Caution Guides
Genetic Testing for Hereditary Cancer Genes

Recent discoveries of cancer-predisposing genes, including BRCA2 in December, have awakened researchers' anxiety about the problems surrounding genetic testing. But in the places where testing is now offered, the health care professionals involved seem thoughtful and creative in their efforts to protect patient privacy and help families make new decisions.

Since the first cancer-predisposing gene was identified more than a decade ago, researchers have identified about a dozen others — most of which have been cloned in the last 2 years. Although this may seem a modest beginning in light of the estimated 200 hereditary cancers (about 5% to 10% of all cancers), the new information has powerful implications — the ability to predict a person's vulnerability to disease.

Determine Destiny

"With the explosive developments in molecular biology, physicians can now determine a patient's cancer destiny with a simple blood test," summed up Henry T. Lynch, M.D., a professor of medicine at Creighton University, Omaha, Neb., and director of Creighton's Hereditary Cancer Institute.

Until now, genetic testing has been conducted primarily in university research settings such as Creighton's, where for 25 years more than 3,000 families with hereditary cancers have been invited for study.

But in the past year or two, genetic testing has begun to move out of its protected research environment into the clinical arena, where the general public has access to this potentially powerful information for the first time.

In a research setting, the patient pays no bills, and test results are not part of his or her permanent medical record. Outside a research study, in a private clinical setting, participants pay for the counseling, education, and testing; insurance coverage is uncertain; and test results are included in a patient's medical record.

In both settings, however, health care professionals are adamant that mechanisms must be in place to protect individual privacy and prevent genetic discrimination by insurers.

And at any time, test results can have profound psychological effects. Surprisingly, perhaps, a negative result may be as upsetting as a positive one.

"There are basically two types of people — the 'want-to-knowers' and the 'avoiders,'" said Barbara Biesecker, co-director of the genetic counseling program at the National Center for Human Genome Research at the National Institutes of Health. "Some people, even in the absence of being able to alter outcomes find information of this sort beneficial . . . the more they know, the more their anxiety level goes down. But there are others who cope by avoiding, who would rather stay hopeful and optimistic and not have the unanswered answered."

Most gene testing today still takes place within the context of a research setting and includes a high dose of education and counseling. Of the 54 NCI-designated cancer centers nationwide, about 15 offer testing for cancer-predisposing genes (see table for list of these genes).

Memorial Sloan-Kettering Cancer Center in New York and Creighton offer across-the-board testing for all these genetic alterations, while most others test for predisposition to a few specific cancers in high-risk families. Mutations predisposing for colon and breast cancer are tested for most frequently.

Commercial Testing

Commercially, LabCorp in Research Triangle Park, N.C., and OncorMed in Gaithersburg, Md., offer testing. Myriad Genetics Inc., Salt Lake City, announced Dec. 20 that it intends "to launch [in late 1996] a genetic predisposition diagnostic test" for the "BRCA1 breast and ovarian cancer gene." The company also said it intends to develop a test "that incorporates the BRCA2 gene," enhancing the "ability to identify genetic predispositions for hereditary breast cancer."

As genetic testing moves into the clinic, cost becomes an issue. For pre-test evaluation, counseling, and medical histories, clinic costs can range between $200 and $300. Then there are the additional costs for testing: For example, tests for each of the two genes involved in hereditary non-polyposis colorectal cancer (HNPCC) cost $870. And costs for BRCA1 testing by OncorMed can range from $150 to $1,600 as larger portions of the breast cancer gene are tested.

Who pays the bills? It may be too early to tell. But at this point, some insur-
ers seem willing to pick up the tab for the pretests. For those who have cancer already, insurers’ willingness to pay for gene tests is unpredictable. Disease-free people, on the other hand, frequently pay their own bills for fear their test results will cause their insurance rates to be raised or their policies to be canceled.

**Patient Privacy**

Another major issue is patient privacy. The Creighton staff is working with Nebraska legislators to pass laws to protect patients from insurance discrimination. The staff at the Clinical Genetic Service at Memorial Sloan-Kettering just completed writing testimony for New York State legislators urging similar patient protection.

But Jill Stopfer, a certified genetic counselor and the Familial Cancer Coordinator at the University of Pennsylvania’s Cancer Center, prefers to attack the problem on a federal level, and is working on national reforms to override state laws. Only a few states have some form of protection against genetic discrimination in health insurance, and no federal laws are in place.

Some individuals who want to be tested are referred by their personal physician or other health care professional, said Stopfer. A large number of self-referred individuals learn about the year-old Cancer Risk Evaluation Program at the University of Pennsylvania through the lay press, support organizations, and cancer referral services.

Penn’s process to determine eligibility for testing begins with two or three meetings with various health professionals, according to Stopfer. Participants share their medical and family histories and are offered education and counseling about the risk factors for cancer and the risks and benefits of genetic testing.

When the family history is confirmed through medical records, a decision is made about eligibility for testing.

At Creighton, a person must have two first-degree relatives with cancer or, at a minimum, one first- and one second-degree relative, to qualify for testing, according to Susan Tinley, a certified genetics counselor who works at Creighton’s new Hereditary Cancer Prevention Clinic. “Of [any] 50 to 100 people interviewed on the phone or in person, most do not have enough family history to be tested,” said Tinley.

