

# GENETICS AND THE MULTIDISCIPLINARY BREAST CENTER

June A. Peters, MS, CGC, and Wendy S. Rubinstein, MD, PhD

In recent years, breast surgeons for the first time in their professional careers may be interacting with a relatively new class of colleagues, genetic counselors, and medical geneticists. These interactions may occur in the multidisciplinary treatment conference, at grand rounds, at oncology meetings, or through patient referrals. This article introduces surgical oncologists to the current applications of genetic counseling in oncology. The practical goal is to foster interdisciplinary teams and referral networks for recognition and management of families with or at risk for inherited breast cancers. Families with inherited cancer susceptibility require genetic diagnosis, possible genetic testing, tailored medical management, possible psychosocial interventions, and appropriate follow-up. Special attention is given to the issues regarding prophylactic mastectomy and prophylactic oophorectomy for those with inherited *BRCA1* and *BRCA2* mutations. Four critical roles for the surgeon in cancer genetics—program organization and high-risk patient recognition, referral, and management<sup>79</sup>—are explored in this article.

## **INITIATION AND OPERATION OF A CANCER GENETICS PROGRAM**

Operational and programmatic issues arise in providing cancer risk counseling services and research. Operational issues involve running a

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From the Department of Human Genetics, University of Pittsburgh Graduate School of Public Health (JAP); and the Cancer Genetics Program, Magee-Womens Hospital and the University of Pittsburgh Medical Center Health System/University of Pittsburgh Cancer Institute (WSR), Pittsburgh, Pennsylvania

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cancer genetics program. Programmatic issues involve the content of a cancer genetics consultation.

### **Genetic Counseling and Familial Cancer Risk Counseling**

It is helpful for the surgeon who works in cancer genetics to become familiar with the fields of genetics and genetic counseling. The surgeon probably has been exposed to some of the consequences of the Human Genome Project (HGP), although that name may not ring a bell. The human genome refers to all the genetic information that resides in human cells. Begun in 1990 by the US Congress, the HGP is jointly supported by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) and the Department of Energy (DOE). The 15-year goals of the HGP and its worldwide counterpart, the Human Genome Organization (HUGO), are to develop methods, train scientists, and establish infrastructure to identify and determine the DNA sequence of all 80,000 to 100,000 genes contained in human cells. The HGP has coalesced and focused molecular genetic research, which was already in progress before this coordinated effort on specific scientific international goals. As a result of the HGP, hundreds of genes for a variety of genetic conditions have been localized and cloned within the past decade (e.g., Alzheimer disease, hypertrophic cardiomyopathy, Marfan syndrome, hereditary deafness, polycystic kidney disease, and several forms of hereditary breast, ovarian, and colon cancers). The availability of this genetic information has created a number of challenges for clinical practice. Some of these are being addressed through funding of ethical, legal, and social issues projects. Efforts are also being made to increase genetic literacy of health care professionals from various fields.<sup>11</sup>

Through the efforts and funding of the National Cancer Institute (NCI) and the National Library of Medicine (NLM), the NIH sponsors another genetic discovery project focused on cancer called the Cancer Genome Anatomy Project (CGAP). CGAP is an interdisciplinary program to establish the information and technologic tools needed to decipher the molecular anatomy of the cancer cell. The CGAP uses the newest technologies, such as laser microdissection and computer chip microarrays, to identify the expression of all the genes responsible for the establishment and growth of various types of cancer, including breast cancer. The goal is to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. More information can be found at the CGAP website listed in Table 1.

