Genetic Testing Set for Takeoff

Testing for flawed genes that cause cancer and other diseases is about to explode. But the risks and benefits aren't clear yet—especially in cases where there are no cures

If your mother had died of Huntington's disease, would you want to be tested to see whether you had inherited the flawed gene that causes this fatal condition? Before answering, you'd want to balance the costs and benefits of testing. A negative result would give you tremendous peace of mind, allowing you to lead an ordinary life. A positive result, on the other hand, would cause you to live the rest of your life knowing your ultimate fate would be the intellectual deterioration and involuntary movements that characterize Huntington's disease. Some studies indicate that as many as one in 10 patients who test positive for the mutation never make a full emotional recovery—not surprising, given that there's currently no cure for the disease.

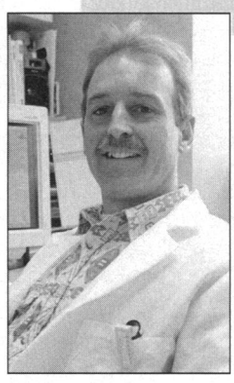
Despite the risk of psychological devastation, and in full knowledge that there's no cure, in March medical geneticist and psychologist Richard Myers of Boston University School of Medicine began offering fee-for-service testing for the Huntington's gene. Myers acknowledges that the benefits of testing for Huntington's are ambiguous. But he offers the service, along with full psychological counseling, he says, because he believes a person has an inalienable right to know his or her genetic destiny. And Huntington's is only one of several heritable diseases for which a test can pick up the genetic defect long before any symptoms appear.

Like prenatal testing in the 1980s, "predictive" presymptomatic genetic testing for diseases that hit later in life is destined to become a medical boom industry. Presymptomatic testing is already available for certain uncommon disorders (see table on p. 466), but the driving force for explosive growth will be the development of genetic tests for susceptibility to two very common cancers. The past 8 months has seen the identification of *MSH2* and *MLH1*, genes that can predispose people to hereditary nonpolyposis colon cancer when they contain specific defects. Nonpolyposis colon cancer strikes one in 20 people, and as many as 18% of these cancers may result from mutations in *MSH2* and *MLH1*.

Commercial genetics labs are already staking their claims on this huge potential market. No fewer than 10 companies have already purchased the rights to develop *MSH2* and *MLH1* tests. And if *BRCA1*—the putative gene that when damaged dramatically increases the risk of breast and ovarian cancer—is "cloned by Christmas" as some researchers have predicted, it will undoubtedly spawn a second presymptomatic gene test with a huge market waiting for it.

But as predictive gene testing gets set to take off, it trails in its wake a swarm of tough questions, some of which are hinted at by the case of Huntington's disease. Is it ethical to test for diseases for which there are no known cures? How reliable are the available tests? What are the psychological consequences for healthy patients of learning their destiny? Is the regulation of laboratories that offer genetic testing stringent enough to ensure that life-shattering errors are not made (see box)? How can perfectly healthy people who may carry a defective gene be protected from discrimination by health and life insurance companies and potential employers?

"I'm very uncomfortable with identifying a mutation and saying this is responsible for disease."
—Richard Fishel



WILLIAM DILILLO/UNIVERSITY OF VERMONT

Those uncertainties have the research, clinical, and patient communities in turmoil about where to go from here. Some favor taking the research high road. "Genetic testing should be considered in the same way as a new drug. It can have efficacy, and it can have toxicity," argues Francis Collins, head of the National Center for Human Genome Research in Bethesda, Maryland. The National Advisory Council for Human Genome Research (NACHGR), which Collins chairs, currently recommends against testing for *BRCA1* (which, in some cases, can already be done, not by DNA testing but by more cumbersome linkage analysis), *MSH2*, or *MLH1*, except in research settings.

Fran Visco, president of the National Breast Cancer Coalition in Washington, D.C., shares some of NACHGR's worries. "We're very concerned about how good the tests will be," she says. She adds, however, that "the demand will be high," and she says her organization is asking that the test "be made widely available," albeit only through peer-reviewed research protocols.

Others argue that confining testing to the research arena is unethical, precisely because it would limit its availability. Medical geneticist David Rimoin of Cedars-Sinai Medical Center in Los Angeles calls the NACHGR's stance "far too restrictive." Rimoin, president of the newly formed American College of Medical Genetics, argues that presymptomatic genetic testing for colon and breast cancer should be available to any individual judged to be at risk by a doctor trained in medical genetics. To "ensure that false diagnoses and false reassurances are not made," he says, tests should not be made available through general practitioners.

