FROM BIRTH TO DEATH AND BENCH TO CLINIC

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CHAPTER 16

Genetic Testing and Screening

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genetic testing and screening

by Nancy Press

Framing the Issue

Before the late 1960s, patients and their families were most likely to experience the world of genetics in the context of rare, single-gene disorders and in the specialty clinic of a medical geneticist—a physician with additional training in genetics. Parents of a child who was not developing normally or had some unusual physical anomaly could be sent for a genetics consultation when no more common explanation could be found. Often just being able to have a name to put with their child's problem ended a protracted and painful diagnostic odyssey. If the mechanism of inheritance was understood, parents could be told what their risks were for having another child with the same condition and could decide whether to risk another pregnancy. Rarely could significant treatment or cure be offered.

The landscape of genetic testing changed dramatically in the early 1970s as several major developments interacted with one another. The earliest of these was the discovery of the chromosomal basis for Down syndrome—one of the most common causes of mental retardation—and the subsequent finding that chromosomes could be examined in amniotic fluid extracted from a pregnant woman's uterus in a medical procedure called amniocentesis. Today, any fetal anomaly whose genetic basis is known can be detected from a sample of amniotic fluid. Diseases commonly screened for include Tay-Sachs disease, sickle cell disease, thalassemia, cystic fibrosis, neural tube defects, and a variety of chromosomal disorders.

In the past decade, genetic testing has expanded significantly. The first step came in 1990, when Mary-Claire King, a genetic epidemiologist, demonstrated the existence of a form of breast cancer that was strongly hereditary. Mutations in genes, identified and named BRCA1 and BRCA2, significantly increase the risk of breast cancer. Similar predisposing genes were later found for a form of colorectal cancer. Mutations that cause a small percentage of what are usually early-onset forms of common diseases have been found for a variety of disorders, including Alzheimer disease and other forms of dementia, as well as certain types of cardiovascular disease.

Genetic testing raises a variety of ethical issues. Prenatal testing was inevitably tied to the debate over abortion because Down syndrome and other chromosomal conditions that the tests screen for are not treatable (see box, "Prenatal Genetic Testing and Abortion"). Whereas diagnosis of and prognosis about the condition affecting a child could bring closure and some hints

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HIGHLIGHTS

- Genetic testing and screening came into wide use with prenatal tests—amniocentesis and alpha fetoprotein testing—for Down syndrome, neural tube defects, and other disorders.
- Since their inception in the 1970s, prenatal tests have been linked with abortion controversy because women who receive positive test results often terminate pregnancies.
- A longstanding concern about genetic testing is that people at increased risk for a serious condition could face discrimination, which prompted passage of the Genetic Information Nondiscrimination Act in 2008.
- Government does not currently regulate direct-to-consumer genome tests, which claim to offer information about a person's genetic risk for disease, as well as nonmedical information, such as ancestry or paternity.
- The accuracy of these tests is in question, and their results can be misunderstood by the consumer. They also raise broader societal concerns—for example, whether the results are admissible in court.

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about symptom management, what was the purpose of undergoing amniocentesis to learn this information before your baby was born? The most obvious answer—so that the pregnancy could be terminated—was neither socially comfortable nor, in 1969, legally possible. The discourse of genetic counseling quickly and firmly came to be centered on the value of information both as an end in itself and, in some cases, as a possible guide for future reproductive planning.

Concerns about genetic tests for cancer and other illnesses include a lack of effective preventive measures or treatments for some conditions, greatly increased anxiety from a positive result, false reassurance from a negative result, and the potential bias against individuals found to have genetic susceptibility to serious conditions. This last concern has led to the passage of many state laws against genetic discrimination, as well as to the passage in 2008 of the Genetic Information Nondiscrimination Act (GINA), a federal law that prohibits discrimination—by health insurers and employers, for instance—on the basis of genetic information. However, there is no government oversight of the latest entrants into genetic testing: commercial tests sold directly to consumers. Some of these tests provide medical information, while others aim to identify ancestry, establish paternity, or even link an individual to a crime. Ethical and legal questions include:

- How good is the scientific data behind the tests being offered? What can consumers do with the information?
- Is it legal for medical information to be provided over the Internet or by mail, without a medical professional involved?
- Are genetic tests used for paternity or forensic purposes admissible in court?
- Is genetic information about ancestry misleading? Can it harm an individual's sense of self?