Genetic counseling deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. In simplified form, genetic counseling is the clinical application of scientific discoveries in genetics. The definition established in 1975 by an ad hoc committee of the American Society of Human Genetics<sup>1</sup> defined the basic components of the genetic counseling process as helping families to (1)

**Table 1.** INTERNET WEBSITES FOR CANCER GENETICS INFORMATION

Organization	Abbreviation	Website <a href="http://www">http://www</a>	Address
National Cancer Institute, CancerNet	NCI	<a href="http://cancernet.nci.nih.gov">cancernet.nci.nih.gov</a>	Bethesda, MD
NCI Cancer Genetics Anatomy Project	CGAP	<a href="http://ncbi.nlm.nih.gov/cgap">ncbi.nlm.nih.gov/cgap</a>	Bethesda, MD
National Human Genome Research Institute	NHGRI	<a href="http://nhgri.nih.gov">nhgri.nih.gov</a>	Bethesda, MD
National Society of Genetic Counselors	NSGC	<a href="http://nsgc.org">nsgc.org</a>	Wallingford, PA
American Cancer Society	ACS	<a href="http://cancer.org/index">cancer.org/index</a>	Atlanta, GA
American Society of Human Genetics	ASHG	<a href="http://faseb.org/genetics/ashg/ashgmenu.htm">faseb.org/genetics/ashg/ashgmenu.htm</a>	Rockville, MD
GeneClinics: Medical Genetics Knowledge	U. of W.	<a href="http://geneclinics.org/public/opening_page.html">geneclinics.org/public/opening_page.html</a>	Seattle, WA
The Genetics of Cancer, Northwestern University	NW Univ.	<a href="http://2ysiwyg://31/http://www.cancergenetics.org">2ysiwyg://31/http://www.cancergenetics.org</a>	Chicago, IL
University of Kansas Genetic Education Center	KUMC	<a href="http://humc.edu/gec/">humc.edu/gec/</a>	Kansas City, KS
OncoLink, University of Pennsylvania	ONCOLINK	<a href="http://oncolink.upenn.edu/">oncolink.upenn.edu/</a>	Philadelphia, PA
Oncology Nursing Society	ONS	<a href="http://ons.org/home_top.htm">ons.org/home_top.htm</a>	Pittsburgh, PA
National Action Plan on Breast Cancer, Genetics Curriculum	NAPBC	<a href="http://napbc.org/napbc/hsedcurr.htm">napbc.org/napbc/hsedcurr.htm</a>	Washington, DC
Berry Model for calculating BRCA 1/2 mutations	BRCAPRO	<a href="http://isds.duke.edu/~gp/brcapro.html">isds.duke.edu/~gp/brcapro.html</a>	Durham, NC
Pamphlet: Genetic Testing for Breast Cancer: It's Your Choice	NAPBC & NCI	<a href="http://rex.nci.nih.gov/nct_pub_index/genbrst/index.htm">rex.nci.nih.gov/nct_pub_index/genbrst/index.htm</a>	Bethesda, MD
Understanding the Genetics of Breast Cancer for Jewish Women	American Jewish Congress	<a href="http://ajcongress.org/women/pamphlet.htm">ajcongress.org/women/pamphlet.htm</a>	New York, NY

comprehend the medical facts of the condition, including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the hereditary contribution and recurrence risk for the disorder in specific relatives, (3) understand their options for dealing with the risk of recurrence in terms of medical care, reproductive decisions, and genetic testing, (4) choose which of the options, including doing nothing, is currently appropriate for the family in view of their risk, disease burden, and family, ethnic, and cultural values, and (5) make the best possible adjustment to the condition, or to the risk of recurrence, of the disorder in oneself or loved ones.

Although the term genetic counseling is sometimes used loosely to encompass any and all professional activities related to familial conditions, genetic counseling is actually a distinct profession with its own code of ethics, nationally accredited master's level training programs, clinical internships, and certification. In hiring qualified staff for a familial cancer genetics clinic, a program director should look for use of the certified genetic counselor designation, which has been established by the American Board of Genetic Counseling, or the Fellow of the American College of Medical Genetics designation used by physician and scientist diplomates certified by the American Board of Medical Genetics. In the United States, most genetic counselors and medical geneticists belong to professional societies such as the National Society of Genetic Counselors, the American Society of Human Genetics, or the American College of Medical Genetics. Nurses who specialize in genetics often belong to the International Society of Nurses in Genetics or a genetics special interest group within a professional society, such as the Oncology Nursing Society.

