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Genetic Testing for Cancer Susceptibility: What Your Institution Needs to Know

by Leslie M. Alexandre, Dr.P.H.

Any hospital starting a genetic screening program should be aware of the many problems, both scientific and ethical, raised by such testing. Some argue that we are unprepared and unable to manage the information that the new diagnostic technology offers. Others argue that a carefully designed genetics counseling and screening program can help patients make better informed choices about the lifelong health care management of themselves, and perhaps their families. Here, author Leslie M. Alexandre makes just that case.

The availability of genetic testing could be one of the century's most important developments in cancer prevention and management. Already genetic testing is available to determine susceptibility to a number of cancers, including medullary thyroid, melanoma, colorectal, and breast-ovarian. Yet, tests for cancer susceptibility have been met with confusion and controversy. Because issues surrounding the breast are provocative in our culture, testing for inherited mutations in the BRCA1 and BRCA2 genes has added highly charged emotion to the debate and led to many misconceptions about the usefulness and consequences of genetic testing for people at high risk for inherited cancer.

When scientific discoveries venture into promising but uncertain new realms, some people understandably react with caution. Although such apprehension can be constructive and lead to further education and knowledge, the reaction can be harmful when it discourages people from seeking a potentially life-saving approach to health care. Health care institutions, particularly those that specialize in cancer care, have the responsibility to turn the current confusion on genetic testing into a constructive opportunity for education by helping to dispel the misconceptions surrounding this powerful new technology.

One of the most unreasonable misconceptions about genetic testing for cancer susceptibility is that it will soon be offered to the public as a form of cancer screening. *Susceptibility tests are not screening tests.* Whereas cancer screening tests, such as mammography and Pap smears, are designed for the early detection of disease, susceptibility tests provide information that can help clarify risk for developing an initial or a second primary cancer. Cancer screening tests are offered periodically (generally on the basis of age and gender) to the asymptomatic general population and are usually relatively inexpensive to perform (less than $100). In contrast, susceptibility tests are appropriate only for individuals at high risk for developing cancer based on family history or early age of onset. Testing is performed just once (excluding confirmational testing) and typically ranges in cost from a few hundred to more than one thousand dollars.

Another frequent and potentially harmful misconception about susceptibility testing is that there is no clinical benefit to knowing if one carries an inherited mutation that predisposes to cancer, particularly if that individual already has cancer. In fact, most people who undergo testing today are already affected with the disease. Genetic testing may profoundly affect the survival of people who have been diagnosed with cancer by alerting the physician to those patients who are most likely to experience a recurrence and may benefit from more aggressive interventions.

If a woman with breast cancer tests positive for BRCA1, for example, there is a 65 percent likelihood that she will develop a second primary cancer. Given that information, a physician may choose to present the option of a bilateral mastectomy that would not necessarily be appropriate for the patient with sporadic breast cancer. Similarly, the same patient would have a much higher risk for developing ovarian cancer (up to 60 percent compared with about 1 percent in the general population), and therefore might be a candidate for prophylactic oophorectomy.

Colorectal cancer patients who test positive for mutations associated with hereditary nonpolyposis colon cancer (HNPCC, also known as Lynch Syndromes I and II), are candidates for total colectomy, since recurrence rates are much higher among this group.

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GENETIC TESTING FOR THE UNAFFECTED

Many cancer patients are sensitive to the risks faced by their children and other family members and seek testing so physicians can design an appropriate monitoring and surveillance program for their family. Here also persists an insidious misconception: If an unaffected individual tests positive for a genetic mutation linked to an inherited cancer, "there is nothing they can do about it anyway."

In reality there are important and potentially life-saving options for individuals identified at high risk for cancer through genetic testing. Indeed, when treating a cancer patient, health care institutions have a responsibility to offer other family members information about their potential risk. A positive test on an unaffected family member can alert the physician that more aggressive medical or surgical management is needed at a much younger age. In some cases, this approach brings extraordinary results. For example, a positive test for mutations in the RET gene is a virtual guarantee of developing medullary thyroid carcinoma, and prophylactic surgery is 100 percent effective in preventing this frequently fatal form of thyroid cancer.