But even those who are not eligible still find this a valuable service, Stopfer observes. “They may be reassured that their cancer risk is actually lower than they thought, and may benefit from further education or a tailored surveillance program.”

In contrast, participants who are eligible for testing have a difficult decision to make.

“Sometimes they are initially very excited about the genetic testing . . . they feel on the cutting edge of technology,” Stopfer said. “But when they learn that there is no known way to reduce the risk of getting breast cancer even if they were to test positive for a BRCA1 mutation, the decision to test seems less clear-cut. And when they face the possibility of future discrimination for health, life, and disability insurance,” she added, “many choose not to be tested.”

Even within the confines of a research environment, “one of the most significant ‘risks’ relates to insurance coverage,” said Katherine A. Schneider, of the Dana Farber Cancer Institute’s Division of Epidemiology and Control, Boston. “Even though participants in a research setting avoid reimbursement problems because they don’t pay for testing, their policies for health, life, or disability insurance might be canceled or their premiums raised,” she said.

“One of the safeguards Dana Farber has put in place to ensure individual privacy is a certificate of confidentiality, provided by the U.S. Department of Health and Human Services. This protects our research records from third-person requests and even subpoenas,” said Schneider.

**No Complete Protection**

Another strategy followed by most researchers is to remove names from the blood samples to be tested. Mary B. Daly, M.D., Ph.D., at the Fox Chase Cancer Center in Philadelphia, replaces donor names on samples she is testing for alterations in the BRCA1 gene with identification numbers. Still, Daly agrees with Schneider. “Since no one can ensure complete protection of information, insurance concerns continue to be a key factor for people choosing not to be tested.”

As a strategy for protecting records in a clinical setting, Tinley and the staff at Creighton don’t allow the release of the medical records without the written consent of the patients. However,
many who are tested in the clinic do not take a chance and pay for the service themselves.

Aside from insurance issues, psychological factors also play a role in people's decision to be tested. Stopfer agrees with Biesecker's categories — the "want-to-knowers" and the "avoiders." She notes that some feel they would have more control over their health care if they knew they inherited an alteration; others decide they could not adjust to a positive test result.

Nevertheless, a recent survey of first-degree relatives of breast cancer patients found that 90% — at least in theory — wanted to know their individual risk. The most common reasons cited were to learn about their children's risk, to know whether to increase cancer screening tests, and to take better care of themselves.

But moving from theory to the actual decision to be tested is not so simple. Writing in the spring/summer 1995 issue of Hereditary Colon Cancer Newsletter about her first experience offering testing to a large hereditary non-polyposis colorectal cancer family, Pam Chapman, a clinical nurse specialist in genetics at the Northern Genetics Service, Newcastle-upon-Tyne, England, commented about the high level of anxiety of family members as they went through the decision-making process.

"I think the source of this anxiety lies mostly in uncertainty," Chapman wrote. "We cannot predict if or when a person will be affected (with HNPCC), or which organs may be affected. We are not sure which screening protocols to follow, and it is difficult to convince surgeons that gene tests are accurate."

Of the 16 family members who received their test results, most apparently adjusted well to the new information, but a few did need minimal psychological support. "It may surprise you to hear that 'good' results have caused great upset," Chapman noted. "This is a common finding in other genetic disorders, and it is not really surprising when you think how complicated family relations are; if we 'survive' the family problem we feel sad for those who don't and guilty for ourselves."

Sometimes, she added, "life decisions are based on a high risk of developing cancer, and if we take away the risk, a major adjustment must begin. . . . We all have a great deal to learn in dealing with new genetic information."

— Nancy J. Nelson

### Cloned Genes Associated With Increased Risk of Cancer

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<thead>
<tr>
<th>GENE (date cloned)</th>
<th>CANCER PREDISPOSITION</th>
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<tbody>
<tr>
<td>RB1 (1986)</td>
<td>Childhood tumors of eye</td>
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<tr>
<td>WT1 (1990)</td>
<td>Childhood kidney tumors</td>
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<tr>
<td>NF1 (1990)</td>
<td>Nerve tumors</td>
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<td>APC (1991)</td>
<td>Colorectal cancer</td>
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<tr>
<td>NF2 (1993)</td>
<td>Acoustic nerve and brain tumors</td>
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<tr>
<td>VHL (1993)</td>
<td>Benign and malignant tumors in kidney, retina, central nervous system, pancreas, adrenal gland</td>
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<tr>
<td>MTS-1/p16 (1993)</td>
<td>Malignant melanoma, pancreatic cancer</td>
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<tr>
<td>RET (1993)</td>
<td>Multiple endocrine neoplasia; thyroid and adrenal cancer</td>
</tr>
<tr>
<td>BRCA1 (1994)</td>
<td>Breast and ovarian cancer</td>
</tr>
<tr>
<td>BRCA2 (1995)</td>
<td>Breast cancer</td>
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— compiled by Nancy J. Nelson

### Behavioral Research Initiatives Given Emphasis

If Americans stopped smoking cigarettes, consumed less fat, and altered their lifestyles in other health-promoting ways, some experts say the number of annual cancer deaths in the United States would drop by 50% or more. Tobacco use, by itself, may be responsible for 30% of cancer mortality, and behaviors such as poor eating habits and failure to get regular breast screening also contribute to the death toll from cancer.

How can people be persuaded to change their behaviors?