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THE DARK SIDE

Does your future health lie in your genes? And if so, are you prepared to face it?

In 1986, while interviewing a leading geneticist for a science magazine, I confided that my father had died of colon cancer at a young age. To my surprise, the scientist suggested I give him a blood sample.

"Why?" I asked nervously.

"Some forms of colon cancer are hereditary, and I might be able to tell if you're at risk," he explained.

"But familial colon cancer can't be easily cured or prevented, can it?" I inquired.

He shook his head.

"Thanks," I said. "But no thanks."

The geneticist, Jorges Yunis, M.D., not only understood my disinclination to be tested, but he went on to share his own misgivings about the merits of genetic knowledge. In the mid-1970s, he had pioneered a new technique for staining chromosomes, which could reveal tiny defects in the genes of developing fetuses. These subtle defects correlated with a host of disorders—cleft palates, IQs that were low but still in the normal range, even a tendency toward premature graying of the hair. The only problem was that the correlations were far from precise, and Yunis was afraid how expectant parents might react to such news. His worst fears were confirmed when a delegation from the Chinese government arrived at his laboratory at the University of Minnesota, requesting information about the test. Owing to stringent population-control measures in China, the representatives explained, couples were permitted to have only one child—so it was imperative that their only heir be as perfect as possible.

Yunis, now at Thomas Jefferson University in Philadelphia, kept a paper explaining his fetal-screening technique locked in a file drawer during the Chinese delegation's visit.

Welcome to the dark side of genetic knowledge. Every other day we read about a new disease that has been traced to an aberrant gene. In the past few months, breast cancer, colon cancer and osteoporosis have been added to the ever-growing list of "family" defects traceable to faulty genes. And recently, two controversial reports even claimed to have unveiled genes that predispose members of certain families to homosexuality or to impulsive acts of violence.

These discoveries raise several critical questions. How useful and reliable is this information? In our headlong rush to apply this knowledge, will we heed the many complexities and limitations of genetic data? And are we psychologically prepared to cope with

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the deeply personal, confounding choices this new science raises? Predicts Paul Billings, M.D., Ph.D., a human geneticist at Stanford University Medical School, "Soon there will be twelve-step programs for dealing with gene anxiety."

No one would deny that medical benefits are sure to emerge from the much-publicized Human Genome Project, the government's massive program to identify and study the estimated 100,000 genes found on our 46 chromosomes. In theory, knowledge of genetic susceptibilities could be a tremendous boon to preventive medicine by encouraging early checkups targeted at specific conditions and by spurring dietary and lifestyle changes that might help individuals lower their risk of getting sick. A better understanding of the genetic foundations of disease is also paving the way for more effective modes of therapeutic intervention, from fine-tuned drugs to novel gene therapies.

Few of us will reap these therapeutic wonders any time soon, however. And therein lies the crux of some of the thorniest legal, ethical and public-policy issues raised by this rapidly accelerating science. Very simply, our ability to detect genetic conditions is far outpacing our ability to prevent or treat them.

OF GENETIC TESTING

BY KATHLEEN McAULIFFE

News stories of the latest gene-linked disease are invariably followed by rosy pronouncements of new treatments around the corner. But it is one thing to find a flawed gene, quite another to correct it. Observes Peter Pearson, Ph.D., scientific director of the Genome Data Base at Johns Hopkins University School of Medicine, "If we look at the track record of developing therapies based on genetic breakthroughs, it's very poor indeed."

That sober assessment conflicts with the hopes inspired by the triumphant outcome of the first human-gene-therapy trial in 1990. The beneficiary of the technology, a little girl with a rare and usually fatal inherited immune-deficiency disease, can now look forward to a healthy life. But as Pearson underscores, the child was chosen for that pioneering trial precisely because her affliction did not offer the usual stumbling blocks to treatment. Her disorder involved a defect in a single, well-studied gene, which is critical only to the functioning of blood cells—one of the most easily accessible parts of the body. To treat her, doctors withdrew some of her blood, genetically repaired the defective cells so that they contained healthy copies of the faulty gene, then simply reintroduced those repaired cells into her body via a standard intravenous hookup to boost her immune system.

That strategy won't work for most disorders. "With genetic diseases that involve muscle, lung or brain tissue, it's much trickier," stresses Dr. Pearson. "Many people are working very hard at introducing repaired genes into difficult-to-reach organs, but it's going to take a major breakthrough." What's more, cancer and heart disease frequently involve multiple genes whose precise functions have yet to be determined. "There's going to be a very long lag period—perhaps decades—between the discovery of where genes are at fault and implementing that knowledge into effective therapies," Dr. Pearson cautions.

