Identifying and Testing for Hereditary Susceptibility to Common Cancers

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ABSTRACT Hereditary cancer syndromes account for an estimated 5% of breast, ovarian, and colon cancers. The rapid discovery of cancer-related genes in the last 15 years has propelled the field of cancer genetic risk assessment forward. With patients becoming increasingly aware of available genetic testing options, it is important that various health professionals become knowledgeable in identifying and advising patients at increased risk for a hereditary cancer syndrome. This article will outline the components of providing a hereditary cancer risk assessment with a focus on hereditary breast and ovarian cancer syndrome and hereditary colon cancer.

INTRODUCTION

Hereditary cancer syndromes are estimated to account for 5% of diagnosed breast, ovarian, and colon cancers. Although uncommon, they are important to recognize because they confer a high risk of multiple primary cancers occurring at younger ages, affecting multiple members of a family who inherit the cancer-predisposing genetic mutation. More importantly, patients and providers are recognizing the potential therapeutic advantages of identifying hereditary cancer risk. With a growing number of preventive care options available to patients and families with hereditary cancer syndromes, the process of systematically assessing risk is becoming increasingly important.

Both provider and patient forces are contributing to the development of hereditary cancer risk assessment. Patients are becoming increasingly aware of cancer genetics through media exposure and, more recently, through direct-to-consumer advertising of commercially available testing. Patient interest and awareness of testing has in turn affected delivery of genetic services. In fact, patient inquiry about cancer genetic testing is one of the strongest predictors of providers ordering or referring for testing.

Nongeneticist health professionals, such as primary care physicians, specialists, and nurses, acknowledge that they will have a growing role in providing cancer genetic services in the future, particularly as patient demand increases. Clinicians in all fields may recognize a legal responsibility for assessing and communicating genetic cancer risk to patients and their families, as cases surface in the courts.

This article will guide the reader through the process of providing a hereditary cancer risk assessment. The first section will outline steps common to risk assessment and testing of hereditary cancer syndromes in general. The following two sections will detail issues specific to hereditary breast and ovarian cancer syndrome (HBOC) due to mutations in BRCA1 and BRCA2 genes, and hereditary colon cancer (HCC), specifically familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), as these generate the most referrals for cancer genetic counseling (L. Acheson, MD, MS, unpublished data, 2001). These syndromes are particularly important because they include common cancers that are amenable to screening modifications based on risk.

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GENERAL ASPECTS OF HEREDITARY CANCER RISK ASSESSMENT

Identifying Individuals at Increased Risk

The majority of patients who develop cancer do so sporadically, that is, there is no familial or hereditary risk. The small percentage of patients with a hereditary cancer syndrome may be suspected on the basis of personal and family medical history. Patients displaying any of the features listed in Table 1 may warrant further evaluation. Specific criteria for HBOC and HCC are outlined in the next sections. Unfortunately, data gathering around family history is often incomplete.17,18 When a family history of cancer is obtained, critical details needed for risk assessment, such as the cancer site and age of diagnosis, are often lacking. This occurs in both primary care and specialty settings.19,20 One study showed that an age of diagnosis was documented in only 7% of relatives identified as having cancer.17 Tools to help facilitate family history gathering, such as medical intake questionnaires, have been in use for many years, but data showing their effectiveness are lacking.

Computer-assisted family history collection tools for clinicians and patients are currently being developed and tested.21–25 For example, the National Society of Genetic Counselors’ Web site (www.nsgc.org) has information to help patients learn how to generate a family history and pedigree.26

Pedigree Construction

If a hereditary cancer syndrome is suspected, a detailed family history must be obtained and confirmed if possible through review of medical records. This is displayed as a pedigree showing three or more generations.27 The pedigree should include both the affected and nonaffected relatives, and ethnicity should be identified. Identifying Ashkenazi Jewish ancestry is particularly important, as some mutation probability models include this ethnicity as a risk factor. For affected relatives, age of diagnosis, death, and specific cancer site should be documented. High-risk lesions such as atypical ductal hyperplasia, lobular carcinoma in situ, and colon polyps should be noted. For syndromes with autosomal dominant transmission, such as HBOC and HCC, the pedigree is often suggestive. However, family history can be unremarkable, for example, with a small family, uncertain family history, de novo mutation, or incomplete penetrance, with some mutation carriers never developing cancer. Whenever possible, the cancer diagnosis in the affected relative should be verified by pathology reports or medical records.

Genetic Counseling and Testing

A recently published national survey reports that approximately 30% of primary care physicians and 33% of specialists have referred patients for hereditary cancer risk assessment or ordered testing for hereditary cancer.10 More than 80% of primary care clinicians believe that the number of patients requesting testing will increase over the next 5 years.12 Among the specialists surveyed, oncologists lead in ordering or referring for testing, followed by surgeons and gastroenterologists. While any physician may order testing, the American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be done only if detailed pretest and posttest counseling are provided.28 This may be accomplished by the ordering physician or, as more commonly occurs, a referral can be made to a genetic health professional. Medical geneticists, certified genetic counselors, and recently, genetic oncology nurses are specifically trained to provide cancer genetic counseling. Medical geneticists are MD or PhD trained and are certified by the American Board of Medical Genetics. Genetic counselors are Master’s degree-level trained and are certified by the
American Board of Genetic Counseling. Genetic oncology nurses are either Bachelor’s degree-trained (registered nurse) or have a Master’s degree (advanced practice nurse in genetics). It is important to recognize that only 42% of the 2,500 genetic counselors in the United States and 1,000 genetics clinics currently provide cancer genetic counseling.29 The available geneticists, genetic counselors, and genetic nurses can be found through www.nsgc.org,26 www.nci.nih.gov/search/geneticsservices/,30 or by calling the National Cancer Institute information service at 1-800-4-CANCER.

The Process of Genetic Counseling

First, a detailed family history is obtained by phone or in person before the interview. Relatives’ medical records are requested to verify the cancer diagnoses. If the person requesting cancer genetic assessment has not had cancer, he or she will be encouraged to identify a relative who has had the type of cancer in question and is willing to undergo genetic testing. If the decision is made to pursue cancer predisposition testing, pretest counseling and informed consent comprise the second stage. Ideally, patients should be given a period of time to contemplate their decision before signing a consent document and proceeding with testing. Finally, the last stage of the process involves posttest counseling when the individual receives test results.