The general practice of genetic counseling has been tailored to the cancer patient during the last decade as a new professional activity known alternately as cancer genetic counseling, cancer risk counseling, or familial cancer risk assessment. Familial cancer risk counseling (FCRC) is a communication process between a health care professional and an individual concerning the occurrence, or risk of occurrence, of cancer in the individual's family.<sup>74,75</sup> As such, FCRC addresses the genetic, medical, psychological, social, and ethical issues that arise in the context of cancer predisposition. The tasks are best provided in a multidisciplinary setting, with the specially trained genetic counselor or genetic nurse practitioner playing a key role.<sup>14,77</sup> A directory of cancer genetics services providers is available on the CancerNet website of the NCI.

The surgeon who wishes to direct a cancer genetics program has a number of resources as guidance regarding the establishment of FCRC programs.<sup>4,18,19,43,48,55,57,63,65,70,81</sup> The FCRC program may be a free-standing clinical service, located in an academic medical center, sponsored by a private testing laboratory, or an adjunct to a medical genetics, surgical, or oncology practice. Some FCRC programs emphasize clinical service, whereas others are devoted primarily to research, with clinical service as secondary.

The director of a FCRC program often is asked to justify the initial expenditure of resources. The main reason for having a FCRC service is that cancer risk assessment and counseling are becoming a routine part of breast cancer management. Incorporation of genetic information into every aspect of cancer care is the wave of future practice. Other practitioners fear medicolegal liability for missing diagnosis of a cancer in a predisposed individual or failing to treat hereditary cancer susceptibility syndromes appropriately. There are financial incentives to accessing the care of an entire family through a proband with hereditary cancer, namely volume. If we assume that 5% to 10% of patients with breast cancer have an underlying genetic mutation, a significant number of relatives of individuals with breast cancer in any surgical practice will require special-

ized cancer prevention and surveillance management. The primary means of identifying this high-risk subset are through screening, triage, and comprehensive risk assessment of the patient population. The most efficient means of carrying these activities is through an organized FCRC program. Several years ago, a national survey demonstrated that only a fraction of NCI-funded comprehensive cancer centers had adequate cancer genetics services.<sup>99</sup> In a follow-up survey in 1998, almost all NCI-funded centers recognized the need for these services, employed cancer genetic counselors, and have instituted FCRC programs (Alvarado M, Wonderlick A, et al., unpublished data, 1998).

The FCRC program requires designated space, human resources, budget, and billing and reimbursement procedures. The clinical consultation space should be quiet, private, comfortable, and large enough for lengthy discussions with multiple family members who may attend FCRC together. The traditional hospital setting and medical examination room are often sterile, cluttered, and an unpleasant reminder of medical visits of ill relatives and should be avoided whenever possible. Empirical evidence confirms the importance to families of the appearance of the genetic counseling space.<sup>89,90</sup> In addition to clinic space, staff members require office space for paperwork, private telephone contact, and data management.

Staffing of a FCRC service varies with location, resources, and focus. Generally, adopting a multidisciplinary approach to cancer genetics is of paramount importance in achieving an effective cancer genetics program. The complementary expertise of surgeons, oncologists, genetic counselors, medical geneticists, pathologists, molecular laboratory scientists, nurses, social workers, and psychologists is often required to meet the needs of the various families who are seen. Each professional provides a unique perspective.

The genetic counselor member of the cancer genetics team may act as clinic or program coordinator or director, research team leader, psychosocial support counselor, or genetics consultant. In the capacity as a genetic counselor, he or she can help to evaluate familial clusters of cancer. This might include presenting referrals to the core group as well as retrieving, reviewing, and summarizing medical records and relevant medical literature. The genetic counselor also has primary responsibility for constructing and interpreting pedigrees, recognizing known hereditary cancer susceptibility syndromes, calculating quantitative risk assessments, and communicating these to patients and families. The genetics team also can offer education about risk factors for cancer, basic concepts of inheritance, and the significance of one's unique family history. The genetic counselor also may delineate and work with family dynamics and social and ethical concerns.

