Genetics in Medicine Having Widespread Impact

When David Botstein of Stanford University was choosing a career several years ago, he ignored pressure from his parents to become a doctor and instead pursued what was then considered an esoteric field — genetics. "I never intended to make a contribution to medicine," he said.

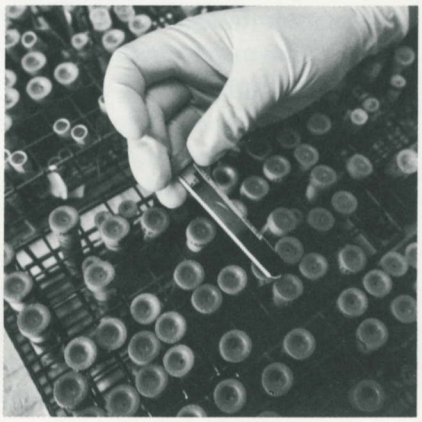
Now well known for his work on mapping the human genome, Botstein was one of many speakers at the Institute of Medicine's annual symposium last October that paid tribute to the successful marriage between genetics and medicine in recent years.

At the "Genetic Revolution in Medicine" symposium, some speakers explored how the infiltration of genetics into mainstream medicine will dramatically change prevention, diagnosis, or treatment of several disorders. These disorders include those to which people succumb as adults, such as cancer, in addition to those that people are born with, such as cystic fibrosis. Other speakers addressed some of the thorny ethical, social, or policy issues, including job and health insurance discrimination tied to genetic screening and the emotional distress such testing can cause if it reveals a person is predisposed to contract an incurable disorder.

The recent advances in genetics, said New York University School of Medicine's Rochelle Hirschhorn, "most of us did not envision as possible for at least another several decades, and so they challenge our ability to develop solutions to the many societal issues they raise."

Pinning Down Disease Genes

In recent years, researchers have pinpointed the genetic causes of more than 20 diseases, including Duchenne's muscular dystrophy and retinoblastoma, an eye cancer. But genes yet to be discovered are thought to be major players in many more disorders. One speaker cited a study that concluded half of all Canadians will develop a disease in their lifetime with a genetic component.



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Because genes have such a powerful influence in making people susceptible to or actually causing various disorders, the government launched the Human Genome Project in 1991. By funding researchers throughout the country, the Genome Project aims to map the location of as many as 100,000 genes within human chromosomes and to uncover the exact molecular structure of these genes. Researchers can then use this information to develop prevention strategies

— including prenatal screening — and more effective tests and treatments for those disorders with a genetic component.

The Genome Project has already completed its initial goal of constructing a rough map that pinpoints the approximate locations of thousands of genes at regular although somewhat wide intervals throughout each chromosome. This map is already useful for medical sleuths hunting for the genetic causes of various diseases, said Francis Collins, director of the Human Genome Project. He noted that the resolution of the map is rapidly being sharpened as research reveals more genes and their locations.

Over the next five years, the Genome Project plans to link the genes on its rough map to more precise biochemical markers on the DNA strands that comprise chromosomes. The exact molecular structure of those DNA strands will be worked out by the end of the decade, Collins predicted.

Prenatal Screening

In the meantime, medical practitioners are already making use of the information gleaned from human genetic research. An understanding of the genetic causes of the severe form of anemia known as beta thalassemia, for example, led to near eradication of the deadly disease on the Italian island of Sardinia. A prenatal screening program for the disorder begun in 1975 fostered a twenty-fold reduction in the emergence of the disease in newborns on the island by 1992. The same dramatic drop in the incidence of Tay-Sachs disease, a fatal neurological disorder, occurred in the Baltimore area after the discovery of its genetic cause and the implementation of a prenatal screening program for the Tay-Sachs gene.

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Genetic testing can also reveal a likelihood of developing certain diseases as an adult. Such testing can uncover, for example, whether people have the defective gene that causes the degenerative nervous system disorder — known as Huntington's chorea — that plagued folk singer Woody Guthrie. On the horizon are genetic tests to indicate whether people have the faulty genes that boost their risk of developing early-onset breast cancer, or some colon or rectal cancers. "These kinds of discoveries are shifting medicine from a discipline where we treat disease that is already far advanced," said Collins, "to a situation where we identify individual risks and try to alter lifestyle or medical surveillance in order to keep that individual from becoming ill in the first place."

The deciphering of the genetics of these disorders should not only foster genetic screening tests, but eventually also lead to better treatments. Unfortunately, as Collins pointed out, most diseases will initially be predictable but not curable. Noting the distress that positive tests for deadly or degenerative diseases can cause, he aptly quoted Sophocles: "It is but sorrow to be wise when wisdom profits not."

Gene Therapy

For some disorders such as cystic fibrosis, however, new treatments are quickly following on the heels of genetic tests. The hallmark of cystic fibrosis is a buildup of mucus in the lungs caused by a defective gene that disrupts the flow of molecules across the membranes of cells that line the body's airways. This condition fosters chronic lung infections that often cause patients to die before reaching their 30th birthday.