Components of Informed Consent

ASCO lists 12 elements that should be covered in counseling before informed consent for cancer predisposition testing.28 In addition, genetic testing laboratories often request specific clinical information and require the patient’s signature on their own informed consent document.31 ASCO lists 12 basic elements of informed consent.

A Description of the Purpose and Type of Test Being Performed

The purpose is to determine whether a mutation can be detected in a specific cancer susceptibility gene. One must specify whether a sample of blood or other cells is to be tested for germline mutations present in every cell of the body or whether the sample is cancer tissue to be tested for mutations.

Technical Accuracy of the Test

The sensitivity of tests for detecting cancer-predisposing mutations is dependent on the molecular method used. Numerous molecular methods for testing exist. For example, genetic testing used in FAP includes full gene sequencing, protein truncation testing, and a combination of the two. Sensitivity ranges from 80% to 95%.32 Techniques used in BRCA1 and BRCA2 testing include exon scanning, direct sequencing, protein truncation test, and allele-specific oligonucleotide testing. Sensitivities range from 63% for exon scanning to greater than 99% for allele-specific oligonucleotide testing.33 Specific sensitivity and specificity rates may be obtained from the individual testing laboratory. However, the positive predictive value of a diagnostic test depends not only on its sensitivity and specificity but also on pretest mutation probability, based on personal and family history and ethnic background.

Implications of a Positive and Negative Result, and Possibility That the Test Will Not Be Informative

Whenever possible, a sample of blood or cancer tissue should be tested from an affected family member first. This test will be a search for mutations known to be associated with the type of hereditary cancer in question, for example, by complete sequencing of the gene(s). If a cancer-associated mutation is found, other family members can be offered mutation-specific analysis (also called single-site analysis). A positive result indicates that the individual is at increased risk for cancer. A negative result (absence of the cancer-associated mutation found in an affected relative) implies that the unaffected individual’s own risk for cancer is no greater than that of the general population. There is a concern that people who test negative will perceive themselves to be at lower risk than the general population.34 They should be
reminded that if they test negative, population-based screening guidelines are advised.

Many individuals do not have an affected relative available or willing to undergo testing. Cancer susceptibility testing is sometimes undertaken nonetheless. A positive result implies that there is an increased risk of developing cancer. A negative result does not rule out the possibility of an abnormality in a gene that cannot be detected by DNA sequencing or abnormalities in other genes responsible but not yet identified for inherited susceptibility to cancer. Therefore, a negative result when no cancer-associated mutation has been found in the family is uninformative.

Some laboratories offer multisite testing to individuals from populations with known founder mutations. Founder mutations are those found unique and specific to a certain population. Women of Ashkenazi Jewish descent have a 2.3% risk of carrying a BRCA1 or BRCA2 genetic mutation, the majority of which are founder mutations. For example, when testing for BRCA mutations in Ashkenazi Jews (those of Eastern European ancestry, as are 95% of Jews in the United States), it is reasonable to start by testing for three cancer-associated founder mutations prevalent in this population: 187delAG, 5385insC, and 6174delT. If none of these are present, one may then elect to pursue comprehensive testing, eg, complete sequencing of the BRCA1 and BRCA2 genes.

DNA sequencing may reveal a genetic variant of uncertain significance. Genetic variants of uncertain significance often result from a missense mutation or a single base pair change in the gene, with unknown effects on the protein product. The clinical implications are unknown, and the test is considered to be uninformative with regard to the risk of cancer. Variant results are relatively common in BRCA1 and BRCA2 testing and occur in approximately 10% of samples.

**Options for Risk Estimation Without Genetic Testing**

Risk prediction models may provide sufficient information for the individual’s needs. Models pertinent to HBOC and HCC are described below. The level of determined risk may prompt patients and providers to consider more aggressive screening and other health protective behaviors.

**Risk of Passing Mutation to Children**

In testing for germline mutations, patients must be made aware that men and women who carry a mutation have a 50% chance of passing it on to each of their children. Testing minor children for hereditary cancer mutations is recommended only when prevention strategies are necessary at a young age (eg, FAP).

**Fees Involved in Testing and Counseling**

The cost of genetic counseling ranges from $150 to $400. A physician’s examination is often required to submit for medical reimbursement. The cost of genetic testing ranges from $300 to $3,000, depending on the type of testing performed. Some individuals choose to pay for testing out of pocket due to concerns of insurance discrimination; however, many insurers will provide at least partial coverage for testing if medically indicated. Some testing laboratories provide reimbursement assistance to interested individuals.

**Psychological Implications of Test Results**

Psychological factors affect both pretest and posttest behaviors. Studies show that pretest anxiety influences an individual’s cancer risk perception as well as the ability to adapt that perception after cancer risk counseling. Exploring how test results will affect an individual, particularly one with baseline anxiety, depression, cancer, or recent bereavement, is important. It can be helpful to ask an individual to contemplate his or her reaction to a positive, negative, or uncertain result and to identify social supports.

**Risks of Insurance and Employer Discrimination**

Health insurance and employment discrimination are significant concerns for individuals.
contemplating testing. Fear of insurance discrimination has been reported as the single most important reason why individuals choose not to get testing.\textsuperscript{39,40} In a 2000 study of genetic health professionals, 68\% stated that they would not bill their insurance company if they chose to get genetic testing for fear of discrimination.\textsuperscript{41}

A combination of federal and state laws addresses insurance discrimination based on genetic information. The Health Insurance Portability and Accountability Act of 1996 became the first federal law to directly address genetic information. The law prohibits health insurance discrimination for group health plans but does not address individual health plans. Individual states have passed various laws addressing this discrepancy as well as other issues more specific to genetic testing. To date, 34 states have passed laws that strictly prohibit the use of genetic information for risk selection and risk classification. A list of individual states and their protections can be found at the National Conference of State Legislators Web site at www.ncsl.org.\textsuperscript{42} State laws for life, disability, and long-term care insurance can be viewed at the same Web site.

The Americans with Disability Act of 1990 protects persons with physical or mental disabilities from discrimination. In 1995, the Equal Employment Opportunity Commission interpreted disability in the Americans with Disability Act to include genetic predisposition; however, it is unclear whether the Supreme Court will consistently accept the Equal Employment Opportunity Commission interpretation. Currently, genetic discrimination is prohibited in the hiring, firing, and terms of employment in 31 states. For a complete listing of state laws concerning employment discrimination, view the Web site listed above.

