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A Model Genetic Risk Assessment Program

by Joseph Halperin, M.D., Cecile Skrzynia, M.S., C.G.C., and Mark Graham, M.D.

Moses Cone Health System's Regional Cancer Center, along with the Division of Hematology-Oncology, and the Clinical Molecular Genetics Laboratory of the University of North Carolina at Chapel Hill have developed a partnership to provide for women in Greensboro, N.C., access to genetic risk assessment for breast and ovarian cancers. The clinic opened in 1996 shortly after the cloning of the two genes, BRCA-1 and BRCA-2, which, when mutated, increase the risk for development of breast and ovarian cancers. The clinic opened amid considerable controversy, in particular from some physicians who stated that defining risk without proven treatment interventions is inappropriate. Nevertheless, community demand won the day with subsequent acceptance, even by many of the physicians who were initially reluctant to support the program. The clinic has since been very successful and fully subscribed. It serves to empower women and their families in deciding, with appropriate information and education, whether to undergo laboratory testing for mutations in BRCA-1 and BRCA-2.

Collaboration with the University of North Carolina allows the physician and patient communities in Greensboro access to the expert skills of the genetic counselors and molecular biologists at the university center. Our arrangement with the university allows us to ensure accuracy in testing by providing independent cross-checking of each test result. At the same time, the university can expand its mission of community service and gain valuable research opportunities.

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ASSESSMENT PROCEDURES

The clinic operates by providing several stages of assessment, as detailed in Table 1. Women and families seen in the clinic speak to a clinic coordinator prior to a visit to learn the mechanics of the clinic visit process, the cost, and the appropriateness of proceeding with formal visits. The genetic counselor may speak with the patient by telephone if there is some question whether a visit to the cancer genetics clinic would be appropriate. Women are encouraged to bring family members along to the initial clinic visit.

Blood for laboratory testing is never taken at the first session. A scheduled break of several weeks is planned between the first and second session so that the client/patient and family can discuss the information presented in the first session. If the client/patient is well but at risk, at the first session we try to establish the principle of testing the most informative member of the family, who usually has been identified from development of the pedigree. This is most often a living member of the family who has had breast cancer at an early age or has had ovarian cancer. We may ask the patient/client to refrain from testing so that a more appropriate first test can be performed in a sister, mother, aunt, or cousin who fits these criteria.

The specimen is tested by two different independent techniques at the Clinical Molecular Genetics Laboratory in the Department of Pathology and Laboratory Medicine at UNC Hospitals. Again, a break of several weeks is planned before the third visit, at which time the results of testing are discussed with the patient.

Prior to Session III, the physicians and genetic counselor attend a conference of the cancer genetics program at UNC-Chapel Hill, which includes the clinical side of the program, along with the molecular biologists. At this meeting, the laboratory results for an individual family are discussed, and strategies are developed to ensure that the laboratory results are consistent with the clinical situation. Additional family members may be tested to confirm an initial finding. If a mutation is definitively established within a family, more extensive testing of at-risk but unaffected members of the family can be planned to confirm the presence or absence of the mutation.

CONFIDENTIALITY AND INSURANCE ISSUES

Several core issues loom over the discussions we have with patients and their families as questions about genetic testing are resolved

during the three sessions. One key problem relates to confidentiality. We ensure genetic medical record confidentiality by keeping records from these visits segregated from the main medical record. No communication occurs to the general physician, surgeon, or oncologist without written consent from the patient; any communication is verbal. Physicians also refrain from documenting entries in the medical record related to testing for the cancer susceptibility genes. The patient may request a letter be sent to his or her physician, or may forward a summary letter received from the clinic. No information is released to third parties without written consent from the patient, and this consent is time-limited. The patient becomes the responsible party to convey information requested on any insurance application.

If the genetic assessment fails to reveal a mutation in BRCA-1 or BRCA-2, then the patient can relate this as a positive endpoint—especially if a mutation is known to be present in the family. When a family history is highly suspicious for the presence of a mutation but none is detected after thorough laboratory investigation, the interpretation is more complex. Since there may be additional laboratory advances that will allow us to discover heretofore unknown mutations or errors in the gene, we tell the patient that the test is "negative for now," but may change in the future. This concept, which is difficult for many individuals to understand, implies that we will continue to maintain contact over time and retest older samples in the laboratory as new techniques become available.

A second important question that is related to cancer susceptibility testing is insurance bias. If the result of a test for a mutation in the breast cancer susceptibility genes is positive, the impact upon a patient with an existing cancer diagnosis is generally insignificant from an insurance perspective. However, if the individual has never had cancer and is determined to be at high risk because of a discovered mutation, the perspective of the insurer could potentially change. Limited data exist on whether carriers of mutations in cancer susceptibility genes frequently encounter insurance bias. However, anecdotal reports in national media have fueled the anxiety of many patients and families to the extent that the fear of losing insurance for an individual, or for the children or siblings

NCI's Cancer Genetics Network

Last year the National Cancer Institute announced the formation of its Cancer Genetics Network to create a national network of centers specializing in the study of inherited predisposition to cancer. The institutions comprising the network include two ACCC member institutions, Georgetown University Lombardi Cancer Center in Washington, D.C., and Johns Hopkins University in Baltimore, Md., as well as Duke University Medical Center in Durham, N.C.; Fred Hutchinson Cancer Center in Seattle, Wash.; University of California in Irvine, Calif.; University of Pennsylvania in Philadelphia, Pa.; University of Texas M.D. Anderson Cancer Center in Houston, Tex.; and University of Utah in Salt Lake City, Utah.