Further exacerbating this difficult transitional period, genetic forecasting is itself scarcely a precise science. It is the rare hereditary condition, such as Huntington's disease, that geneticists can detect before its onset with virtually 100 percent certainty. More commonly, individuals seeking genetic testing will be presented with risks that span a broad range of probabilities. At several medical research centers across the country, for example, people with a familial history of late-onset Alzheimer's disease can be tested for a gene called APOE4, which is involved in nerve function. In the absence of any copies of APOE4, the risk of developing Alzheimer's is 20 percent by the age of 80. If a person has one copy (from one parent), the risk is about 30 percent. And if two copies of the gene (one from each parent) are present, the risk shoots up to 90 percent. Other tests—also presently limited to high-risk families on a research basis—offer similar guesstimates of a person's likelihood of acquiring specific diseases. For instance, such tests might reveal that you have a 50 percent to 70 percent risk of getting endometrial cancer, a 70 percent risk of colon cancer or an 85 percent risk of breast cancer.

It is often assumed that as scientists gain a better understanding of the hereditary underpinnings of disease, any current error margins will disappear. But the prophetic powers of geneticists will always be hampered by a fundamental law of nature: Genes don't act in isolation. The impact of one gene may be offset by the presence of another, and exposure to toxins, chronic stress, diet, exercise habits and many other factors may all affect the occurrence of disease. Efforts to link mental illness to specific genes are especially fraught with peril because of such hard-to-pin-down variables as an individual's upbringing, traumatic experiences and cultural influences. Earlier studies suggesting genetic culprits behind alcoholism, schizophrenia and manic depression have now been discredited. Many researchers believe genetic tests will be, at best, weakly predictive of such conditions, because even if predisposing genes are isolated, a sea of environmental variables is likely to obscure their contribution.

If murky odds make your head swim, be forewarned that as part of a general physical exam, you could soon be offered a profile of your susceptibilities to dozens and eventually even hundreds of diseases. The biotechnology industry is gearing up to run numerous genetic tests simultaneously on a single blood sample by using a system that will spit out the results on a computer printout.

Meanwhile, a small biotech firm based in Gaithersburg, Maryland, has begun to market a cancer-susceptibility screen through local doctors and hospitals that was hitherto only available at a limited number of medical-research centers. The company, OncorMed Inc., is offering its genetic-testing service and counseling to families with a high prevalence of cancers of the breast, ovary, colon and uterus.

DNA-testing technology is also being harnessed by at least one group of people in an effort to eliminate disease-causing recessive genes from its population. A group of Orthodox Jews in New York and Israel whose faith prohibits abortion or the use of birth control are urging young adults contemplating marriage to join a testing program to see if they carry genes for three disabling hereditary disorders—Tay-Sachs disease, cystic fibrosis and Gaucher's disease. If would-be partners find that they are at risk of producing children with one of those diseases, the couple may opt to end the relationship. Some have already done so. *(Continued)*

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Even though prenatal diagnostic screening is still limited to a handful of hereditary conditions, there are no scientific obstacles to prevent biotech businesses or other groups from promoting susceptibility tests designed for adults to be used on a fetus or even on a "test tube" embryo prior to implantation in the womb. In this way, an expectant mother could be forewarned of diseases that her offspring might get in adolescence, midlife or even old age. Such a scenario may not be far off: The recent birth of a healthy baby girl whose eight-cell embryo tested negative in vitro for Tay-Sachs helps pave the way for expanded testing.

What all this means is that many of us may soon be asked to make decisions about lifestyle, marriage and procreation based on a bewildering array of statistical probabilities. Tests might show that individuals or fetuses are susceptible to diseases they may never get, leading to unfortunate consequences: adherence to unnecessarily severe dietary constraints, or worse, the termination of a promising relationship or pregnancy. Conversely, a person might be falsely reassured by a negative test result. "If you tell a 50-year-old woman that she doesn't carry a mutation for breast cancer," points out Neil Holtzman, M.D., professor of pediatrics, health policy and epidemiology at Johns Hopkins Medical Institutions, "she might think she need not bother with self-exams or mammography when, in fact, she's still at risk." (A woman who doesn't carry the gene still has roughly a 12 percent lifetime risk of developing breast cancer from a spontaneous mutation.)

Even when the onset of disease in presymptomatic individuals can be predicted with a high degree of reliability, what then? How many of us would really want to know, for example, that we carry the gene for ataxia, an incurable syndrome in which the brain cells controlling motor movement gradually waste away?