Confidentiality Issues

Laws in all states and the Health Insurance Portability and Accountability Act rules restrict access to medical records. Laws pertaining to informed consent, disclosure of genetic information, and genetic samples as personal property all vary by state and can be found at www.ncsl.org.\textsuperscript{42} Some clinicians keep a separate medical record for genetic information to further protect privacy.

Strategies for Surveillance and Cancer Prevention Following Testing

This is the most important reason for many people who seek cancer genetic risk assessment. Details of the prevention options for HBOC and HCC are outlined below.

Importance of Sharing Genetic Test Results With At-risk Relatives So That They May Benefit From This Information

The medicolegal responsibility of providers to disclose results of testing to family members remains unclear.\textsuperscript{14,15} The American College of Medical Genetics states that the results of genetic testing should not be disclosed to family members without the patient’s consent, except if there is an imminent danger of harm to the relative that could be averted by knowing the information.\textsuperscript{43} Because of incomplete penetrance and uncertain time course, hereditary cancer susceptibility may not meet these criteria; however, most members of the public (>95\%) believe that they themselves would have a duty to disclose results to family members if the knowledge would enable the relative to prevent hereditary cancer.\textsuperscript{44} ASCO and others believe that the most appropriate approach to relative notification is through discussion with the tested individual who would then have the responsibility of notifying family members.\textsuperscript{28}

Testing Facilities

Many academic centers have genetic testing laboratories, but most perform a limited range of tests. In the United States, comprehensive analysis of the BRCA1 and 2 genes is performed only at Myriad Genetics Laboratory.\textsuperscript{31} Specific BRCA mutation analysis and genetic testing for FAP and HNPCC are available at a number of locations in the United States. A complete list of Clinical Laboratory Improvement Amendments-certified laboratories for
each of the hereditary cancer syndromes can be found at www.genetests.org.45

**Result Reporting and Posttest Counseling**

Turnaround time for result reports averages 3 to 6 weeks, although some laboratories will provide results sooner for an additional charge. Test results are provided in writing by the laboratory to the referring clinician only, and the report usually includes the raw data, clinical interpretation of test results, sensitivity and specificity information, and references. Geneticists advise informing the tested individual in person, in conjunction with posttest counseling. This includes interpreting the results, discussing their implications for preventive care and for family members, referral to support groups and other information resources as appropriate, and providing emotional support to the person receiving the results. Information, support, and advocacy groups for specific diseases can be accessed at www.genetests.org45 and at www.geneticalliance.org,46 among others.

### HEREDITARY BREAST AND OVARIAN CANCER

**Hereditary Syndromes**

There are several types of hereditary syndromes that are associated with breast and ovarian cancer. Between 80% and 90% of all hereditary breast and ovarian cancers are caused by mutations in \(BRCA1\) or \(BRCA2\).36 Recent data indicate that these estimates may be high as more research evolves regarding the role of low penetrance gene mutations in breast cancer.47 Among these inherited syndromes, the most commonly occurring is HBOC syndrome. Several personal and family history characteristics are suggestive of HBOC (see Table 2). HBOC syndrome is caused by mutations in \(BRCA1\) or \(BRCA2\). The \(BRCA1\) and \(BRCA2\) genes function primarily as tumor suppressor genes working to recognize damaged DNA. Research is being done to identify a possible “\(BRCA3\)” genetic mutation, but so far this has proven elusive.48

The mutations in \(BRCA1\) or \(BRCA2\) causing HBOC are inherited in an autosomal dominant fashion and are highly penetrant. Mutations in \(BRCA1\) typically confer a lifetime risk between 50% and 85% for women to develop breast cancer and a 15% to 40% lifetime risk for the development of ovarian cancer.49 \(BRCA2\) genetic mutations can lead to a lifetime risk for the development of breast cancer between 6% and 7.5% for men, 50% and 85% for women,49 and approximately 14% and 27% for ovarian cancer.50–52 These numbers vary depending on the family history and population studied. The prevalence of HBOC in the general population is not known with certainty. In a population-based study, \(BRCA4\) mutations were found in 5.9% of women diagnosed with breast cancer at an age of less than 36 years and in 4.1% of women diagnosed at ages 36 to 45.53

Breast and ovarian cancer susceptibility is a feature of other less common hereditary syndromes, including Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, ataxia-telangiectasia syndrome, and hereditary nonpolyposis colon cancer. The emphasis of this review will be on mutations of \(BRCA1\) and \(BRCA2\), as these compose the vast majority of hereditary breast and ovarian cancers. First, however, it is important to place HBOC in the context of epidemiologic models for estimating breast cancer risk.

### Risk Models

Making recommendations for patients based on risk for breast and ovarian cancer can prove challenging for clinicians. Empiric risk models use

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**TABLE 2.** Personal and Family History Characteristics Suggestive of Inherited Breast and Ovarian Cancer

| Personal history |
|------------------|
| Breast cancer diagnosed at less than 40 years of age |
| Bilateral breast cancer, especially when first cancer is diagnosed at less than 50 years of age |
| History of breast and ovarian cancer |

| Family history |
|----------------|
| Two or more family members diagnosed with breast cancer at 50 years of age or younger |
| Both breast and ovarian cancer in the family |
| One or more family members diagnosed with breast cancer at 50 years of age or younger and of Ashkenazi Jewish ancestry |
| One or more family members diagnosed with ovarian cancer and of Ashkenazi Jewish ancestry |
| Male breast cancer |
personal and family history to estimate the cumulative probability or relative risk for future breast cancer development. They are most accurate for people at low or moderate risk. This differs from mutation probability models discussed later, which estimate the probability of an individual or family having a BRCA1 or BRCA2 mutation.

Many factors, both intrinsic and extrinsic, influence the development of breast and ovarian cancer. Intrinsic risk factors for breast cancer include family history, genetic predisposition, levels of endogenous hormones, and benign breast lesions. Extrinsic factors that affect development of breast cancer include geographic location, exogenous hormones, environmental exposures, and lifestyle. Risk models use data from epidemiologic studies to weigh some of these variables to identify a patient who may be at higher risk for cancer. The two most common risk models for breast cancer are the Gail model and the Claus model.