Benefits and Limitations of Genetic Testing

It was hoped that the discovery of genetic mutations associated with particular disorders would rapidly lead to better understanding of and better treatments for them. Although research is constantly increasing our understanding of how genes interact with each other and with the environment to cause disease, at the present time, the hopes for a direct connection between genetic testing and disease prevention and cure have not yet borne fruit.

Gene therapy or drugs targeted specifically at mutation carriers do not yet exist. Thus, the benefits of genetic testing depend on the efficacy of standard screening, prevention, and treatments for the condition in question. An individual found through a genetic test to have a substantially increased risk of disease can, for example, take advantage of these techniques at a younger age than is recommended for the general population, thereby increasing the chance of finding the disease when it is still treatable.

So far, the benefits of genetic testing in preventing or managing particular diseases have been mixed. There is a powerful benefit from genetic testing for some hereditary forms of colon cancer. A positive genetic test result can actually prevent cancer by leading people to have early colonoscopy screening to find and remove precancerous polyps. The benefits of breast cancer genetic testing—which has been the object of particularly strong interest—are less impressive precisely because less is known about the natural history of the disease, and fewer effective methods of prevention exist. In addition, breast cancer screening tests have limitations, such as the inability to detect the disease in a

Prenatal Genetic Testing and Abortion

It is extremely difficult to get good statistics on the number of pregnancies that are terminated following a positive prenatal diagnostic result. However, the paucity of data is in keeping with the continued discomfort with, and perhaps even increasing debate about the morality of, abortion in the United States. Thus, the goals of prenatal testing—presented in patient education materials, doctors' offices, and even in the professional literature–emphasize information and reassurance, with pregnancy termination mentioned only in the context of "reproductive choice."

The limited available data suggest that rates of termination vary by genetic condition as well as the mother's background. The rate of termination is around 85% for Down syndrome and lower for less severe conditions. Hispanic women are the least likely of all women to have abortions following prenatal testing. The California State Genetic Disease Branch, which keeps the best records on pregnancies diagnosed with a severe neural tube defect, suggest a large range, from less than 20% for Hispanics to more than 90% for all women beginning prenatal care in the first trimester of pregnancy.

Milestones in Prenatal Testing

While amniocentesis is perhaps the best known prenatal test, the test which truly revolutionized prenatal diagnosis was **maternal serum alpha fetoprotein screening (MSAFP)**. This test, which uses a sample of blood from the pregnant woman, became the first screening test offered to all pregnant women, regardless of their risk of having a baby with Down syndrome or neural tube defects, serious malformations of the brain and spine. Women with positive test results were then referred for more testing, including amniocententis. The accuracy of the test, now called "triple screen," has improved over the years.

Prenatal screening and testing has become a routine aspect of pregnancy, presenting couples with new sorts of information and decisions. Many feel that it has, in fact, deeply changed the experience of pregnancy for couples.

precancerous stage. Data indicate that breast MRI may be more effective than mammography for early detection of breast cancer in women at high risk. But the most effective disease prevention option—prophylactic mastectomy—appears to be unacceptable to the majority of women at risk, and perhaps also to their physicians.

In light of the so far disappointing results of genetic susceptibility testing, a great deal of interest has turned to pharmacogenomics, the study of how variations in the human genome affect the response to medications. The promise of pharmacogenomics is the prospect of tailoring existing drug regimens to individual patients in ways that will improve effectiveness, reduce adverse side effects, and provide more cost-effective care (see Chapter 29, "Personalized Medicine").