With HNPCC, earlier and more frequent colonoscopies can help physicians locate and remove potentially dangerous polyps. It is well documented that this approach is lifesaving among individuals at high risk for HNPCC based on family history.[1] Gene testing provides an easy way to determine which members of a high-risk family really need to undergo this more aggressive, relatively costly, and uncomfortable screening program, and which could reduce the type and frequency of screening to something closer to American Cancer Society guidelines.

Women testing positive for mutations linked to hereditary breast and ovarian cancer should begin routine mammograms and breast examinations at a younger age, and prophylactic surgery (mastectomy and oophorectomy) should be discussed as an option.[2] This is especially important for ovarian cancer, for which there are no well-established methods of early detection. While studies show that such prophylactic surgeries do not eliminate all risk of cancer, the limited data that do exist suggest that such procedures dramatically reduce the risk for both breast and ovarian cancers. If surgery is not an acceptable option, vigilant surveillance of the high-risk individual may result in life-saving early detection.

INFORMED CONSENT

Another common misconception about genetic testing for cancer susceptibility is that it should be confined to research settings, which are best able to select appropriate candidates and ensure patients are adequately counseled and protected from discrimination. As we know, good quality counseling requires committed and well-educated health care providers who are willing to spend the necessary time with their patients. The availability of such providers is not limited to research environments. As for discrimination, if the patient is given his or her test results, the fact that the testing occurred as part of a research study offers no protection from potential future discrimination. And the best way to ensure only high-risk patients are offered testing is to require the use of a protocol that specifies exactly who may and who may not be tested.

Institutions that create their own testing protocols must fully inform patients about the risks and limitations as well as the benefits of testing. Individuals must be counseled before the test is performed and again after the results are known. Patients must be educated about the implications of a positive and a negative result, potential clinical utility of testing, options for risk estimation without testing, psychological and familial considerations, implications for insurance (health, life, and disability), and confidentiality.

Institutional positions on genetic counseling and informed consent should parallel guidelines issued by the American Society of Clinical Oncology. ASCO states that all individuals at risk for inherited cancer "should have access to appropriate genetic testing and associated medical care," and that "oncologists must assure that informed consent has been given by the patient as an integral part of the process of genetic predisposition testing."[3]

As part of the informed consent process, people seeking genetic testing for cancer susceptibility, or any other diagnostic evaluation, should be advised that they may be psychologically affected by the results. This leads us to another misconception: Individuals who seek testing for a mutation linked to cancer are apt to be psychologically devastated by a positive result, and those who test negative are apt to suffer from survivor guilt. While such results are often reported anecdotally, the only study published to date that systemically examined this issue showed quite different results.[4] Researchers found that at one month after being tested for BRCA1 mutations, high-risk women who tested positive showed no significant change in their psychosocial scores from their baseline (pretesting) measures. Women who tested negative showed marked improvements in their psychosocial scores.

These initial data are encouraging in that they suggest when well-counseled, high-risk women are presented with genetic information as they should be—as one tool in a cancer-fighting arsenal and not as the final answer or promised cure—they need not be psychologically damaged by that information. Furthermore, the findings focus perspective on the primary psychological issue: People with a strong family history of cancer are often gripped with fear and must live with the related stress and anxiety—with or without testing.

INSURANCE AND PRIVACY ISSUES

Fear of losing existing health insurance and not being able to obtain alternative coverage in the future is one of the main reasons high-risk women choose not to undergo testing for mutations on the BRCA1 and BRCA2 genes.

The fear is that insurers need genetic test results to discriminate against current or potential members who may have any inherited predisposition to cancer. As noted, most genetic tests for cancer susceptibility are currently provided to cancer patients. Sadly, these individuals are already extremely vulnerable with respect to their

medical coverage. It is unlikely that a genetic test result could worsen their situation with respect to any insurance or employment-related discrimination.