The Gail model was derived from the Breast Cancer Detection Demonstration Project data, which involved over 280,000 Caucasian women who underwent regular mammograms. Using this model, clinicians can estimate a woman’s 5-year and lifetime risk for breast cancer development. Major risk factors include number of breast biopsies and findings of atypia or dysplasia, young age at menarche, older age at first live birth, and number of first-degree relatives with breast cancer. Disadvantages to using the Gail model are that it has not been validated for non-Caucasian women and women who do not get regular mammograms; it cannot be used in women younger than age 35, and it does not take into consideration second- or third-degree relatives, family history of male breast cancers, ovarian cancer, or bilateral breast cancer (see Table 3).

The Claus model was developed using information from the Cancer and Steroid Hormone Study, a population-based, multicenter, case-control study of over 9,000 women. Risk factors that were found to be major predictors for breast cancer include age, age of onset for breast cancer in affected first- or second-degree relatives, and the type and number of relatives affected with breast cancer. The disadvantages to the Claus model are that its applicability to non-Caucasian women is unclear, and it does not take into consideration third-degree relatives, family history of bilateral breast cancer, ovarian cancer, or male breast cancer (see Table 3).

There have been some studies to compare the concordance between the Gail and Claus models in terms of risk prediction for breast cancer. One study (in which potential BRCA1 or BRCA2 carriers were excluded) showed that Gail risk estimates were slightly higher than those calculated by the Claus model. Overall, these models provide a useful tool for clinicians to help guide risk assessment and counseling for patients. When the family history is strongly suggestive for genetic mutation, it is more appropriate to look at mutation probability models.

**Mutation Probability Models**

Mutation probability models serve clinicians as a guide to estimating the chances of finding a

| TABLE 3 | Pros and Cons for Gail and Claus Models in Breast Cancer Risk Assessment |
|---------|-------------------------------------------------------------------------|
| **Risk Assessment Model** | **Factors in Consideration** | **Pros** | **Cons** |
| Gail model | Age | Calculates factors other than family history | Does not consider: second-degree relatives, age of affected relatives, family history of ovarian cancer, ethnicity |
| | Age at first live birth | Calculates individual risk | Overestimates risk in those with benign breast biopsies |
| | Age at menarche | Calculates risk over specified time interval | |
| | Number of first-degree relatives with breast cancer | | |
| | Number of breast biopsies | Consideration of first and second-degree relatives | Risk based only on family history |
| | Number of first- and second-degree relatives with breast cancer | Risk based on specified relationship to affected relative | |
| | Age of diagnosis for affected relatives | Calculation of lifetime risk or risk over specified 10-year interval | |
BRCA1 or BRCA2 mutation in an individual or family. The 1996 ASCO guidelines indicate that testing should be considered in women whose mutation probability is greater than 10%. More recent ASCO guidelines do not specify a percentage threshold. Four commonly used models of this kind are the Couch, Shattuck-Eidens, Frank, and BRCAPRO models (see Table 4).

The Couch model is based on data from 169 families, of whom 16% had BRCA1 mutations. The model is currently being expanded to cover both BRCA1 and BRCA2. In its original and more extensively studied form, it is used to estimate the probability of finding a genetic mutation in a family that has at least two cases of breast cancer. Predictors of a BRCA1 mutation were family history of ovarian cancer, Ashkenazi Jewish ancestry, and average age at breast cancer diagnosis in the family of less than 55 years. Disadvantages of this model are the limited sample size and the fact that it does not consider ovarian cancer without breast cancer or a relative with both breast and ovarian cancer.

The Shattuck-Eidens model is based on data from 798 unrelated people, 13% of whom had BRCA1 mutations. Predictors of being a mutation carrier were younger age, bilateral breast cancer at diagnosis, ovarian cancer, a relative with breast and/or ovarian cancer, and Ashkenazi Jewish ancestry. The Shattuck-Eidens model can be used in people with no family history of breast or ovarian cancer and those with a family history of ovarian cancer alone. Disadvantages of this model include the facts that other than the proband, only one affected relative is used to determine risk; BRCA2 mutation risk is not calculated; and there is varying risk from person to person within a family even with identical family histories.

The Frank model is based on data from 238 women, of whom 39% had BRCA1 or BRCA2 mutations. A history of ovarian cancer, bilateral breast cancer, and age less than 40 at breast cancer diagnosis predicted mutation carrier status. It is most helpful for use in families having multiple women diagnosed at less than age 50 with breast cancer or with ovarian cancer. An advantage to the Frank model is that it takes into consideration both BRCA1 and BRCA2 mutations. Disadvantages of this model, as with the Shattuck-Eidens model, are that it provides risk probabilities for individuals and not families, so that extrapolation to unaffected relatives is still needed.

The BRCAPRO is a Bayesian model that uses BRCA1 and BRCA2 mutation frequencies, cancer penetrance in mutation carriers, cancer status and age of first- and second-degree relatives to predict the probability of a BRCA mutation in the family. Advantages of this model are risk calculation for both BRCA1 and BRCA2 mutations and the fact that it provides information for both

| Probability Model | Gene | Predictors | Disadvantages |
|-------------------|------|------------|---------------|
| Couch             | BRCA1| Ovarian cancer, Ashkenazi Jewish descent, Average age of breast cancer diagnosed <55 years old | Based on smaller sample size, Not useful for families with site-specific ovarian cancer, Need extrapolation for unaffected women |
| Shattuck-Eidens   | BRCA1| Younger age at diagnosis, Bilateral breast cancer at diagnosis, Ovarian cancer, Relative with breast and/or ovarian cancer, Ashkenazi Jewish descent | Not for use in women diagnosed with breast cancer before age 30, Need extrapolation for unaffected women |
| Frank             | BRCA1 and BRCA2 | Ovarian cancer, Bilateral breast cancer, Age <40 years at breast cancer diagnosis, Cancer status | Not for use in women diagnosed with breast cancer at 50 years or older, Need extrapolation for unaffected women, Need computer software, Time consuming, Varying probability depending on affected relative chosen for analysis |

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**TABLE 4** Probability Models to Estimate the Likelihood of a BRCA Mutation
affected and unaffected relatives. Disadvantages of BRCAPRO are that its utility in lower risk populations is unclear, probability calculations vary based on which affected relative is chosen for analysis, and specific computer software is necessary to do the calculations.61

**Recommended Screening for BRCA Mutation Carriers**

Enhanced surveillance is recommended to promote early detection of breast and ovarian cancer in women with a known or suspected genetic mutation. Table 54,65,66 summarizes the recommendations of a National Institutes of Health (NIH) consensus panel and other recommendations for screening women who test positive for a BRCA1 or BRCA2 mutation. Current recommendations come from expert opinions and case series rather than controlled trials. The NIH panel recommends clinical breast examination every 6 to 12 months beginning at the age of 25. Self-breast examination is recommended monthly after the age of 18 to 21.