Actually, some people would. Darla Brockus, a 24-year-old mother from Yucaipa, California, who is at risk for ataxia explains: "It's good to be able to prepare your family both financially and emotionally. Also, I'd definitely have another child if I knew that I wasn't going to leave this terrible legacy behind."

Brockus is not exactly typical, however. When neurologist Lawrence Schut, M.D., of United Hospital in St. Paul, Minnesota, notified 100 high-risk people about the new test for ataxia last July, only a dozen responded with inquiries about getting tested. Another 24-year-old mother from a family afflicted with ataxia, Tammi Spooner of Hartland, Minnesota, typifies the majority response. "I could die tomorrow in a car accident. You can't live your life worrying all the time about getting sick."

When preventive steps can be taken, genetic information is potentially life-saving. Contrast the impact of an impersonal warning from the surgeon general on the hazards of smoking versus telling a smoker that he or she carries a gene for lung cancer (no such gene has yet been identified). The latter message would probably be a more potent stimulus for giving up cigarettes.

In some cases, however, the prophylactic measure is almost as frightening as the disease it would prevent. Consider the dilemma confronting women who find out through a genetic test that they are at grave risk of developing breast cancer at a young age. Their options are to do nothing, to get into an intense surveillance program including frequent mammograms, or proceed with the much more aggressive approach of surgery—a double mastectomy. "The preventive strategies we can offer them right now are frightening, and certainly in the case of surgery, draconian," admits Francis S. Collins, M.D., Ph.D., who heads the National Center for Human Genome Research in Bethesda, Maryland. Still, he argues that medicine has an obligation to offer genetic testing to women with a strong family history of the disease because the option of disfiguring surgery is a lesser evil than "having to deal with the horrors of a metastasized cancer."

My own concerns about genetic testing focus not so much on the dearth of prophylactic measures available to me (in the years since my encounter with Dr. Yunis I have learned that a high-fiber diet and an invasive exploratory procedure known as a colonoscopy might lower my risk of getting colon cancer). Rather, I worry such information might have a negative psychological impact. Perhaps I will start to think of myself as diseased even though I am ostensibly well. According to Stanford geneticist Dr. Billings, my anxiety is by no means unique. "Many healthy people don't want to be tested out of fear of being treated like a patient who must now be subjected to lifelong medical monitoring," he says. In addition, mounting evidence from so-called "brain-mind" research shows that depression and anxiety can harm the immune system. Indeed, the stress associated with an alarming test may even bring on full-blown symptoms.

As if genetic knowledge did not pose enough problems for individuals, the confidentiality of this information is by no means assured. In just the past five years, according to a report by Dr. Billings and his colleagues, there have been hundreds of cases of discrimination based on a person's genetic status. Among other things, people labeled susceptible to genetic disorders have been denied health insurance, jobs and the opportunity to adopt children. Abuses are sure to mushroom as new tests for genetic predilections flood the marketplace. On the other hand, the introduction of universal health coverage could go a long way toward eliminating the most prevalent offenses. Whatever form health reform takes, let's hope all Americans are guaranteed coverage. After all, if we continue to let insurance companies set their own agendas, almost everyone will be branded with a preexisting condition. And then—as Hillary Clinton herself pointed out while discussing the Human Genome Project—who will be insurable?

Eventually, the stigma associated with genetic risks will probably subside as innovative gene therapies and other corrective treatments become available. But the forward march of technology will never solve all our problems. As new techniques become routine, the distinction between medical and cosmetic uses of gene therapy will blur. That in turn will raise a host of sticky questions: What constitutes a defect in need of fixing? How will society determine who deserves a genetic boost in life? Will gene augmentation be reserved for the medically needy? Or will it be offered on the basis of who can pay, creating even grosser class inequities in our society?

Already, parents of children only slightly shorter than average have been besieging doctors to give their youngsters a genetically engineered human-growth hormone—a compound intended for victims of pituitary dwarfism, who, without treatment, would attain an adult height of less than four feet six inches. Most of the parents backpedal when they learn how little is known about the drug's long-term effects, reports Yale pediatric endocrinologist Susan Boulware, M.D. But if further study confirms the compound's safety and efficacy, she is convinced the demand for human-growth hormone will skyrocket—even at the current lofty price tag of $10,000 to $20,000 for a single year's treatment.

Suppose that doctors could perform genetic surgery on embryos to "correct" short stature or any number of other perceived handicaps—say, a predilection toward early baldness or an ear with less than perfect pitch (scientists are currently trying to isolate the genes for both baldness and perfect pitch). Would these techniques also be in high demand?