An issue that deserves special mention is that of information management. Genetic consultations are often extremely lengthy and time consuming and are documented thoroughly in progress notes and letters to both referring physicians and patients. Due to lack of protections against genetic discrimination in employment and insurance, certain aspects of

genetic information are often kept extremely private in "shadow files" in genetics departments, with only brief mention of the visit in the hospital chart. Genetic testing results especially should be treated as extremely private and confidential information. As such these results are not generally communicated to physicians, insurers, or other family members without thorough discussion and written permission of the person tested. An individual patient may reveal genetic testing to the surgeon only if seeking extraordinary care. This has implications for medical management and prophylactic surgery sections to follow.

### **THE CANCER GENETICS PROGRAM: ASCERTAINMENT, SCREENING, AND TRIAGE**

There are a number of recognized risk factors for breast cancer, including female gender, increasing age, family history, reproductive and menstrual history, estrogen therapy, history of previous benign breast disease or malignancy, radiation exposure, lifestyle, and other factors. The genetic contribution to breast cancer risk is indicated by the increased incidence of breast cancer due to a positive family history of breast cancer and by the observation of rare families in which multiple family members are affected with breast cancer.

Most women who present to a surgeon with concerns about familial breast cancer do not have a family history of breast cancer that is striking enough to suggest the presence of a breast cancer predisposition syndrome.<sup>66</sup> These families are heterogeneous and comprise different subgroups of those with multiple genetic or environmental agents; single gene mutations conferring low penetrance for cancer; chance cancer clusters of a common cancer; and true hereditary susceptibility, which may or may not be recognized as such.

The surgeon is one of the professionals responsible for correctly identifying and treating the 5% to 10% of the breast cancer population who represent hereditary cancer families. One way to begin to meet this challenge is through developing and systematically using a useful family history screening tool to screen patients consistently. It is not sufficient to ask "Is there anyone in your family with cancer?" or "Did your mother have breast cancer?" Accurate triage requires more information. The screening tool, which may be inserted into routine intake forms, may range from a single sheet that asks patients to list relatives and their cancers<sup>38</sup> to sophisticated, computerized systems that may generate pedigrees and stratify the patient population by risk category.<sup>71</sup> In our own cancer genetics program, we have agreements and procedures in place to review short questionnaires used by several medical practices in order to identify patients for whom genetics referral is warranted. We also have demonstrated that brief breast cancer risk assessment can be carried out by a trained genetic counselor with a laptop computer in the mammography waiting room.<sup>73</sup> Breast cancer risk assessment is fast, causes no disruption in clinical procedures, and provides automated database compilation of risk fac-

tors. Clinical use of breast cancer risk assessment could become the basis for streamlined referral to more comprehensive genetic evaluation, for modified screening recommendations or chemoprevention trials, and may be useful in identifying target populations for participation in research protocols. The purpose of any of these preliminary screening activities is not to make a definitive genetic diagnosis but rather to identify those persons who have potentially increased cancer risk and merit further quantitative evaluation.

Increasingly, there will be molecular means of screening tumors for specific genetic markers that may indicate the presence of an underlying genetic cancer susceptibility.<sup>78,83</sup> One example from colon cancer is the microsatellite instability seen in some colon, endometrial, and other cancers. Often, high levels of microsatellite instability raise suspicion that one is dealing with a case of hereditary nonpolyposis colorectal cancer.<sup>76</sup> Although the yield of this type of genetic screening seems low, one could foresee a day when panels of multiple markers may be available to improve the sensitivity of molecular screening of tumors to indicate hereditary cancers.

The surgeon might well ask what sort of patient should be considered for referral to a genetic professional. The surgeon should refer if he or she is not prepared to spend the approximately 90 face-to-face minutes necessary to take a complete family history and offer comprehensive counseling as described later. Other customary indications for referral include patients diagnosed with breast, ovarian, or colon cancer with a positive family history, those with early onset (i.e., less than 50 years old), men with breast cancer, women with bilateral breast cancer or multiple primary tumors, women with both breast and ovarian cancer either in themselves or their relatives, Ashkenazi Jewish women with any of these risks, and individuals with extreme cancer anxiety, even in the absence of obvious risk. Also, the surgeon should refer women with family or personal history of telltale combinations of cancers (e.g., the association of thyroid, breast, and skin manifestations in Cowden syndrome).