A mammogram is recommended by the NIH panel and others every 6 to 12 months beginning at the age of 25.65 Often, breast ultrasound is used as an adjuvant for screening with mammogram.66 It has been shown to increase sensitivity and specificity, particularly in younger women. Data regarding the usefulness of breast magnetic resonance imaging (MRI) are mixed. It was found that MRI had a high sensitivity with high predictive value for detecting breast cancers when compared with mammogram and ultrasound.68 In a study of surveillance for high-risk younger women (mean age of 41), the sensitivity of MRI for invasive cancer was 80% compared with 33% for mammogram and 18% for clinical breast examination; specificity was 90% compared with 95% for mammography.69 However, others have found a high false-positive rate, and some conclude that breast MRI is more appropriate as an adjunct to mammographic screening. Furthermore, MRI is not always feasible because of its higher cost and lack of availability in certain locations. Ultrasound and breast MRI are useful as adjuvant screening modalities to mammography.

The use of ductoscopy and breast ductal lavage is based on the fact that 95% of breast cancers involve the ductal system and, therefore, might be detected by this method. Ductal lavage has been found to be no more uncomfortable than mammogram and is successful in 80% of women.71 The role of ductoscopy and breast ductal lavage in breast cancer screening has not been clearly defined.

To screen for ovarian cancer, the NIH panel and others recommend transvaginal ultrasound and serum CA-125 measurements every 6 to 12 months beginning at age 25 to 35 years, although there is no clear evidence to support this. Clinical pelvic examination is recommended every 6 months. Jacobs, et al.72 studied almost 22,000 postmenopausal women at varying levels of risk screened for ovarian cancer with CA-125, followed by ultrasound for levels over 30 U/mL and surgery if an adnexal mass was present. This protocol had a specificity of 99.9% with a sensitivity for ovarian cancer of 78.6% at 1 year and 57.9% at 2-year follow up.

**Risk Reduction Strategies**

Several risk reduction strategies have been proposed to help patients lower their risk for developing breast or ovarian cancer. Most of these are more pertinent to breast cancer. Before making these recommendations, clinicians should look at each patient’s case individually and weigh the risks and benefits for each.

Lifestyle changes, such as diet and exercise, are being studied. BRCA mutation carriers with higher levels of activity during adolescence and a nonobese weight at menarche and at age 21 developed breast cancer at later ages than other mutation carriers.35 Recommendations such as increasing activity and maintaining nonobese weight are generally encouraged regardless of mutation carrier status. However, clinicians should be careful not to mislead patients about the potential benefits for these practices, as more long-term studies are needed.

The use of oral contraceptive pills has been controversial as a potential cancer reduction
method in high-risk women and mutation carriers. One study showed that oral contraceptives increased the risk of breast cancer in women who were $BRCA1$ mutation-positive. In another study, the use of oral contraceptive pills for an increased duration in women who were $BRCA1$ or $BRCA2$ mutation-positive did not reduce their risk for ovarian cancer. Based on this information, oral contraceptive pills are not routinely recommended for breast or ovarian cancer prevention in $BRCA$ mutation carriers.

Some data indicate that for every 12 months of breast-feeding, the relative risk for breast cancer decreases by 4.3%. Jernstrom et al. found women with $BRCA1$ mutations who breast-fed for 1 year had a reduced risk of breast cancer. Based on this information, oral contraceptive pills are not routinely recommended for breast or ovarian cancer prevention in $BRCA$ mutation carriers.

The data regarding chemoprevention with tamoxifen and raloxifene are growing. In the Breast Cancer Prevention Trial, the use of tamoxifen for primary prevention of breast cancer reduced the risk of invasive breast cancer by 49% while increasing the risk of thrombotic events. The women in this trial were not known mutation carriers but rather were determined to be at increased risk using the Gail model. Tamoxifen has been shown to reduce breast cancer incidence in $BRCA2$ mutation carriers. In the Multiple Outcomes for Raloxifene Evaluation trial, which enrolled average-risk postmenopausal women, raloxifene was shown to reduce the risk of estrogen receptor-positive breast cancers. Fewer data regarding the role of these drugs in mutation carriers are available, but based on available data in high-risk women, their efficacy appears to be good. In general, estrogen receptor modulators are useful in prevention of estrogen receptor-positive tumors. Before starting women on these medications, the risks and benefits should be discussed.

Prophylactic mastectomy and oophorectomy can prevent cancers in mutation carriers, but surgical menopause may have other deleterious effects, and mastectomy in particular is not acceptable to some women. A retrospective study on a cohort of 639 women with a strong family history of breast cancer demonstrated that prophylactic mastectomy reduced the risk of breast cancer by at least 90%. Rebbeck et al. demonstrated similar results in their prospective study of over 400 women who were mutation carriers. Another study showed that prophylactic mastectomy could increase life expectancy by 3 to 5 years depending on a woman’s age and baseline risk of $BRCA1$ or $BRCA2$ mutation. The greater effects were seen in the higher risk group and younger women.

