Editor’s Note: This invited review discusses a service available to REX Healthcare physicians to assist with patients who are concerned about genetic susceptibility for cancers of the breast, ovary, endometrium or colon. The pre-test and post-test counseling of patients regarding the significance of test results is complex and time-consuming. The testing facility (Myriad Laboratories) requires the ordering physician to obtain an informed patient consent and sign a document to that effect. Myriad also requires prepayment of the entire laboratory test fee (between $2000 - $3000) for those patients whose insurance will not cover the cost. If the patient’s insurance agrees to pay for the test, either pre-authorization or 20% co-payment is required prior to testing. For these reasons, we strongly encourage physicians to refer patients interested in such testing to the Rex Cancer Genetics Clinic (784-3433), rather than the Laboratory.

Cancer Genetic Testing

Currently there are genetic tests available to determine if a predisposition to breast, ovarian, colorectal and endometrial cancer is present. Genetic susceptibility testing determines if an individual carries a gene mutation that increases the likelihood of developing a certain disease. Through deciphering a patient’s genetic code, genetic analysis can determine whether the patient possesses a mutated version of the BRCA1 or BRCA2 gene – both of which greatly increase the likelihood of developing breast and ovarian cancer or MLH1 or MSH2 gene – both of which increase the risk of developing Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and endometrial cancer. A genetic test is scheduled for release in 2002 to determine if a man is at increased risk for developing prostate cancer.

Genetic Susceptibility Testing for Breast & Ovarian Cancer

An estimated 7% of all breast cancers and 10% of all ovarian cancers are hereditary. Health professionals are often challenged to identify patients in whom genetic susceptibility testing may be of value. An understanding of the genes and how to identify individual at risk is an important first step in this process. BRCA1 (BR for “breast,” CA for “cancer”) was the first major breast cancer gene to be isolated. The BRCA1 gene was mapped to chromosome 17 in 1990. This gene was fully sequenced in 1994, and specific mutations were characterized. Larger than most genes, BRCA1 codes for a protein 1,863 amino acids long. BRCA2, located on chromosome 13, was the second major breast cancer gene to be isolated (1995). It is about twice the size of BRCA1 and codes for a protein 3,418 amino acids long. Both are tumor-suppressor genes: loss of either of their function confers an increased risk of breast and ovarian cancer.

BRCA mutations may be passed down from either mother or father, and each offspring has a 50% chance of inheriting susceptibility. Women and men normally possess two copies (alleles) of BRCA1, one from each copy of chromosome 17. Women who inherit one mutated copy of the BRCA1 gene from either parent are at a much greater risk of developing breast and ovarian cancer.
cancer. This is because a cell with one mutated allele does not have a “backup” if the other allele is damaged or lost. Half of all women who carry mutations have inherited susceptibility from their fathers. That means a woman can carry a BRCA mutation even if there is little or no history of breast or ovarian cancer on her mother’s side. For this reason, it’s important to assess both the paternal and maternal sides of the family when evaluating a woman’s risk. Men have an equal risk of carrying mutations, some men may wish to consider genetic testing to learn if they carry a BRCA mutation that could be transmitted to offspring. It is estimated that 84% of hereditary breast and ovarian cancers are caused by mutations in BRCA1 and BRCA2.

American women have about a 10% chance of developing breast cancer by the age of 80. The risk of breast cancer increases with age, with the majority of sporadic breast cancer occurring after menopause. The risk sharply increases in women who have inherited a single mutated copy of either BRCA1 or BRCA2; 56% to 87% by age 70. Women with these mutations have a significantly increased risk of developing breast cancer before the age of 50 of between 33% - 50%. There is also a significant increase in the risk for women with breast cancer who carry BRCA mutations to develop a second malignancy, which may arise in the ovary or as second breast cancers. Although breast cancer is rare in men, the risk is increased in men who carry BRCA mutations.

Ovarian cancer, although representing only 4% of women’s cancer, accounts for more deaths than any other reproductive cancer. Overall, American women have about a 2% risk of developing this disease. However, if a woman carries a BRCA1 or BRCA2 mutation, her risk jumps to between 27% - 44%. In 1996, the American Society of Clinical Oncology (ASCO) recommended that genetic susceptibility testing be offered in the setting of a “strong family history of cancer or very early onset of disease” when the results will influence medical management. ASCO recommended genetic testing in individuals with a greater than 10% probability of carrying the mutation. This may be determined through the use of a Mutation Prevalence Table (insert). Factors, which suggest a patient may benefit from genetic testing, include:

1. A diagnosis of breast cancer or ovarian cancer, especially premenopausal breast cancer
2. A family history of breast or ovarian cancer
3. A blood relative who is known to have a mutation in BRCA1 or BRCA2.
4. Ashkenazi Jewish women who have breast or ovarian cancer or a family history of one or both diseases.