Is knowledge power?

In the face of these widely varying opinions, what are the real pros and cons of presymptomatic genetic testing? One key issue is whether the knowledge provided by gene testing will actually save lives. For Huntington's disease, the answer is clearly no. For hereditary nonpolyposis colon cancer and breast and ovarian cancer, however, the answer is far from clear. In general, early detection of these cancers is associated with improved survival. But "the question everyone is asking," says Collins, is whether interventions that work for the general population "are going to apply to these individuals who have a very strong genetic risk."

For instance, mammograms, which have been shown to save lives among women 50 and over by detecting breast cancer early, won't necessarily help when *BRCA1* mutations trigger breast cancer. In fact, says Collins, it is conceivable that "these may be the people who are most sensitive to very low doses of radiation and therefore should avoid mammograms." Nonetheless, Mary-Claire King of the University of California at Berkeley, a leader in the hunt for *BRCA1*, points out, a woman who tests positive might choose to be more rigorous about breast self-examinations. Some women who test positive opt for prophylactic mastectomy.

Gene Tests: Who's Minding the Store?

When it comes to testing for disease-causing genes, it's important to get the results right, because they can have life-shattering consequences, determining whether a patient refrains from having children, becomes uninsurable, or is plunged into depression (see main text). Given the importance of accuracy, a panel of the National Academy of Sciences (NAS) came up with a disturbing conclusion last year: Federal oversight of gene testing is in dire need of an overhaul. In theory, the Health Care Financing Administration (HCFA) and Food and Drug Administration (FDA) are responsible for ensuring high-quality testing in commercial and academic labs. In practice, however, such authority "is not being applied to genetic testing at all," the NAS panel said last November in a report called "Assessing Genetic Risks: Implications for Health and Social Policy." And "without regulatory backup," says Patricia Murphy of OncorMed Inc. in Gaithersburg, Maryland, who set up the genetic testing regulations for the New York State Department of Health, "nightmares occur, mistakes are made, and you don't get equivalency between labs."

The problem is that HCFA has no standards specific to labs that analyze DNA. Moreover, says geneticist and health policy expert Neil Holtzman of Johns Hopkins University in Baltimore, a member of the NAS panel, "HCFA inspectors are not trained to recognize how to run a genetic test—for susceptibility to cancer, for example—and to ensure its quality."

The FDA isn't doing much better. The agency requires that manufacturers win marketing approval for test kits and that labs offering experimental genetic tests obtain an Investigational Device Exemption or conduct the tests under Institutional Review Board–approved protocols and mark the results "for investigational use only." Few do. "We've had a paucity of genetic tests that have actually been cleared or approved," says Steven Gutman, acting director of the FDA's division of clinical laboratory devices, the unit that oversees genetic testing. Gutman admits that part of the problem is that the FDA prefers to leave oversight of genetic testing to HCFA.

But there may be some hope for improvement on the horizon. The American College of Medical Genetics, the College of American Pathologists, and the human genome project's Ethical, Legal, and Social Implications branch in Bethesda, Maryland, are working with FDA and HCFA to tighten up their methods for oversight of gene testing. It remains to be seen, however, whether any improvements will come before the explosion of genetic testing that is expected soon.

–R.N.

But even in the absence of any clear-cut treatment strategy for people who carry cancer susceptibility genes, presymptomatic gene testing still has something important to offer a fortunate group of testees: a negative result. If a patient gets that result, the physician is able to "say 'go in peace. Do whatever you plan to do with your life,'" says Frederick Li of the Dana-Farber Cancer Institute in Boston, who is studying the pros and cons of testing members of high-risk families for the mutations that may trigger the multiple early-onset cancers that constitute Li-Fraumeni syndrome. A negative test also saves patients discomfort, disfigurement, and dollars, clinicians say, as they avoid screening procedures such as colonoscopies and prophylactic therapies such as mastectomy.

Bearing false witness

In spite of those potential advantages, widespread testing now would be a mistake, says Collins, because we don't yet "understand what type of false positives and false negatives are going to occur." Such errors are easier to avoid when testing is conducted in a meticulous research environment and is restricted to members of large high-risk families in which the specific mutation afflicting them can be identified.