Two prospective studies have shown significant reductions in both breast and ovarian cancer in $BRCA1$ or $BRCA2$ mutation carriers who undergo prophylactic oophorectomy. In another study, prophylactic oophorectomy increased life expectancy between 0.3 to 1.7 years, preventing both ovarian and breast cancers. Despite the fact that there are benefits to prophylactic surgery, the long-term quality of life as well as medical and psychological effects of such surgeries are unclear. Because of the diversity of attitudes toward prophylactic mastectomy and oophorectomy, these decisions should be the product of informed decision making that considers individual attitudes, childbearing status, and the clinical context, including $BRCA$ mutation status. Clinicians should thoroughly discuss these issues with patients considering prophylactic surgery. Patients should strongly consider ge-

### Table 5: Screening Recommendations for $BRCA1$ or $BRCA2$ Mutation Carriers

| Screening Test                  | Starting Age | Interval         |
|--------------------------------|--------------|------------------|
| Breast cancer                  |              |                  |
| Self breast exam*              | 18 to 21 years | Monthly          |
| Clinical breast exam†          | 25 to 35 years | Six to 12 months |
| Mammogram*†‡                  | 25 to 35 years | Six to 12 months |
| Ultrasound‡                   | Possible adjuvant to mammography |       |
| MRI‡                          | Possible adjuvant to mammography |       |
| Ductal lavage/ductoscopy       | Role not clearly defined |       |
| Ovarian cancer                 |              |                  |
| Clinical pelvic exam†          | Uncertain    | Six months       |
| Transvaginal ultrasound*†      | 25 to 35 years | Six to 12 months |
| CA-125*†                      | 25 to 35 years | Six to 12 months |

*Reference 4.  
†Reference 65.  
‡Reference 66.
Familial and Hereditary Colon Cancer

A family history of colon cancer is common in the general population. It is important to identify this family history, because in many cases, it is recommended for relatives to begin colorectal cancer (CRC) screening at an earlier age than 50. For example, the presence of CRC or adenomatous polyps in just one first-degree relative before age 60 or in two or more first-degree relatives at any age justifies earlier screening (beginning at age 40 or 10 years before the youngest age at diagnosis of an immediate family member) and with a more intensive protocol (colonoscopy every 5 to 10 years). One-fifth of cases of CRC occur in individuals with a family history of the disease, but most are not due to one of the known high-risk, hereditary syndromes described below. However, families with these less common genetic syndromes are important to recognize, because the chance of developing cancer is so high in affected individuals.

Hereditary Syndromes

An estimated 2% to 5% of all people with CRC are born with one of the known hereditary CRC susceptibility syndromes. In many cases, but by no means all, hereditary CRC susceptibility is evident by a multigenerational (autosomal dominant) pattern of CRC and related types of cancer in more than one close relative. Other clinical features pointing to possible hereditary CRC are cancer at an early age (less than 50 years), multiple (10 or more) intestinal polyps, or an individual with more than one primary CRC or HNPCC-associated cancer. Hereditary CRC syndromes have been classified as those with FAP or without numerous colon polyps (HNPCC). However, as a result of genotyping, it is now appreciated that there is overlap between the clinical manifestations of familial polyposis and those of HNPCC. Furthermore, CRC susceptibility is a feature of various hereditary syndromes, including juvenile polyposis, Peutz-Jeghers syndrome, syndromes associated with BRCA1, and a newly discovered autosomal recessive type of polyposis due to mutations in the MYH gene.

Syndromes Involving Adenomatous Polyposis Coli (APC) Gene Mutations

Familial Adenomatous Polyposis

FAP accounts for less than 1% of CRC, but it is important to diagnose because of its implications for high cancer susceptibility in the patient and family members. Clinically, the hallmark of FAP is the development of numerous colorectal adenomatous polyps, often thousands carpeting the mucosa, in the second or third decade of life. With numerous polyps, the lifetime probability of developing carcinoma of the colon is almost 100%. The average age at cancer diagnosis with untreated FAP is approximately 39 years. In addition to CRCs, people with FAP are at increased risk of childhood hepatoblastoma and small bowel, biliary, gastric, and thyroid cancers. Desmoid tumors or retinoscopic observation of congenital hypertrophy of the retinal pigment epithelium can be clues to the diagnosis of FAP.

FAP is due to germline mutations in the APC gene. FAP is inherited in an autosomal dominant pattern. Approximately 10% to 30% of these mutations arise de novo, with no one else in the previous generations affected. A family history of FAP is an exception to the general rule that predisposition testing should not be done on children, because polyposis, with the potential for malignant transformation, can begin in the teens. Fifty percent of people with FAP develop adenomas by age 15. If an APC mutation has been identified in an affected family member, then expert consensus recommends genetic counseling and consideration of APC mutation testing at approximately age 10 years. If the child tests negative for the cancer-associated mutation in the family, then one or two screening sigmoidoscopic examinations are recommended in the late teens and young adulthood; if no polyps are observed, then this individual is unlikely to have inherited FAP and can follow the same screening recommendations as the general
population. If the child tests positive for a cancer-associated \textit{APC} mutation, then yearly sigmoidoscopic surveillance is recommended beginning at age 10 to 12.\textsuperscript{94-98,100} Single polyps should be removed, but when numerous adenomas begin to develop, surveillance should begin to be done by colonoscopy, and serious consideration should be given to prophylactic colectomy.\textsuperscript{94} Expert counseling and support are needed for the family as an adolescent or young adult undergoes this life-altering process of medical care.

In classic FAP, prevention of colon cancer once numerous polyps appear entails colectomy. Subtotal colectomy with ileorectal anastomosis can preserve continence, but continued surveillance of the remaining rectal tissue every 6 to 12 months is needed lifelong.\textsuperscript{101} To detect associated small bowel and biliary cancers, surveillance with upper endoscopy (and possibly endoscopic examination of the bile duct) is also recommended every one to three years beginning at age 25. In addition, small bowel x-ray (such as abdominal and pelvic computed tomography with oral contrast) is recommended if duodenal adenomas are detected or before colectomy.\textsuperscript{98-100} Research is ongoing to identify effective forms of chemoprophylaxis. Although trials of nonsteroidal anti-inflammatory drugs (sulindac and cox-2 inhibitors) have had mixed results,\textsuperscript{102-105} if there is no contraindication, a cox-2 inhibitor\textsuperscript{106} and possibly other preventive strategies not proven for FAP can be suggested, including daily exercise, daily aspirin use, folic acid at 400 \textmu g/day, and calcium at 1,200 mg/day.\textsuperscript{107-111}