### **MANAGEMENT OF HEREDITARY BREAST CANCER: COMPREHENSIVE CANCER RISK COUNSELING AND TESTING**

A wide variety of activities have been described as part of comprehensive cancer risk counseling. These include genetic evaluation, genetic pedigree construction and interpretation, record review and documentation, genetic syndrome diagnosis, risk calculation and communication, genetic susceptibility testing, DNA banking, psychosocial evaluation and counseling, tailored medical surveillance, and participation in genetic research. Many of these components may be introduced by the astute surgeon so that the patient has a basic understanding of the key issues when she or he meets with the genetic counselor.

## Genetic Education

Persons who deal with genetic diseases such as hereditary cancer must assimilate a great deal of new information that is complicated and abstract. The genetic counselor can facilitate learning and assimilation of genetic information by imparting and explaining clearly principles of medical genetics and patterns of inheritance and by offering an appreciation of the probability of having a genetic mutation or developing cancer. Cancer risk counseling generally also includes a discussion of cancer epidemiology, the multistep process of carcinogenesis, and spectrum of disease presentation, diagnosis, treatment, and prevention. In teaching families the language and concepts of cancer genetics, the counselor can help them formulate a conceptual framework that paves the way for future information and decision making as well as empowers and encourages them to become active participants in their health care.<sup>58</sup> Websites are available in Table 1.

## Cancer Risk Assessment

It has been said that, "Surgeons will need to recognize whether a genetic syndrome should be suspected in their patients, decide whether or not there is an appropriate referral to be made. If you are committed to specializing in cancer genetics, others will refer to you."<sup>79</sup> There may even be medicolegal implications of failing to diagnose hereditary cancers.<sup>37</sup> What can the surgeon expect from requesting such a risk assessment evaluation?

Risk is a complex concept that means different things to different people.<sup>36,72</sup> The concept of risk incorporates both a statistical or probabilistic notion and some measure of adversity or threat.<sup>44</sup> Risk encompasses the attributes of ambiguity and uncertainty that make genetic inheritance so difficult for patients, families, and physicians alike to deal with.

Cancer risk assessment refers to the process of quantifying the statistical probability of an individual's developing cancer due to the presence of variables such as family history, cancer susceptibility gene mutations, lifestyle, environmental exposures, and chance.<sup>66</sup> Breast cancer risk can be approached from two ways: (1) what is the risk of developing breast cancer based on a variety of recognized risk factors and (2) what is the risk of having an alteration in a known breast cancer susceptibility gene. These shall be considered in order.

Although the data from various epidemiologic studies often have been useful for identifying potential breast cancer risk factors, results of individual studies are often contradictory and presented in the form of relative risk, which is not clinically useful to patients. Recent efforts have been made to design risk tables and Windows-based tools that are more easily interpretable to families.<sup>5,10,28,29</sup> Depending on the putative mode of inheritance of cancer risk in a particular family, different methods are currently used; it is extremely important for the genetic counselor to

choose the correct model for a specific family in order to avoid gross overestimates or underestimates of risk.

The initial step in classifying families as moderate or high risk is to examine the family history to ascertain the constellation of tumors and evaluate potential inheritance patterns.<sup>66</sup> Once the provider has taken a three-generation pedigree, he or she can search for various characteristics that suggest autosomal dominant inheritance of cancer predisposition, including vertical transmission of cancer predisposition, transmission of susceptibility through both male and female relatives, with approximately 50% of at-risk individuals inheriting a predisposition and 50% spared.

