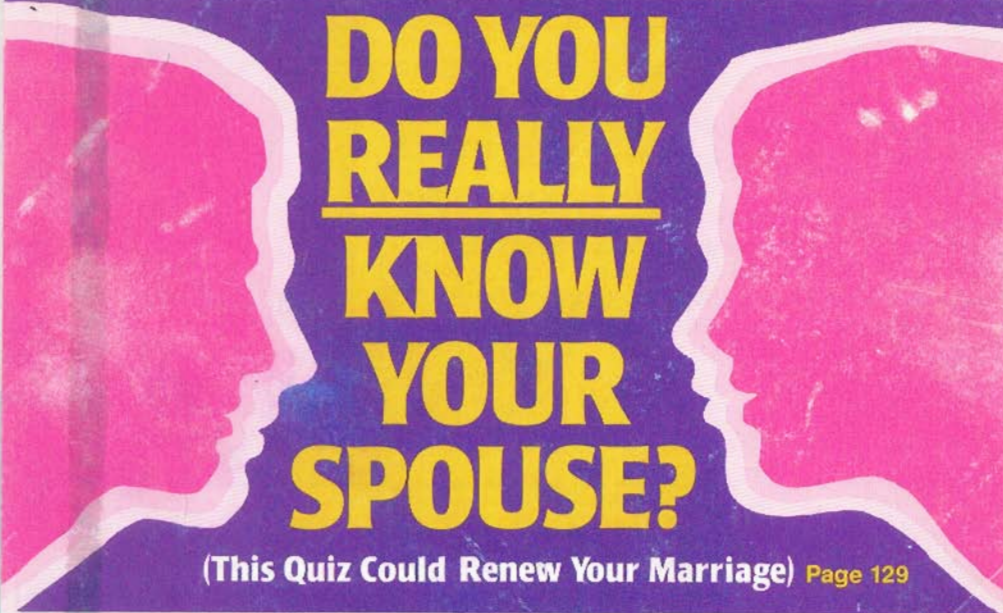


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GENES THAT PREDICT DISEASE

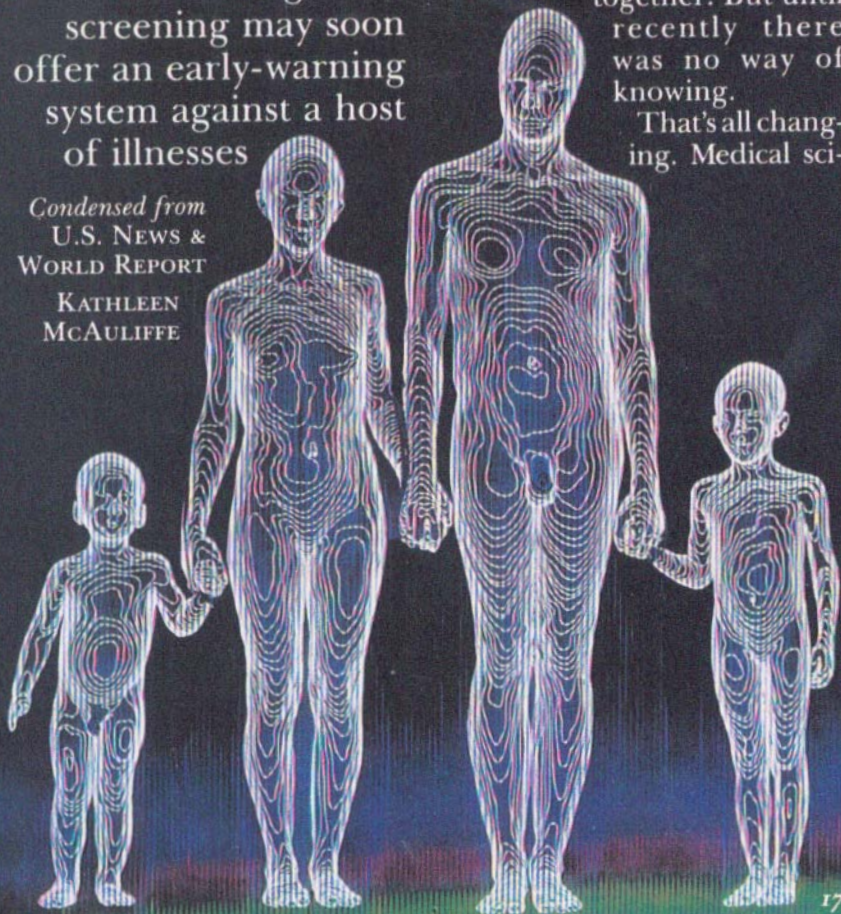
Precise genetic screening may soon offer an early-warning system against a host of illnesses

Condensed from
U.S. NEWS &
WORLD REPORT

KATHLEEN
MCAULIFFE

WHY DO some smokers get lung cancer while others puff away happily? Why does one man die of a heart attack in his early 40s while his brother gorges on marbled steaks to no ill effect? If doctors knew the answers, they could catch illnesses early, perhaps even prevent them altogether. But until recently there was no way of knowing.