Insurers who want to underwrite policies to exclude individuals at high risk for developing cancer already do so on the basis of family history. At least until technology improvements speed the turnaround time and reduce the cost of genetic tests, it is unlikely any insurers will require testing, for which they would have to pay, to confirm what they already suspect. Hopefully, by that time we will have passed strong legislation to preclude this possibility.

There is, however, good reason to be optimistic about federal legislation to preclude individuals from being discriminated against on the basis of genetic or other health-related information. The recently passed Health Insurance Portability and Accountability Act of 1996 took some important first steps in addressing concerns about genetic discrimination by health insurers. Specifically, this new law mandates that:

1. Genetic information, including genetic test results, may not be treated as a pre-existing condition in the absence of a diagnosis of the condition for which testing was provided.

2. Medical plans cannot deny a person coverage (or continued coverage) based on health status, including genetic information, and

3. Group medical plans cannot require any person to pay a higher premium than other similarly situated members of the plan (e.g., all full-time employees) on the basis of health status, including genetic information.

Beginning July 1, 1997, this new law will protect existing group policyholders from discrimination based on the results of subsequent genetic testing. Clearly, however, additional legislation is needed to further protect people covered by individual medical policies, or who do not yet have health insurance. Federal legislation is also needed to set a national standard for the privacy of all personal medical information, including genetic information. This topic is expected to be an important issue during the 105th Congress.

MAKING GENETIC TESTING MEANINGFUL

Although legislative issues are important, they have little meaning unless appropriate patients are identified who can benefit from genetic testing. Molecular genetics must be responsibly integrated into the management of cancer patients and their families. This means providing a continuum of cancer management services, and not just a singular test. For a susceptibility test to provide meaningful clinical information, the result must be analyzed within the context of the patient's family history. Any company or institution that offers cancer susceptibility testing without prior assessment of the patient's hereditary cancer risk is not offering a test with practical value, and may well cause unnecessary worry and expense.

Most of us take it for granted that health care providers are gathering the information they need to take care of patients and, potentially, their families. As health care providers, we know this is often not the case. Medical records of patients often contain insufficient data to assess the risk for having a familial or inherited cancer.

In conducting hereditary cancer risk assessment, the clinician should attempt to take a family history that records all cancers in the family at least three generations back. Age of onset is an important factor, since inherited cancers tend to strike at earlier ages than sporadic cancers. Correct identification of the type of cancer may require pathology records to confirm. Even then, what is documented as the primary site may be vague, inaccurate, or missing altogether, particularly in much older records.

Evaluating the pedigree, or cancer family history, is more complicated than it seems, because many different cancers can be related. For example, mutations in the BRCA1 and BRCA2 genes are associated not only with breast and ovarian cancers, but also with prostate and colorectal cancers. Lynch Syndrome, or HNPCC mutations, are linked to endometrial and ovarian cancers in addition to colorectal. Some pedigrees are straightforward and can be readily interpreted by genetic counselors and other properly trained health professionals. Others require evaluation by an expert in hereditary cancers.

LOOKING TO THE FUTURE

Identifying people at high risk for developing inherited cancer is just one of the many potential benefits that genetic technology offers to cancer detection and management. Among the most exciting studies underway in cancer genetics—which could ultimately lead to significant improvement in treatment outcomes—are those attempting to show that the effectiveness of various cancer treatments depends on the types of mutations found in the tumor. For example, there is a growing body of peer-reviewed medical literature suggesting that p53 gene mutations are associated with tumor responsiveness to conventional therapies, such as chemotherapy and radiation.

The genetic test can help patients make better informed choices about their lifelong health care management. Those who test positive may benefit from frequent diagnostic procedures that begin at a young age. Those who test negative, although still a population at risk for developing cancer, will be spared years of unnecessary, costly, and anxiety-provoking exams. Patients can make educated choices about prophylactic surgery. For some, there is a simple peace of mind in just knowing.

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