\textit{Attenuated FAP}

The ability for genotyping to identify \textit{APC} gene mutations has led to the recognition of a less severe form of FAP when mutations occur in the ends of the \textit{APC} gene,\textsuperscript{110} with fewer polyps (5 to >300), occurring at somewhat older ages. The mean age of development of polyposis is about 30 years;\textsuperscript{111} the mean age of diagnosis with colon cancer is about 55 years.\textsuperscript{110} The risk of colon cancer is nearly 100\% by age 70. This syndrome has been termed attenuated FAP. Its features vary even within the same family and overlap with those of classic FAP; therefore, distinct management recommendations have not yet emerged, except that surveillance should be done by colonoscopy, not sigmoidoscopy.\textsuperscript{112,113}

\textit{APC Gene Polymorphism in Ashkenazi Jews}

A common variant in the \textit{APC} gene sequence (I1307K) is present in approximately 20\% of Jews of Eastern European ancestry, owing to a founder effect.\textsuperscript{114} This single nucleotide substitution is very rare in other populations. The presence of this \textit{APC} gene variant approximately doubles the risk of developing colon adenomas and CRC and shifts the onset to a somewhat younger age, similar to the situation with familial CRC of unknown cause.\textsuperscript{115,116} Earlier colon screening, beginning at age 40, is thus recommended for people in whom the I1307K mutation has been found and for their first-degree relatives, but screening of asymptomatic Jews for this genotype is not recommended. Because of its low penetrance, the presence of the gene variant has low predictive power; its absence does not change the need for colon screening based on family history and general recommendations.

\section*{HNPCC}

\textit{Clinical Features and Genetic Testing for HNPCC}

HNPCC was described as a clinical entity, characterized by a strong family history of early-onset colon and associated cancers without numerous polyps long before causative genetic alterations were identified. It has been discovered that in many cases the syndrome is related to germline mutations or epigenetic silencing of DNA mismatch repair (MMR) genes, sometimes \textit{MSH6}, \textit{PMS1} or \textit{PMS2}, but principally \textit{MLH1} and \textit{MSH2}.\textsuperscript{88} These mutations and the resulting high susceptibility to cancer are inherited in an autosomal dominant pattern. Testing for mutations in \textit{MLH1} and \textit{MSH2} is clinically available. Most are “private” mutations (different for each affected family), although one particular founder mutation in \textit{MSH1} appears to be widespread in
the United States. MMR gene alterations are not found in every family that fits clinical criteria for HNPCC, and thus this hereditary high susceptibility to cancer still remains a clinical diagnosis.

Clinicians who identify the clinical features should recommend intensified cancer prevention and surveillance for patient and family members, even if a genetic test for MMR gene mutations is negative or if testing has not been done. Unlike the situation with HBOC, quantifying risk prediction and mutation probability is less well defined for HNPCC.

Table 6 summarizes a sequence of defining clinical criteria for HNPCC originally used to determine eligibility for cancer genetic research but increasingly applied clinically. Table 6 begins with the most specific but less sensitive Amsterdam II criteria based on a strong family history alone and ends with the more inclusive but less specific modified Bethesda criteria, which include diagnosis at age younger than 50, multiple primaries, particular histologic features, associated extracolonic cancers, and CRC. The modified Bethesda criteria will identify people without a strong family history of CRC who are considered to be at high risk and offer intensified preventive care and/or mutation testing, but the prevalence of HNPCC-associated mutations in groups chosen by these criteria is less than in groups that meet the strict Amsterdam criteria. Of course, definitive test results (ie, cancer-associated, germline mutations in MMR genes) also lead to the diagnosis of HNPCC. In interpreting these results, clinicians must recognize that the presence of an HNPCC-associated gene mutation increases the likelihood of cancer but is not an absolute predictor of future cancer events.

**Risk of Cancer with HNPCC**

HNPCC involves a high lifetime risk of CRC developing at an earlier age than sporadic CRC. In cases of HNPCC with a strong family history of cancer, the lifetime chance of a mutation-positive individual developing CRC may be as high as 80%, with an average age at diagnosis of approximately 45 years. The risk for mutation-positive individuals without a typical family history of cancer is not yet known. However, mutations in *MSH6*, in particular, have been discovered more frequently than expected in older CRC patients without a striking family history of cancer. In addition to colon cancer, HNPCC confers increased risks of other cancers, especially cancer of the endometrium and ovary but also including the

### TABLE 6 Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Criteria

| Amsterdam criteria II | Bethesda criteria, simplified for this publication* |
|-----------------------|---------------------------------------------------|
| Patient must meet all of the following: | Individuals with cancer in families who meet the Amsterdam criteria. |
| Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two, and familial adenomatous polyposis has been excluded. | Individuals with two HNPCC-related cancers, colorectal and/or extracolonic (see list above). |
| Colorectal cancer involving at least two generations. | Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed before age 45 and the adenoma diagnosed before age 40. |
| One or more colorectal cancers diagnosed before age 50. | Individuals with colorectal cancer or endometrial cancer diagnosed before age 45. |

**Modified Bethesda criteria†**

- A consensus conference of the American Gastroenterology Association recommended raising the cutoff age for suspecting HNPCC. Substitute colorectal or endometrial cancer diagnosed before age 50, rather than age 45, in the above Bethesda criteria.

*Full criteria in References 120, 121.
†Reference 94.
stomach, small bowel, renal pelvis, ureters, and biliary tract. The risk of developing endometrial cancer by age 70 for a woman with HNPCC is 40% to 60%, with onset in midlife. Therefore, she is almost as likely to be diagnosed first with endometrial cancer as with CRC; yet awareness of HNPCC as a cause of susceptibility to endometrial cancer is not widespread. The risk of ovarian cancer is 10% to 12%.87

Young Age at Onset

Certain features of colon cancer, even in the absence of family history, suggest the possibility of HNPCC. HNPCC should be suspected when CRC is diagnosed at an exceptionally young age (especially <45 years; see Table 6). Certain types of histology can also suggest the diagnosis; these are solid/cribiform (poorly differentiated carcinoma composed of irregular sheets of large eosinophilic cells and containing small glandlike spaces) and signet-ring type colorectal cancers (composed of greater than 50% signet-ring cells).120