That's all changing. Medical sci-



entists are rapidly zeroing in on the genes that influence, and occasionally dictate, an individual's health even into old age. In just the last few years, researchers have identified patterns of genes that raise a person's susceptibility to heart attack, emphysema, insulin-dependent diabetes, multiple sclerosis and certain cancers. Since January, scientists have found genes associated with Alzheimer's disease, cleft palate and two types of manic depression. In May, British researchers identified a pattern of inherited cell proteins that could explain why only some people exposed to the AIDS virus get the disease. Soon after, a gene linked to schizophrenia came to light.

Collaborative Research, a company in Bedford, Mass., that leads in developing genetic tests, claims to be less than one year away from a complete map of the 23 pairs of human chromosomes. It will enable scientists to pinpoint all the genes associated with genetically based human illness. (Some 3000 disorders fall into this category.) In most cases, people alerted to the genetic liabilities they carry can develop healthy habits or be treated at the earliest possible stage.

Most of the new genetic tests are still being evaluated and improved, and the few available are offered piecemeal. But a pilot program by Focus Technologies, Inc., of Washington, D.C., is already incorporating genetic tests into an innovative "wellness" plan for 1000 employees

at Chesapeake & Potomac Telephone. Computers analyze detailed family histories for volunteer participants. Then each patient's blood is subjected to more than 40 tests for 14 diseases, including cervical cancer, gum disease, diabetes and coronary heart disease. A "health advocate" reviews the results with the patient, who signs a "health contract" describing preventive steps he or she will take.

Most people will be getting risk profiles by the year 2000, predicts Michael McGinnis, director of the U.S. Office of Disease Prevention and Health Promotion. The ability to target health care will improve dramatically, he adds. "It is one thing to tell a smoker he has a tenfold greater chance of getting lung disease on the basis of national statistics," says McGinnis, "and quite another to tell him he lacks the gene for a lung-protective protein and will almost certainly get emphysema."

Researchers caution against expecting too much too soon. Most of today's probes aren't capable of pinpointing a defective gene. They can detect only sequences of healthy genes, called markers, that are usually found near a defective gene. Finding an abnormal gene in such an indirect way is expensive and can take months. And because the marker can be inherited without the defective gene, findings may be misleading.

By the mid-1990s improved tests may allow scientists to home in on

defective genes. The finely targeted probes will first be used to screen fetuses and adult carriers for illnesses caused by a single gene—such as cystic fibrosis, Duchenne muscular dystrophy and adult polycystic kidney disease, which affects up to 400,000 Americans a year.

Meanwhile, other advances are coming swiftly:

Heart Disease

IN 1984 Dr. Michael Brown and Dr. Joseph Goldstein, geneticists at the University of Texas Health Science Center at Dallas, isolated mutations in a gene involved in the premature onset of atherosclerosis. People with this genetic defect cannot efficiently remove low-density lipoproteins, or LDLs—the “bad” combination of cholesterol and protein that contributes to heart disease. The mutant gene appears in about one in 500 individuals. Such carriers are prone to heart attacks in their 40s or 50s, often with no warning.

Building on these discoveries, other scientists have identified additional genes believed to play a role in heart disease, including one associated with heart attacks that occur before age 60. This gene is suspected of indicating lower-level production of high-density lipoproteins, or HDLs—the “good” lipoproteins that transport cholesterol out of the bloodstream. The defect is carried by one in 25 people, placing it among the most common genetic causes of cardiovascular

disease. This genetic marker appears to be prevalent among patients with confirmed heart disease.

With one in four Americans at risk of heart disease, several biotech companies are competing to manufacture probes to detect some of the genes believed to be implicated. California Biotechnology, Inc., of Mountain View expects to develop a genetic test for predisposition to atherosclerosis by 1989. “If we could forewarn those at risk,” says John Lewicki, Cal Bio’s vice president of research, “it would be a huge step forward. Stress, exercise, smoking, diet—all these factors, unlike genes, are readily modifiable.”

Cancer

SINCE the early 1980s, scientists have revealed some 40 human genes involved in cancer. These genes are essential for normal growth, but can be subverted to cause a tumor.

Dr. Jorge Yunis of the University of Minnesota Medical School in Minneapolis has found that 70 percent of oncogenes, or cancer-causing genes, are located near inherited weak points on chromosomes. Varying from individual to individual, these fragile sites are particularly vulnerable to chemical carcinogens, X rays and other cancer-inducing agents.

