasonable efforts to persuade the patient to disclose the information to relatives have failed, (2) there is a high probability of serious harm to an identifiable family member, (3) disclosure will help to avert harm to the relative, and (4) only the minimum information needed to effectively warn the relative is disclosed.

While the potential for family conflicts might explain the hesitancy of some people to inform relatives about genetic test results, disclosure to other third parties is problematic because issues of privacy and fairness are deeply intertwined. There is a long history of stigmatization and discrimination against those who are viewed as “abnormal.” The availability of detailed information about genetic characteristics means that information about individuals’ genomes might become the basis for differential treatment that imposes unjustified burdens or places limits on the opportunities open to those now considered genetically abnormal.
Fears of new forms of genetic discrimination have therefore been a prominent part of the public debates fostered by the HGP. Much confusion has resulted from a tendency to cast discussion within a framework that has been called “genetic essentialism” or “genetic determinism” according to which a person’s innermost nature and ultimate destiny are thought to be fixed by their genes.\textsuperscript{56,57} Fortunately, the idea that “we are our genes” is coming to be recognized as an oversimplification which should not guide policy making, and media portrayals of the new genetics are increasingly emphasizing the partial nature of the explanations provided by genetics for complex human traits and behaviors.\textsuperscript{58}

Even if extreme forms of genetic determinism are on the wane in our society, however, the predictive knowledge afforded by genetic testing could be used by employers and insurers to discriminate against those who are at increased risk of disease. It is this possibility that has generated the most concern among commentators addressing the need to protect the privacy of genetic information. In the employment setting, genetic discrimination might take place in the hiring process or in providing compensation for injuries. If an individual with a particular genetic trait is more likely to develop a disease when exposed to certain workplace environments, employment or advancement might be denied. The Americans with Disabilities Act of 1990 (ADA), which prohibits discrimination on the basis of disability, might provide some protection if those with the genotypes in question are viewed as disabled. But the ADA does not prevent employers from making medical examinations, including genetic tests, a precondition of employment. The ADA thus remains an incomplete and untested mechanism for preventing genetic discrimination in employment.\textsuperscript{59}

The possible use of genetic information to discriminate in health insurance is due largely to the fact that in the American health care system, the cost of insurance, and so the ability to secure access to coverage, is dependent on an individual’s risk of disease. Insurers routinely rely on information about such risks to determine who they will insure, and at what price, and policies
are written to exclude coverage for “preexisting conditions.” One result of this system of financing is that those with the greatest need may have the greatest difficulty in obtaining coverage. As more information about genetic risks becomes available, the problems with this system are likely to be exacerbated. More people will encounter difficulties in securing affordable health insurance for themselves and their families, and insurers will attempt to treat genetic susceptibilities to disease as preexisting conditions in order to deny coverage when symptoms eventually do appear.  

In its final report, issued in 1993, the ELSI Task Force on Genetic Information and Insurance concluded that information about past, present, or future health status should not be used to deny health care coverage to anyone. It argued that the most important step that could be taken toward preventing genetic discrimination in health insurance would be to reform the U.S. health care system to ensure universal access to and participation in a program of basic health care services. While universal access would provide protection against discrimination, universal participation was viewed as necessary to guard against the possibility of “adverse selection” in which individuals choose not to purchase insurance until they already are ill or anticipate a future need for health care. The Task Force also concluded that from both a practical and moral standpoint it is untenable to distinguish between genetic and nongenetic diseases in order to determine eligibility for health care coverage. Recognizing that the envisioned broad reform of the U.S. health care system would require extended public debate, the Task Force recommended that in the interim health insurers should consider a moratorium on the use of information from genetic tests in underwriting.

In the aftermath of the ELSI Task Force report, there have been a number of proposals and initiatives for preventing insurance discrimination on the basis of genetic information. A growing number of states have passed laws to restrict the use of genetic information in health insurance, but the patchwork of state
legislative approaches does not provide a comprehensive solution to the problem. The primary limitation is due to the fact that employer-sponsored health plans that are self-funded are exempted from state insurance laws by the Employee Retirement Income Security Act (ERISA). Since nearly half of all Americans are covered by such plans, these state initiatives leave them without protection against genetic discrimination in health insurance. In addition, most state laws focus narrowly on information from genetic tests, neglecting the information about genetic risks that can be gleaned from family histories, physical examinations or medical records.

In 1996, Congress enacted the Health Insurance Portability and Accountability Act (HIPAA) to expand access to health insurance for Americans and prohibit the use of genetic information to limit or deny coverage for members of a group plan, including both self-insured plans and plans purchased from an insurer. HIPAA specifically prohibits using genetic information to exclude an asymptomatic individual under a preexisting condition clause, or to determine eligibility for enrollment. The Act also employs a broad definition of genetic information. The protections provided by HIPAA are limited, however, since it does not require an employer to provide a health plan or, if an employer does provide a plan, to include coverage for any particular disorders as long as all the members of the plan are treated similarly. Finally, HIPAA does not limit an insurer’s access to genetic information or restrict the release of such information to others who might use it to stigmatize and discriminate against people with particular genetic traits.

An alternative to restricting the use of genetic information by health insurers is suggested by the Genetic Privacy Act (GPA) which was drafted to provide a model for federal or state legislation or to be used to develop professional guidelines. This model act would provide protection primarily by requiring an individual’s informed authorization for the collection, analysis and disclosure of genetic information. The GPA identifies several
elements that must be included in the authorization, such as a specification of the parties involved, the uses for which authorization is given, and the individual’s rights. It has some of the same limitations as state initiatives, however, since it too focuses narrowly on information derived from molecular analysis of an individual’s DNA, neglecting other sources from which information about genetic risks can be constructed.

The problems of genetic discrimination in health insurance are thus deeply rooted in our present health care system and might, as the ELSI Task Force concluded, only be resolved by broad reforms that assure basic health care coverage for all. The difficulties of defining genetic information and determining what constitutes legitimate access and fair treatment have only begun to be addressed, and the rapid growth of genetic testing will surely present new challenges to our values and our institutions. As scientists and entrepreneurs “push the envelope” of what is technologically possible in genetic medicine, we must continue to assess the impact of these technologies on patients and families who utilize them, or are denied them, while pursuing their personal health care goals.
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