Direct-to-Consumer Genetic Testing

There has been an explosive growth of genetic testing that bypasses health care providers through direct-to-consumer (DTC) marketing. DTC genetic testing has been fueled by the growth of the Internet, the plummeting costs of genome sequencing, and a lack of government regulation. DTC genetic testing can be roughly divided into nonmedical and medical services.

Nonmedical tests. Two types of services dominate the nonmedical category: ancestry testing and "private eye" testing. Ancestry testing builds on the longstanding interest in genealogy. For fees of about $100 to $400, you can send in a specimen via a cheek swab kit and receive results about your heritage. Some scientists criticize these tests for using technology that is flawed, both conceptually and methodologically. For example, one test uses markers in individuals from the Middle East or India to indicate Native American ancestry, even though there is no sound historical or archeological data on migration patterns to support this connection. Broader societal issues about ancestry testing include the concern that it may revive a belief in the scientifically contested concept of biological race. In addition, there are the questions of whether what you discover about yourself from genetic testing will overwhelm your own sense of who you thought you were, and whether this prospect makes DNA-based ancestry testing more pernicious than other approaches to genealogy.

The other major type of nonmedical DTC testing might be called "private eye" testing, of which the most common service is paternity testing. Fees range from under $100 to over $500. Many of the sites devoted solely to these detective services also offer a variety of so-called infidelity tests, in which a collected sample is compared with a reference sample to see if it is from the same person. One might think of this as the "lipstick on your collar" test.

There is a disturbingly surreptitious aspect to the private eye tests, since the person whose DNA sample is tested may not even be aware that a sample has been taken. The testing services, in fact, suggest sources of DNA that are relatively easy to obtain without the subject's knowledge, such as licked envelopes, toothbrushes, or even semen or blood-stained clothing. Again, there is a question of whether the use of DNA samples makes these tests more socially destructive than simply hiring a private detective to track someone without his or her knowledge. The invasion of privacy experienced may be far deeper with genetic testing.

Medical tests. By far the most common use of DTC genetic testing—and that which has caused the greatest concern—is for medical information. Companies that provide such testing offer a broad range of services, such as predicting adverse reactions to specific medications, estimating susceptibility to various complex diseases, and diagnosing predominantly genetic disorders.

In the case of drug reactions, tests examine individuals' genetic markers supposedly linked to adverse effects for hundreds of medications. However, there is not a single such test that is con-

sidered standard of clinical care or has even been shown to have health outcome benefit.

With genetic tests that estimate susceptibility to common, complex diseases such as type 2 diabetes, mutations are neither necessary nor sufficient to predict disease occurrence. The hope is that knowledge of an increased risk will lead to increased surveillance or provide motivation for individuals to reduce their risk by changing their diet and exercise patterns. However, research has not supported the view that genetic test information is a motivator of behavioral change.

Direct-to-consumer genetic tests that have the potential to diagnose a condition (an example is alpha-1 antitrypsin deficiency, which raises the risk of some lung diseases) are on shakier ground, since government regulations prohibit diagnoses from anyone other than a medical professional. Companies that market such tests often get around this constraint by stating that a positive result must be confirmed by a health care provider. However, less cautious statements can be found on some company Web sites about the reassurance of a negative test result. Such reassurance is worrisome because negative results rarely mean that there is no risk of developing a disease. But individuals may delay doctor visits or avoid routine screening because of the mistaken belief that they will remain disease-free.

While some DTC testing services are specialized, others offer a gamut of medical and nonmedical information, as well as a cross between the two, such as "nutrigenomics" tests that promise to individualize a diet and nutrition program based on the analysis of genetic markers. There is no real science to support these claims, but they are probably no more—or less—harmful than other widely marketed dietary schemes.