But such families include only a tiny minority of all potential testees, and when testing moves beyond these families, it enters a much more complex arena. To reliably test individuals for hereditary susceptibility to cancer without reference to affected family members, it's necessary to be able to identify a whole range of possible mutations (each gene has room for hundreds); the risk of cancer associated with each mutation; and the difference between a dangerous mutation and a polymorphism, a harmless genetic variant. Richard Fishel of the University of Vermont School of Medicine, who with Richard Kolodner of the Dana-Farber led one of the teams that pinpointed *MSH2* and *MLH1*, says "the very first mutation we identified may turn out to be a polymorphism—a potential false positive that needs to be rigorously examined."

"We're very concerned about how good the tests will be."

—Fran Visco

The assays currently available "aren't guaranteed to find a mutation. They are prone to false negatives," says Kenneth Kinzler of the Johns Hopkins University Medical School, who, with Hopkins' Bert Vogelstein and Albert de la Chapelle of the University of Helsinki in Finland, led another team that identified *MLH1* and *MSH2*. One problem is that, even with automated sequencers, it takes days, even weeks, to reliably sequence each gene. By necessity, the assays concentrate on the gene's protein-coding regions rather than on their regulatory regions or their introns (the pieces of the code that are chopped out after the DNA is converted into RNA). Yet mutations in these regions may also trigger cancer.

"Everyone sees some grand potential," says molecular geneticist Raymond Fenwick of Dianon Systems Inc., a Stratford, Connecticut, diagnostics company that offers gene testing for Huntington's, "but until someone comes up with some dynamo technology to search through the whole gene, it's going to be too expensive" to do widespread testing for all possible mutations in *MSH2*, *MLH1*, and, once it's been tracked down, *BRCA1*.

Fishel thinks it's too early even for testing in high-risk families. "I'm very uncomfortable with identifying a mutation and saying this is responsible for disease," he says, because in all but the largest families it is impossible to conclude definitively that a mutation present only in family members that have cancer is actually causing the cancer rather than simply being a chance association.

Rather than relying solely on mutation testing, Fishel says, "we need to develop functional assays in order to assess what a mutation means." Functional assays, which monitor the action of the gene's protein product, can more easily pick out defective genes. Fishel's lab is in the process of developing such a test for *MSH2* and *MLH1*.

Even when the whole spectrum of mutations is bagged and functional assays are

GENETIC TESTING FOR HEALTHY PEOPLE

Condition	Test	Approximate Cost	Approximate Size of U.S. Market
Huntington's disease	Number of CAG triplet repeats in the *Huntingtin* gene	$250–300	30,000 families
Charcot-Marie-Tooth disease	*PMP22* gene deletion	$350	100,000 families
Multiple endocrine neoplasia type II (cancer of the endocrine glands)	*RET* gene mutations	$500	A few thousand families
Myotonic dystrophy	Number of CTG triplet repeats in the myotonin kinase gene	$275	36,000 families
Hereditary breast/ ovarian cancer	Linkage analysis for *BRCA1*	$0–200/family member (minimum of four required)	Only possible for large families with multiple affected members
Alzheimer's disease	Apolipoprotein E genotype	$195	3–5 million cases
Familial adenomatous polyposis (a precursor of colon cancer)	Adenomatous polyposis coli (*APC*) gene mutations	$750 for first family member, $500 for subsequent members	7000 families
Li-Fraumeni syndrome	*p53* gene mutations	up to $1000	3000 carriers
Hereditary nonpolyposis colon cancer	**MSH2, MLH1* mutations	?	Mutations are carried by one in every 200 people and cause up to 15% of colon cancers

*under development
SOURCE: Helix, National Directory of DNA Diagnostic Laboratories, Children's Hospital and Medical Center, Seattle, Washington.

available, problems will remain, as geneticists need to tighten up their estimates of the actual risk of cancer—or "penetrance"—associated with each mutation. Geneticists usually give the penetrance for mutations in *MSH2*, *MLH1*, and *BRCA1* as about 85%. But those estimates are derived from studies designed to pin down the genetic basis for cancer by homing in on families with extremely high incidence of early-onset cancers.

The degree of penetrance, however, is likely to be different for each of the hundreds of different mutations that are floating around in the population. Those high-risk families may suffer peculiarly damaging mutations, or may be unusually vulnerable to a given mutation, so using them to calculate cancer risk associated with the mutated gene is likely to lead to a huge overestimation. "When you are not picking those glorious pedigrees that allow you to identify genes, there's remarkably less penetrance," says Stephen Friend of Harvard Medical School in Boston, a cancer-gene expert.