Moderate-risk families are characterized by a less striking family history, absence of ovarian cancer, and older average age at time of diagnosis. The most common breast cancer risk models used with women at moderate breast cancer risk, the Gail and the Claus models, are named after their primary authors. Both are derived from large population-based datasets and thus apply to a broad range of women, particularly those without a strong family history. The Gail model is the basis for the widely available NCI risk disk and the risk calculator available from AstraZeneca used to determine whether a woman's breast cancer risk is high enough to consider prescription of tamoxifen for breast cancer chemoprevention. Although the Gail model has been validated for use in women with multifactorial disease, the practitioner should be aware that these risk assessment tools are limited in identifying patients with hereditary cancers who could benefit from genetic testing.<sup>84</sup>

For families suspected of manifesting a hereditary breast cancer susceptibility, there are a number of models to predict mutation carrier status for either *BRCA1* or *BRCA2* or both. These models were derived from small populations, mostly ascertained on the basis of a prior strong family history, and apply mainly to individuals with similar backgrounds. The Ford study is based on linkage data from the Breast Cancer Linkage Consortium,<sup>84</sup> whereas the others are based on gene sequencing data from high-risk families who participated in research studies or chose to be tested during the early days of test availability. These data are likely to be subject to selection biases demonstrated by the lower cancer penetrance figures derived from studies that are more population based.<sup>24</sup> Models in these categories include those from Shattuck-Eidens et al,<sup>88</sup> Frank et al,<sup>25</sup> Couch et al,<sup>12</sup> and Berry et al.<sup>6</sup> Because each model is based on a different population and includes different parameters in the model, careful interpretation of multiple calculated mutation probabilities is necessary. In our experience, calculation of the likelihood range for detecting a mutation is often useful to persons who are making decisions about spending hundreds to thousands of dollars to have a genetic test. The quantitative probabilities should be considered as guiding a decision rather than dictating a course of action based on absolute risk thresholds.

It is essential that risk information be communicated in a way that is meaningful to the patient or relative. For example, some counselors use fractions (e.g., one in five), whereas other counselors describe risk in terms of percentages (e.g., 20%). It is also customary to turn the risk figure

around to state the individual's chance of not developing the condition (e.g., a 20% risk of breast cancer means an 80% chance of not getting breast cancer).

Despite efforts to communicate statistical risks clearly, it has been demonstrated that "efforts to counsel women about their breast cancer risks are not likely to be effective unless their breast cancer anxieties are also addressed."<sup>6</sup> Sometimes familial cancer risk counseling raises awareness in the family of patients who battled cancer and of the impact that these first-hand experiences may have had on certain people.<sup>15,50,61</sup> Individuals with moderate statistical risk for cancer may be just as anxious about their perceived risk as people at high statistical risk. Sufficient time and attention should be dedicated to all risk counseling interactions, not only to the high-risk hereditary cases.

Currently identification of hereditary cancer syndromes is based largely on clinical and family history criteria. If pedigree analysis or physical examination supports the identification of a known hereditary syndrome, risk assessment can proceed using the laws of Mendelian inheritance of a known mutation. Additional models help the genetic counselor establish how likely it is that a patient carries a genetic mutation in a breast cancer susceptibility gene such as *BRCA1* or *BRCA2*, which predisposes to hereditary breast-ovarian syndrome. One of these models, BRCAPRO, is currently available via the internet. All of the available models to estimate likelihood of carrying a mutation are based on prevalence, penetrance, and mutation frequency data derived from the high-risk families who participated in research studies or chose to be tested during the early days of test availability. Most persons tested were affected with cancer; thus the data incorporated in most models are likely to be subject to selection biases. These models also fail to recognize known syndromes that predispose to hereditary breast cancer and their associated susceptibility genes, as listed in Table 2.

### Genetic Susceptibility Testing

Frequently in medical practice, only minimal information is given to the patient about medical testing being performed unless and until there is an abnormal result. The situation differs dramatically for genetic testing because of the profound impact that this information may hold for both the patient and the family. For persons eligible and motivated for cancer predisposition testing, there is uniform expert opinion and published professional guidelines indicating that it is necessary to offer a pretest counseling session for education, informed consent and adequate exploration of the risks, limitations, and benefits of testing.<sup>3,21</sup> The genetic counselor can be highly effective in nondirectively assisting eligible persons in deciding whether to undergo a genetic test.