Genetic Susceptibility Testing for Colorectal and Endometrial Cancer

Colorectal cancer is the second most common cause of cancer deaths in the United States. Endometrial cancer is the fourth most common cancer in women. These two cancers are also hallmarks of an important hereditary cancer syndrome known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC). Formerly known as “Lynch Syndrome,” HNPCC is the most common hereditary colon cancer syndrome and is responsible for 3 – 5% of all colorectal cancers. It is in an inherited autosomal dominant pattern and if present indicates a 80% lifetime risk of colon cancer and a greatly increased risk of endometrial cancer, as well as upper gastrointestinal, ovarian and urinary tract cancers. Mutations in the MLH1 and MSH2 genes account for over 90% of HNPCC. Characteristics of HNPCC syndrome include:

1. Cancers are early onset, usually < age 50.
2. Colorectal cancers usually demonstrate tumor microsatellite instability.
3. Individuals with HNPCC develop polyps, but not in large numbers.
Individuals who inherit a mutated MLH1 or MSH2 gene are at an increased lifetime risk of several different cancers:

<table>
<thead>
<tr>
<th>HNPCC ASSOCIATED CANCERS</th>
<th>HEREDITARY RISK*</th>
<th>POPULATION RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>.80%</td>
<td>2%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>40 – 60%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Gastric</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>9% – 12%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Kidney/Urinary Tract</td>
<td>3% - 10%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Biliary Tract &amp; Gallbladder</td>
<td>2% - 18%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>1% - 4%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Risk of cancer by age 70

The first step in hereditary risk assessment is identifying patients who may have HNPCC. If your patients have any of the following hallmarks you should consider genetic testing.

1. A personal or family history of early onset colorectal or endometrial cancer.
2. A personal or family history of multiple HNPCC-associated cancers in the same person (such as two colorectal cancers or colorectal cancer and endometrial cancer).
3. It is most appropriate to begin testing with the individual with the cancer, prior to testing other family members.

**Genetic Testing Process**

Genetic testing for cancer predisposition may seem deceivingly simple in that the actual laboratory testing is performed only on a sample of the patient’s blood. However, there are several complex and time-consuming steps necessary before performing the actual test. These steps include obtaining informed consent, insurance authorization and counseling. Genetic testing for cancer susceptibility is certainly not for all individuals who present with an increased cancer risk. Some individuals, after understanding the process and the implications of the test results, decide that they are not interested in knowing their genetic status. Genetic testing is very expensive with the cost averaging between $2000.00 - $3000.00. Patients must have prior authorization from their insurance company or be willing to pay up front before the testing can be requested.

We are very fortunate at Rex to offer a Cancer Genetics Clinic that provides consultations and testing for individuals in need of this service. At the Rex Cancer Genetics Clinic patients who are at an increased risk for hereditary cancer meet with a genetic counselor and/or medical geneticist from University of North Carolina’s Lineberger Comprehensive Cancer Center. A family pedigree for the past three generations is recorded and the patient is evaluated. If it is determined that the patient would benefit from DNA testing and/or further evaluation, arrangements are made for the testing. (Some patients after the initial evaluation are not deemed at particularly high risk. Those patients are encouraged to contact the clinic annually for new tests or interventions that might have an impact on them.) Test results are reported back to the medical geneticist or counselor for their interpretation. Patients are counseled prior to the testing as well as after the results are in for interpretation of what a mutation or the absence of a mutation means for their medical care. Medical recommendations developed specifically for the patient are then reviewed. Due to the sensitive nature of genetic testing and the possible implications for health insurance, this process and any results from the testing are maintained under the strictest confidentiality.
Patients must give their permission for their results to be shared with anyone, including their personal physician. All clinic records are maintained through the UNC Medical Genetics Department.

The Rex Cancer Genetics Clinic meets on a monthly basis in the Radiation Oncology Department at the Cancer Center. The team from UNC consists of a medical geneticist and genetic counselor that work with an oncology clinical nurse specialist and a medical and radiation oncologist from the Rex Cancer Center. Patients seen through this program have the added benefit of being evaluated for any national research opportunities that UNC participates, which includes test funding through grants at UNC. If you have a patient that is thought to be at an increased risk for hereditary cancer, you can refer them (or patients may self refer) to the Rex Cancer Genetics Clinic by calling 784-3433.

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Coordinator, Rex Cancer Genetics Clinic

References:


Test Notes: The TORCH is Passed

Effective immediately, the N C State Public Health Laboratory will no longer accept specimens for TORCH panel testing. Requests for this panel (“TORCH titer”) will be referred to Mayo Medical Laboratory for a TORCH profile composed of *Toxoplasma* IgM antibody, *Rubella* IgM antibody, *Cytomegalovirus* IgM antibody, and *Herpes Simplex* IgM antibody. The cost of the test is $153.42.

John D. Benson, MD

The REX Healthcare Laboratory staff extends their best wishes to you and your family during the approaching holiday season. We look forward to serving you in 2002.