Such complexities, says breast-cancer gene prospector Bruce Ponder of Cambridge University's Addenbrooke's Hospital in Cambridge, England, mean that "we are going to have to do a lot of genetic epidemiology, correlating mutations and risk in different families," before widespread gene testing for cancer risk will be a reliable proposition.

Yet despite the current weaknesses in testing methods, Ponder says he would be hard pressed to deny members of a high-risk breast cancer family the right to take a presymptomatic gene test. "We are dealing with adults," he says, "and if people ask, you have a duty to inform them of what's available and what the potential advantages and disadvantages are."

Testing testing

Like others involved in this field, which is poised to take off before it's fully explored, Ponder is of two minds about testing. Although he doesn't think it should be denied to adults, he recognizes there's a risk the tests might actually increase cancer mortality. Specifically, he and others are concerned that positive tests, by triggering depression, could actually worsen a patient's chances of survival. For example, "do they become so frightened that they stop [breast] self-examination?" asks genetic counselor Barbara Biesecker of the National Center for Human Genome Research.

The answer to her question isn't known, but with the medical axiom "first do no harm" firmly in mind, teams of geneticists, oncologists, and psychologists around the world are gearing up to find out. The studies they are planning will test the impact of testing for susceptibility to Li-Fraumeni, breast, and colon cancer. Most studies will provide intensive pre- and post-test counseling similar to what is given in Huntington's gene testing.

Six months ago, Ponder and his co-workers started a pilot study to test testing in members of families who have an increased incidence of breast cancer. "One or two [women] have been fairly cracked up about [a positive result], despite our best attempts at counseling," he says.

Similarly, positive Huntington's results have led to depressions so severe that a few patients have had to be hospitalized. One longer term Huntington's study did, however, suggest positive benefits of testing. According to a 1992 study by the Canadian Collaborative Study of Predictive Testing, one year after testing, 37 patients who tested positive and 58 who tested negative for Huntington's scored higher on standard psychological tests of well-being and lower on tests for depression than the 40 whose test results were ambiguous. That result suggests that for patients who know they are at risk (because they come from families in which some members have already fallen prey to Huntington's), testing for a genetic defect can have benefits based on the relief of uncertainty.

But studies like these are conducted under excellent conditions by researchers at topflight medical centers, who provide plenty of reliable information to their patients. Many medical geneticists worry about what will happen when gene testing leaves the setting of the university hospital and enters the doctor's office. Counseling is essential to educate patients about genetics, about probabilities, and about false negatives and false positives, as well as to prepare them to handle the impact of their results. But there are currently only a handful of genetic counselors—a mere 1000 in the United States—and "most doctors, let alone most members of the general public, have only the foggiest idea of the implications of a result," says Ponder.

Ill without symptoms

Even if a patient receives an accurate result and thorough counseling to go with it, their problems are not over. Myers points out that "all the time, people are turned down for life and health insurance" on the basis of test results for the Huntington mutation. In a 1992 article in the *American Journal of Human Genetics*, a team led by Paul Billings of the California Pacific Medical Center in San Francisco reported 41 cases of discrimination against healthy people based solely on their genetic risk. In most cases, the victims were refused health or life insurance. Some were refused jobs. Others were banned from adopting children. Billings calls these people the "asymptomatic ill."

But moves are afoot to stamp out this new form of discrimination. A draft version of a treaty released in June by the 32-nation Council of Europe proposes banning gene testing for insurance and employment purposes (*Science*, 8 July, p. 175). A National Academy of Sciences report called "Assessing Genetic Risks: Implications for Health and Social Policy," released in November, recommends a legal ban on discrimination based on genetic risks; that option is being pursued by some states.

It seems clear that, at the moment, the dangers of genetic testing are substantial, and the benefits, though they may one day be much larger, are small for some who test positive. Yet public demand is likely to lead to widespread testing long before all the glitches have been ironed out. *Time*/CNN pollsters recently asked 500 Americans whether they would take an imaginary genetic test that would tell them which diseases they would suffer later in life; half said yes.

Since Myers started offering his Huntington's gene testing service, he's had two inquiries a day, which he calls an "unbelievable number" for a rare disease. One breast-cancer activist says she understands that response. Patients at risk of inheriting an incurable disease want every weapon they can get. And for many patients, in the absence of a cure or an effective form of preventive therapy, all that's available is a mental weapon: the knowledge offered by testing.