The network will be a national resource to support collaborative investigations into the genetic basis of cancer susceptibility, explore mechanisms to integrate this new knowledge into medical practice, and identify means of addressing the associated psychosocial, ethical, legal, and public health issues. The network will also facilitate the exchange of information on cancer genetics and research resources within the larger cancer and cancer genetics communities. Mechanisms will be developed to provide broad access to information about genetic services and educational materials for use by researchers, health care professionals, and the public.

Some of the scientific questions to be explored include:

- What is the prevalence of germline (heritable) mutations of familial cancer susceptibility genes in different populations?
- What determines whether someone with such an inherited genetic alteration develops cancer?
- What environmental exposures may interact with susceptibility genes to cause cancer?
- How can genetic discoveries be translated into cancer prevention strategies for susceptible individuals and into more effective treatments?
- What ethical and psychosocial issues affect healthy individuals and their families who may carry cancer susceptibility gene mutations?

SIGNING UP

The network will invite people at high risk of cancer due to family or personal history to add their names on a roster of potential study participants. These individuals will periodically receive practical information on cancer genetics and new developments in the field. Genetic testing and biospecimen collection will not be part of enrollment in the network, but are likely to be part of participation in a study. Participation in the network, and in any studies conducted through it, will be confidential, and all individuals will be protected by the latest in informatics safeguards.

With NCI funding, the network will also support pilot studies on cancer genetics and will foster collaborative research among the participating centers and between them and researchers outside the network. The aim is to encourage optimal use of this potential national resource.

Interested individuals can contact the NCI's Cancer Information Service (CIS) at 1-800-4-CANCER to learn about opportunities to participate.

of the patient, frequently affects the decision to be tested.

In reviewing numerous insurance application forms, our experience is that information regarding genetic mutations is usually not solicited. Thus the applicant is free from the dilemma of giving an appropriate answer when questioned about genetic testing. For those few individuals who are asked questions, and who have learned that they carry a mutation but do not have cancer, the issue is more complex. Since 1997 legislation has existed in North Carolina that prohibits discrimination based on genetic information. Other protections exist nationally under the Health Insurance Portability and Accountability Act; however not all situations are covered under these laws. Despite the laws that have been passed, many patients with cancer and their family members remain suspicious of the insurance system and refuse testing to protect their present and future rights to employment, health insurance, and life insurance.

DEALING WITH RESULTS

The last regularly discussed issues at all stages of cancer genetic testing deal with the psychology of being a carrier of a cancer susceptibility gene and interfamily relationships. In our experience, many individuals come to the clinic with an overestimation of their cancer risk; when provided with negative results, they are usually very relieved. However, this negative result is certain only when a definite gene mutation has been shown to be present in the family. Others have a negative result or a variant of DNA sequence of unknown significance when a definite mutation has not been proven. For these patients we must reemphasize our inability to exclude genetic mutations that may be discovered in BRCA-1 or 2 with better laboratory techniques, or in other still-to-be-discovered cancer-causing genes. No test is 100 percent accurate. We make a commitment to those with negative results that their samples will be re-tested in the event of new discoveries.

For those with positive results, we have learned that in most cases the predisposition was assumed by the patient. For these patients, the positive test confirms a more definite knowledge of the problem and allows for a proactive response. The pros and cons of different health management strategies (prophylactic mastectomy, prophylactic oophorectomy, chemoprevention, and increased surveillance) then can be discussed with the patient and all involved family members. In the case of a positive result, dilemmas can arise as families react to the information. We aid these families by discussing with them the best way to deal with this complicated issue. Our social worker provides invaluable assistance in this task.

We close each case by assuring those we have counseled that we remain available for further discussion and access in the event that new mutations are discovered or information is learned about existing mutations. We also invite patients to contact us if the family history changes or if the media report new genetic findings that may raise questions. Some may simply want to stay in touch to learn about new information regarding cancer genetics as it becomes available.

The experience of genetic testing can be daunting. For those individuals and families who pursue testing, our team provides education, information, laboratory expertise, and emotional support. ■

Table 1. Stages of Assessment

Session I: 1 to 1.5 hours

Attendees

- Patient (with or without family)
- Genetic Counselor
- Physician
- Social Worker (as needed)

Procedure

- History
- Pedigree development
- Genetic education
- Begin discussion of:
  - Who is the most appropriate family member to undergo genetic testing
  - Likelihood of the history representing a hereditary predisposition syndrome
  - Likelihood for the clinic attendee of having a positive or negative result if tested
    - Risk of positive or negative results
    - Possible interventions for positive result
    - Discussion of informed consent
    - Written informed consent form provided

Session II: 30 minutes to 1 hour

Attendees

- Patient (with or without family)
- Genetic counselor
- Physician (as needed)
- Social worker (as needed)

Procedure

- Answer questions generated by the first session and from the patient's own discussions with his or her family members
- Informed consent discussed and possibly signed
- Blood sample drawn if informed consent agreed upon and signed

Session III: 30 minutes to 1 hour

Attendees

- Patient (with or without family)
- Genetic counselor
- Physician (as needed)
- Social worker (as needed)

Procedure

- Discuss results of testing
- Surveillance issues if negative result
- Psychosocial issues
- Potential interventions if positive result; however, final decisions are deferred to the patient and his or her own physicians