“If a chromosome snaps apart in the immediate vicinity of an oncogene,” says Yunis, “normal genetic control mechanisms could break down and the stage would be

set for the formation of cancer." Yunis has shown that such a sequence occurs at the onset of numerous leukemias, lymphomas and some tumors of the lung, colon and breast.

Yunis and other investigators have found that petroleum-based products—notably pesticides and insecticides—damage specific sites on at least two of the 23 pairs of human chromosomes that carry genetic information. Similarly, tobacco smoke tends to attack a part of another chromosome.

AIDS

AN ESTIMATED 1.5 million Americans have come into contact with the AIDS virus but remain free of symptoms. British researchers have

just learned that vulnerability to the lethal virus depends at least in part on genes. A team led by Anthony Pinching of St. Mary's Hospital Medical School in London looked at six combinations of an inherited protein found on some human and animal cell surfaces. The researchers concluded that one of the protein combinations makes the people who carry it highly resistant to AIDS, while another makes them highly vulnerable. The other four combinations fall in between.

The work may shed light on why the disease is spreading so rapidly among heterosexuals in Central Africa. Blacks from that region are nearly ten times likelier than Caucasians to carry the "most susceptible" protein.

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Mental Illness

RESEARCHERS at the University of British Columbia in Vancouver, Canada, have found a possible genetic link to schizophrenia. Other research groups are hot on the trail of genetic markers for certain panic disorders.

The practicality of such susceptibility tests will depend on whether genes are the main—or even frequent—cause of mental disturbances. Consider Huntington's and Alzheimer's, two neurological disorders that usually strike late in life. "Huntington's is always caused by a gene, but only an estimated ten percent of Alzheimer's cases have been traced to heredity," says James Gusella, director of the Neuroge-

netics Laboratory at Massachusetts General Hospital in Boston.

It's difficult to recognize early warning signs of mental disease. There are likely to be several biochemical arrangements that can all lead to the same clinical diagnosis. In one Pennsylvania Amish family with a history of manic depression, for example, the culprit gene was traced to chromosome 11, whereas a gene on the X chromosome is thought to account for the same disorder in several large Jewish families in Israel.

THERE ARE NO LONGER insurmountable obstacles to screening fetuses for diseases that won't strike until midlife or even old age. Since last fall, for instance, pilot programs

it.



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for Huntington's-disease families have offered an in-utero test as an extension of their adult-screening project.

Such advances, coming in rapid succession, have staggering implications. Some people might prefer that the information contained in our genes remain a secret. How would a couple make sense of the news that their unborn child will be prone to Alzheimer's in old age?

Ironically, our increased predictive powers bring increased uncertainty. A predisposition is not a black-and-white pronouncement but an estimate based on probabilities. This raises concerns that someone might abort a fetus or forgo a career opportunity on the basis of relatively minor risks.

The reliability of many genetic tests has not yet been established. Nor are there guidelines that clarify just who is entitled to make use of such personal data. Questions have been raised about how the health-insurance industry might use genetic-risk data. Americans with private coverage—people not

covered through employee group policies—might see rising health-insurance premiums if they are at risk. But genetic screening may reduce the cost of medical insurance for others. "If people pay attention to genetic tests, and actually take preventive steps that make them healthier, then the group-insurance rate will go down," says Benno Isaacs, a spokesman for the Health Insurance Association of America.

Michael McGinnis points out that people have long been heeding disease forewarnings. In the past 20 years, there has been a 25-percent drop in smoking, contributing to a 40-percent drop in the heart-attack death rate and a 55-percent drop in the stroke death rate.

Still, smoking costs at least 300,000 lives a year. Poor diet, obesity and elevated cholesterol probably kill hundreds of thousands more. It's in these areas, stresses McGinnis, that personally targeted genetic tests can make a difference. "People will no longer be able to say, 'Why me?'" Instead, they'll be having a say in why *not* me."



Street Song

BEFORE LOUIS ARMSTRONG became world famous, he spent a lot of time walking in his neighborhood on the South Side of Chicago. One afternoon he noticed a small crowd gathered around two street musicians. He stopped to listen and, to his delight, they were playing his improvised chorus of "Struttin' With Some Barbecue." At the finish of the number, Armstrong walked over and said, "Man, you're playing that *too slow!*"

"How would you know?" the musicians challenged.

"I'm Louis Armstrong. That's my chorus you're playing!"

The next day the pair had a sign next to their tin cup. It read: "Pupils of Louis Armstrong."

—Bud Freeman, *You Don't Look Like a Musician* (Balamp)