–Rachel Nowak

NIH GRANTS

Peer Review Reforms Get Good Review

One of the biggest experiments going on right now at the National Institutes of Health (NIH) doesn't involve rats, mice, cell cultures, or viruses. Instead, the research subjects are biomedical scientists, and the research focuses on how they wriggle through a maze of reviews each year to obtain $8 billion in federal funds. The experiment is designed to see whether NIH's peer review system—which sorts these 38,000 grant seekers into winners and losers—can be made simpler, fairer, and more efficient.

NIH began testing new approaches to peer review shortly after Harold Varmus became NIH director in 1993, in response to suggestions that the venerable system is in need of a tuneup. Last week, Varmus and his deputies met with scientists from around the country at a "round table" to discuss how the experiments are going. Varmus came away so encouraged by the response, he says, that he wants to start implementing some reforms and expand the testing of others.

In a telephone interview, Varmus said he and his assistant director for extramural research, Wendy Baldwin, want to make wider use of the "triage" approach to sorting grant applications, tested this year by 12 review panels. This technique is designed to eliminate 30% to 50% of the submissions off the top as "noncompetitive" before they're sent to a panel for full review. Varmus adds, however, that "we may change the terminology," because noncompetitive is "a pretty rough term" to use in rejecting first-time applicants.

Baldwin said NIH also intends to implement a "just-in-time" rule for providing data, so that only those who make it through the first cut would be required to submit detailed budgetary and administrative data. And to make it easier to submit such data, NIH plans to increase the use of electronic networks, giving researchers a personal identification number (PIN) so that they can access government computers to send or retrieve information. NIH managers also aim to broaden the scope of some peer review groups (study sections) and test a system of "chunk grants," allowing applicants to apply for small but fixed amounts of cash and thereby minimize the need for detailed budget estimates. Finally, Varmus wants to find new ways of rewarding innovative ideas. He says "a lot of people are concerned that study sections have become too conservative," nitpicking at flaws rather than concentrating on scientific merit. There ought to be a way of giving an advantage to risk-taking applicants, he says.

Most of these ideas are now being tested on a small scale, and most received warm support from the several dozen attendees at the round table. One idea, however, sank like a lead weight: a suggestion that NIH switch from evaluating grant proposals prospectively to a retrospective evaluation of the applicant's previous research. The goal of such an experiment, advocated by Nelson Kiang, director of the Eaton-Peabody Laboratory for eye and ear research in Boston, would be to drastically simplify the review process.

RICK KOZAK

Peer pressure. NIH director Harold Varmus.

Kiang said that anyone seeking a grant should be asked to provide detailed information about previous accomplishments, but only a brief sketch of the research for which they seek funding. Postdocs, for example, could be reviewed on the basis of their theses. He notes that the current system requires pages of detailed descriptions of future work, along with precise data on staff and equipment costs in each future phase of study. Such details, David Botstein of Stanford University said, are mere "bureaucratic fantasies," created to satisfy the review process but rarely followed. But when an NIH staffer presented this idea to the round table, several speakers—particularly women and others who spoke for minority or young scientists—objected that retrospective review would favor the "old boys" who are already well established.

Varmus noted that NIH already uses retrospective review in some ways—openly in judging the work of intramural staffers and implicitly in awarding extramural grants. "It would be naïve," he told *Science*, "to think that when we review applicants we are just looking at the proposal." Reviewers also take into account an individual's experience, track record, and his or her sources of funding. Varmus said he recognizes that "people are concerned about squeezing the new blood out of the system." However, it might be possible to use retrospective review more often for scientists seeking grant renewals.

While this idea got a mixed response, the related proposal for "chunk grants," put forward by David Boettiger of the University of Pennsylvania, got a warmer reception. "I was a little surprised by the enthusiasm" for the concept, says Varmus, who likes it himself. The idea is to set aside a pool of money for research projects costing, say, $50,000 to $200,000 a year, and to award a specified number of small, fixed-price grants each year. The goal would be to have applicants and reviewers spend less time on budgets and focus almost exclusively on science. Varmus says it "is definitely going to warrant more attention" and will be tested first by the National Heart, Lung and Blood Institute.

Varmus predicts there will be "more pilot studies" and "more discussions" before NIH endorses any of these concepts for use across the board. Some people, he adds, "have criticized me for paying attention to peer review as though I'm considering it a substitute for getting more money," but, he argues, this is not the case. Varmus says he is "just facing reality" in recognizing that NIH isn't likely to get a big budget increase. Meanwhile, he does want to "instill confidence" in the system and persuade researchers that "we're doing things as fairly as we can."

–Eliot Marshall