"Just as parents spend a great deal of time selecting the right school for their children today, I have no doubt that in the future parents will spend a great deal of time selecting the right embryo," predicts Arthur Caplan, Ph.D., director of bioethics at the University of Pennsylvania. Thomas Murray, Ph.D., director of the Center for Biomedical Ethics at Case Western Reserve University in Cleveland, concurs: "We're such an individualistic culture; if we can give our kids a leg up, we'll go for it."

Indeed, more than 40 percent of 1,000 Americans polled in 1992 by the March of Dimes Birth Defects Foundation said they approved of the use of gene therapy to improve the physical characteristics that their children would inherit. A similar percentage approved of its use for the improvement of their children's intelligence. And although no survey has posed the question, many gay-rights activists worry that many Americans would abort a fetus thought to be predisposed to homosexuality.

These trends raise the disquieting specter of a new age of genetic materialism, in which genes deemed desirable would be coveted like BMWs—for their social-status value. Such trends also underscore what scientists refer to as the increasing "geneing" of America: the reliance on genetic science to explain and deal with such complex traits as criminality and mental illness, traits known to have multiple social roots irrespective of biology.

How can misuses of genetic knowledge be curbed, while the awesome health-giving potential of that knowledge is maximized? This year the Human Genome Project has devoted 5 percent of its $106 million budget to answering that question—the single-largest investment in ethical research in the history of the world. Legions of social workers, theologians, legal scholars and other interested parties are now hard at work pondering the staggering implications of this science. A broad consensus has been reached on the following general guidelines:

● **Consent** No doctor, hospital or other group should be able to order a genetic test for an individual without obtaining his or her prior consent. To prevent parents from pressuring children to be tested, DNA analysis for late-onset diseases should be limited to people over age 18.

● **Counseling** More information needs to be gathered about how people respond to susceptibility data. So-called multiplex testing could conceivably overwhelm an individual with too much information at once, sowing the seeds of confusion, misunderstanding and even panic.

● **Health insurance** Until the U.S. health-care system is reformed, insurers should declare a moratorium on the use of genetic-risk data as a qualification for health coverage. Insurers' claims that covering those with inherited ills will erode profits are unfounded, since the prevalence of genetic disease in the U.S. population has remained stable for as long as the insurance industry has existed.

● **Protection against discrimination** Discrimination based on genetic data must be prohibited by state or federal statutes. So far, only a handful of states—notably, Iowa, Oregon, Rhode Island and Wisconsin—have enacted legislation addressing genetic discrimination on a broad basis.

● **Privacy protection** The security of personal DNA data, like that of most computerized medical records, is woefully inadequate. Nor is there any federal oversight panel responsible for enforcing health-privacy guidelines. The Clinton health-care reform plan calls for the establishment of just such a supervisory group. Whether or not the Clinton plan passes, federal oversight in this area will be critical, since DNA data banks usually operate across state lines.

● **Education** A massive education campaign is urgently needed to better inform both health providers and the public about the genetic technologies now in the pipeline, and to increase awareness of both the promise and perils of these advances.

Many experts believe that it's not too soon to address whether cosmetic uses of gene therapy should be restrained. W. French Anderson, M.D., the medical researcher who collaborated on the first gene therapy trial, advocates that genetic surgery be offered only to individuals suffering from serious debilitating conditions. "To take an acceptable quality of life and try to enhance it would be more disruptive to society than beneficial.... Society quite legitimately is concerned that the richest, most powerful, most famous will get the good genes first."

What constitutes a defect in need of fixing via gene therapy? How will society determine who deserves a genetic boost in life?

It behooves us to meet these problems head on, or face the consequences: Discrimination and social inequalities will flourish, while gene therapy and abortion for frivolous purposes could become as widespread as cosmetic surgery.

Education, guidelines and laws are certainly a good starting point. But in the end, it's not institutions but individuals who will have to grapple with the deeply personal decisions about when—or if—genetic technology should be applied in each of our lives. In this uncharted realm, there are no ironclad rules: What's right for one person may be terribly wrong for another. Each of us will have to weigh a host of factors—from risk data and personal finances to our most closely held beliefs about sickness and health, parenthood, marriage and religion.

For some, the options may be relatively straightforward. Others, like myself, will agonize over the choices.

Now that I'm pushing 40, an age when the immortal glow of youth fades, that test for colon cancer is looking more attractive. On the other hand, perhaps ignorance is the lesser evil. I'm still undecided. If you were in my shoes, what would *you* do?

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