The cystic fibrosis gene was discovered in 1989. In 1993, researchers began experimentally treating cystic fibrosis patients with a genetically altered cold virus known for ferrying its genes into the cells it infects. Researchers slipped the normal cystic fibrosis gene into the genetic material

Social Guidelines for Genetic Testing

The expanding technology for detecting genetic diseases and conditions raises many ethical, legal, and social issues. Not enough effective treatments are available nor safeguards in place to prevent the misuse of the information these tests would reveal. The possibility of developing a disease later in life could affect an individual's employment opportunities and health insurance.

An Institute of Medicine committee studied advances in genetic medicine and their significance to the individual and to society. It emphasized caution in using genetic testing. Four ethical and legal principles — autonomy, confidentiality, privacy, and equity — should anchor efforts to determine the level of control people will have over uses of genetic testing and information.

The committee recommended that Congress draft laws to protect people from discrimination in insurance and employment, and it urged federal agencies to monitor quality control in laboratories. Although the committee said it would prefer all screening be voluntary, it noted that if a state requires newborn screening for a specific condition, the state should do so only if strong evidence exists that a newborn would benefit from effective treatment.

Genes, often in concert with environmental factors, are being linked to the cause of many common adult diseases, including hypertension, certain cancers, and heart disease. The committee's guidelines on predictive testing stressed the importance of conducting tests for those conditions that are preventable and treatable. Children should be tested only for disorders where effective treatments or preventive measures can be applied early in life.

The committee also advised fully informing pregnant women about the risks and benefits of prenatal testing procedures as well as the nature and variability of the fetal disorders they would disclose. And it urged couples in high-risk populations to consider carrier screening to detect genes that might cause disease in their future offspring.

— Barbara Rice

Assessing Genetic Risks: Implications for Health and Social Policy. Committee on Assessing Genetic Risks, Division of Health Sciences Policy, Institute of Medicine (1993, 356 pp.; ISBN 0-309-04798-6; available from National Academy Press, tel. 1-800-624-6242; $34.95 plus $4.00 shipping for single copies).

of this cold virus, which was inactivated so it could not cause disease. They then injected the modified virus into patients' lungs. The goal was to provide lung cells with a functional cystic fibrosis gene, and thereby prevent the deadly buildup of mucus.

Three patients have been treated with this experimental therapy. One of the patients developed a lung inflammation. The other two showed no adverse reactions to the therapy.

Several other patients had the virus with the normal cystic fibrosis gene sprayed into the nose — an extension of the lung's airway. Follow-up studies show that the gene was taken up and the cystic fibrosis defect corrected, at least temporarily, in the cells lining the nasal passages.

"We have a combination of safety data in the lung and efficacy data in the nose that really are quite promising," said James Wilson of the University of Pennsylvania School of Medicine. Wilson conducted one of the clinical trials of the pioneering gene therapy.

Other treatments for genetic disorders aim to replace, alter, or mimic the protein gene products that are missing or defective, rather than provide the genes themselves. Bert Volgelstein of Johns Hopkins University School of Medicine has identified four genes that, when faulty, can together cause colon or rectal cancer. Test tube studies reveal that restoring the function of just one of those genes, however, is sufficient to stop cancer growth. One feasible treatment might be, consequently, to give cancer patients a drug that converts the faulty product of that key gene into a functioning one, Volgelstein suggested.

Social Dilemmas

Lurking behind each medical advance fostered by genetic findings, however, often is a social dilemma posed by how those findings might be put to use. As Margery Shaw of the University of Texas Health Science Center in Houston projected, genetic screening for several different disorders will someday become ubiquitous, the results of which will be keyed into a computerized database system. "This will make it difficult if not impossible to keep our genes secret," she said.

With such genetic knowledge in hand, employers and insurance companies can discriminate against people likely to develop costly debilitating or deadly disorders. Such discrimination surfaced when mandatory screening for sickle cell anemia was instituted by several states in the 1970s. Some people were denied jobs or had their health insurance rates raised when testing revealed they were carriers of the sickle cell gene, even though they did not have the anemia.

Incidents like this prompted an Institute of Medicine committee to issue guidelines for genetic screening (see box). Among the committee's recommendations was more extensive education and counseling of people receiving genetic testing.

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Such education and counseling usually falls on the shoulders of genetic counselors, who also arrange the necessary follow-up services. These services include scheduling abortions for those who decide against carrying to term a fetus known to have a severe genetic defect, or developing a medical and social support network for those who decide to keep the baby.

Despite its growing importance in the medical arena, genetic counseling is not presently reimbursed by Blue Cross and Blue Shield, and 17 states each have three or fewer genetic counselors. "We must leave our ivory towers," said conference speaker Betsy Gettig, president of the National Society of Genetic Counselors, "and take [genetic counseling] services to underserved populations through public health agencies."

One of the last speakers made a plea that the role of genetic services in medicine be recognized and incorporated into any new national health care plan that is adopted. "There's a need for policy-makers to think genetic," said Jessica Davis of Cornell University Medical College. There currently is no mention of genetics in Clinton's health care plan, she said, adding "genetics would fit in nicely if it were allowed to join the dance."

Genetics has certainly already entered the dance in medicine, most speakers concurred. Summed up Stuart Orkin of Harvard Medical School: "The impact on treatment and prevention is really here now." Looking ahead, Davis added "the future seems very bright, very exciting."

— *Margie Patlak*

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