Microsatellite Instability (MSI) Testing

DNA replication instability characterizes tumors with loss-of-function mutations in MMR genes. These can be detected as MSI, which is the finding that, in the same individual, the number of repeats in a given repeating sequence of DNA varies from cell to cell instead of being constant. Several (usually five or six) such repeating sequences—termed “instability”—can be examined for variability, indicating errors in DNA replication. MSI is termed “low” if zero or one of the markers shows instability and “high” if a high proportion of the markers is unstable.88 More than 90% of CRCs in people with DNA mismatch repair gene mutations have high MSI, whereas less than 15% of sporadic CRCs do. A recent economic analysis compared the cost per year of life gained for three strategies for identifying cases of HNPCC: (1) genotyping everyone with colon cancer for MMR gene mutations (the most expensive); (2) testing every cancer for MSI and genotyping those with high MSI; or (3) applying the Bethesda criteria (family history, age, and histology) to all cases of CRC, testing for MSI on those meeting the criteria, and genotyping the subset with high MSI.128 Given the expense of genotyping, strategy 3 was the most cost-effective. This analysis also pointed out that the cost-benefit ratio for MMR gene mutation testing decreases dramatically if one assumes that identifying one person with MMR gene mutations leads to the offer of testing and institution of preventive measures in siblings, sons, and daughters rather than the tested individual alone.128

Risk Reduction for HNPCC-associated Cancers

In contrast to FAP, where prophylactic surgery is the main method for colon cancer prevention, CRC risk reduction in HNPCC is mainly through colonoscopy to identify and remove polyps.

### TABLE 7 Screening Recommendations for Patients with Confirmed or Highly Suspected HNPCC*

| Cancer Risk                                      | Procedure                          | Age to Start (years) | Frequency (years) |
|--------------------------------------------------|------------------------------------|----------------------|-------------------|
| Colon cancer (60% to 80% lifetime risk)          | Colonoscopy                        | 20 to 25             | 2†                |
| Endometrial cancer (30% to 60% lifetime risk) and ovarian cancer (10% to 13% lifetime risk) | Gynecologic examination (± endometrial sampling), transvaginal ultrasound, CA125 | 30 to 35 | 1 to 2 |
| Urinary tract cancer‡                             | Ultrasonography, urine cytology     | 30 to 35             | 1 to 2            |
| Stomach cancer‡                                  | Gastroscopy                         | 30 to 35             | 1 to 2            |

*International Collaborative Group on HNPCC recommendations.121
†The Cancer Genetics Study Consortium³ and National Comprehensive Cancer Network guideline106 recommend colonoscopy every 1 to 3 years starting at age 25.
‡Screening recommended if at least one family member has had this type of cancer.87
Surveillance for various types of cancer in individuals with HNPCC is based on expert recommendations and on case series that have demonstrated a reduction in CRC incidence with periodic colonoscopic surveillance.3,88,129 These recommendations are listed in Table 7.3,87,106,121

Clinical chemoprevention trials are more difficult in HNPCC than in FAP because the number of polyps cannot be used as a surrogate endpoint over short intervals. Therefore, the efficacy of chemoprevention in HNPCC is unknown.

CONCLUSIONS

With the advent of newer technology available to identify genetic mutations associated with increased cancer risk, and with newer modalities available to prevent cancer, it is becoming in-

### TABLE 8  Cancer Genetic Resources

| Organization                                      | Web Site                                           | Telephone         | Information Provided                                                                 |
|---------------------------------------------------|----------------------------------------------------|--------------------|--------------------------------------------------------------------------------------|
| American Cancer Society (ACS)                     | www.cancer.org                                     | (800) 227-2345     | Links to ACS reviews of recent medical articles                                      |
| American Society of Clinical Oncology             | www.asco.org                                        | (703) 299-0150     | Not always specific to hereditary cancers                                            |
| American Society of Human Genetics                | www.faslcb.org/genetics/ashg/ashgmnu.htm            | (301) 571-1825     | No specific link for hereditary cancer                                                |
| Centers for Disease Control and Prevention         | www.cdc.gov                                         | (404) 639-3311     | Family history data collection info for patients                                     |
| GeneReviews                                       | www.geneclinics.org                                 |                    | Info for patients and providers: articles, fact sheets, perspectives, statistics, conferences, etc. |
| GeneTests                                          | www.geneclinics.org                                 |                    | GeneReview articles                                                                  |
| Genetic Alliance                                   | www.geneticalliance.org                             |                    | Links to genetic lab directory                                                        |
| Genetics Education Center                         | www.kumc.edu/gec                                    |                    | Educational material on genetic testing                                               |
| Genetics in Primary Care (Genetic and Newborn Screening Resource Center of the US) | www.genes-r-us.uthscsa.edu/resources/genetics/primary.care.htm |                    | GeneReview articles                                                                  |
| International Society for Cancer Risk Assessment and Management | www.isc-ram.org                                    | (215) 985-0216 or (800) 815-4928 | Links to selected readings and resources                                              |
| International Society of Nurses in Genetics       | www.isong.org                                       | (703) 698-7355     | Protocol data through University of Iowa                                              |
| National Action Plan on Breast Cancer             | www.4women.gov/napbc                                | (202) 401-9587     | General breast cancer data geared toward patients                                     |
| National Cancer Institute (NCI)                   | www.nci.nih.gov                                     | (800) 4-CANCER      | Data for patients and providers on background, mutation probability, prevalence, tools for risk calculation |
| NCI Cancer Genetics Services Directory            | www.nci.nih.gov/search/geneticsservices             |                    | PubMed cancer topic link                                                              |
| National Human Genome Research Institute           | www.nhgrl.nih.gov                                   | (301) 402-0911     | Genetics provider directory                                                          |
| National Society of Genetic Counselors            | www.kumc.edu/GECC/prof/sngc.html                    | (610) 872-7608     | Genetic testing data for patients and providers                                       |
| National Coalition for Health Professional Education in Genetics OMIM™ Online Mendelian Inheritance in Man | www.nchpeg.org                                      | (410) 583-0600     | Geared toward genetic counselors                                                     |
|                                                    | www.ncbi.nlm.nih.gov/omim                          |                    | Data on genetic testing/discrimination (legal/ethical issues)                         |
|                                                    |                                                    |                    | Multiple links to other sites                                                        |
|                                                    |                                                    |                    | Family history data collection for patients                                          |
|                                                    |                                                    |                    | Educational resource listing for providers                                           |
|                                                    |                                                    |                    | Search engine generates medical articles                                              |
creasingly important that all physicians become familiar with the elements of hereditary cancer risk assessment. We hope that this review has provided the necessary information to assist physicians in this task. A growing number of resources are currently available to physicians, which are listed in Table 8.

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