"Cadillac" genome testing. Some DTC testing companies seek return business by offering a subscription service that allows subscribers to access new research findings on a continual basis. The "Cadillac" versions of this are 23andme (www.23andme.com) and deCODEme (www.decodeme.com), which, for just under $1,000, will sequence your entire genome and provide a report that lets you compare yourself with others in terms of height, intelligence, the ability to avoid decisional errors, and many other traits. You can also discover your risk for a variety of conditions and traits such as addictions, as well as genetic factoids like earwax type and sensitivity to the

RESOURCES

Web sites

- www.dnapolicy.org – the Genetics and Public Policy Center. Includes news and events, issue briefs, polls and social science research, and publications.
- www.geneticalliance.org – the Genetic Alliance. Includes resources and publications on policy issues, Wiki informational tools, podcasts, and news.
- www.gene-watch.org – the Council for Responsible Genetics. Includes reports and issue briefs on the Council's Programs, a bookstore, and the magazine *GeneWatch*.
- www.geneticsandsociety.org – the Center for Genetics and Society. Includes a newsletter, publications, and a blog.

Recent news

- Andrew Pollack, "California Licenses Two Companies to Offer Gene Services," *New York Times*, August 20, 2008.
- Amy Harmon, "Congress Passes Bill to Bar Bias Based on Genes," *New York Times*, May 2, 2008.
- Kenneth Offit and Harry Ostrer, "People Need Protection from Unreliable Genetic Tests," *Washington Post*, May 27, 2008.
- Rick Weiss, "Genetic Testing Gets Personal," *Washington Post*, March 25, 2008.
- Melissa Healy, "Genetic-Testing Consumers Have Tools But Little Guidance," *Los Angeles Times*, March 24, 2008.

Further reading

- Mary Ann Baily and Thomas H. Murray, "Ethics, Evidence, and Cost in Newborn Screening," *Hastings Center Report*, May-June 2008.
- Helen Pearson, "Genetic Testing for Everyone," *Nature*, May 28, 2008.
- Jeanne Lenzer, "Direct to Consumer Genetic Testing," *British Medical Journal*, April 21, 2008.
- Deborah A. Bolnick et al., "The Science and Business of Genetic Ancestry Testing," *Science*, October 19, 2007.
- Michael J. Hall and Olufunmilayo I. Olopade, "Disparities in Genetic Testing: Thinking Outside the BRCA Box," *Journal of Clinical Oncology*, May 10, 2006.
- Maurie Markman, "Advertising Genetic Testing," *Hastings Center Report*, November-December 2002.
- Sara Chandros Hull and Kiran Prasad, "Reading Between The Lines: Direct-To-Consumer Advertising of Genetic Testing," *Hastings Center Report*, May-June 2001.

See relevant legislation in appendix.

See online-only campaign appendix at www.thehastingscenter.org/briefingbook

smell of sweat. The 23andme Web site is meticulous in stating the level of evidence on which each result is based. Whether individuals can titrate their own level of belief based on the site's evidence levels is an open question.

Promise and Perils of Genetic Testing

The entire enterprise of DTC genetic testing, especially medical testing, raises multiple concerns:

- People may order these tests without realizing their serious personal and family implications.
- Test results presented via mail may be misunderstood.
- Individuals might change their own drug dosages based on adverse drug effects testing reports.
- The very existence of DTC genetic testing offered on the Internet might increase a deterministic view that there is a "gene for" complex disease risks or behavioral traits just at a time when genome science is becoming most aware of the exquisite complexity of gene-gene and gene-environment interactions in any health or disease outcome.

In all, genetic testing has moved with startling rapidity in the past half century from the obscure province of a small medical specialty dealing with extremely rare conditions to center stage in medicine and in the public imagination. Nevertheless, the promise of genetics has so far outstripped actual benefit, while concerns about societal risk have probably also outstripped actual harms. Whether the attention and financial investment in genetics will ultimately bear fruit is an open question.