Informed consent for genetic testing should include a description of test procedures, test specificity and sensitivity, and risks, benefits, and

**Table 2.** INHERITED BREAST CANCER: SELECTED SUSCEPTIBILITY SYNDROMES

Syndrome	Features	Gene
Breast ovarian	breast, ovarian, possible colon and prostate	BRCA1
Breast ovarian	male and female breast, ovarian, prostate, pancreas, gallbladder and bile duct, stomach, malignant melanoma, possible buccal cavity, pharynx, and other	BRCA2
Cowden disease	hamartomas and benign and malignant tumors of breast, thyroid, skin, other	PTEN
Ataxia-telangiectasia (AT) heterozygosity	homozygotes have ataxia, telangiectasia, hematologic malignancies; heterozygotes with possible increased breast cancer due to radiation sensitivity	ATM
Li-Fraumeni syndrome (LFS)	sarcoma, breast, brain, leukemia, lymphoma, lung, adrenocortical, other; early onset; many primaries	P53

limitations of testing.<sup>32,62</sup> This has not always occurred.<sup>105</sup> Patients should be informed of alternatives to testing (e.g., medical management with no test, deferred testing, or DNA banking for future testing). In genetic testing it is also important to explore the impact that testing may have on individual mood, insurance, employment, economic status, and family dynamics. In particular, individuals should understand clearly the difference between susceptibility to future cancer and diagnosis of present cancer. They also should be told the probabilities of having a positive, negative, or inconclusive test result based on currently available information.

It is important for prospective genetic testing candidates and their physicians to be able to interpret test results. For example, it is important to distinguish between mutations and polymorphisms. Mutations are DNA sequence alterations that affect the protein function and predispose the person to development of breast and ovarian cancer, whereas a polymorphism is a benign variant that is not associated with increased risk. There is a high frequency of uninterpretable results such as polymorphisms of unknown significance; therefore, the ordering physician should be prepared to work with the testing laboratory to clarify the interpretation and perhaps to coordinate the testing of additional relatives whose genotypes may help to clarify the significance of uninterpretable results. The patients must be prepared for the possibility of ambiguous results before undertaking testing in order to avoid confusion and distress afterward.

It is also important that patients understand the wide range of penetrance estimates from studies in different populations. Initial penetrance estimates for *BRCA1/BRCA2* mutations were generated from high-risk families. Data from the more than 200 Breast Cancer Linkage Consortium families predicted that women who carry a *BRCA1* mutation have approximately an 80% lifetime risk of breast cancer.<sup>33</sup> A study of more than 5000 Ashkenazi Jewish individuals in the Washington, DC, area yielded a breast cancer risk in mutation carriers of three selected founder mutations to be approximately 56% and a 16% ovarian cancer risk.<sup>17,96</sup> In a smaller study of 268 Jewish women from New York City with breast can-

cer ascertained without regard to family history, the penetrance was 36%.<sup>97</sup> A similar modest penetrance was found in an Icelandic study of a single *BRCA2* mutation in a population-based study of more than 500 women with breast cancer.<sup>23</sup> The results of the same test, showing the same mutation, may differ from patient to patient depending on ethnic background, family history, and other as yet undiscovered genetic and environmental modifying factors.

Another complicating factor in genetic counseling for hereditary breast cancer is the variable expression of mutations in different individuals, even within the same population. It is clear that not all women who carry *BRCA2* mutations develop breast or ovarian cancer. Some women may develop other cancers besides breast. Currently we have limited insight regarding what causes these variations, but there is evidence that penetrance is modifiable by hormonal, environmental, and genetic factors, boding well for prevention and treatment based on the underlying genotype.<sup>67,82,84,100</sup>

Often the question is not whether to test but whom. For genetic susceptibility testing to be most effective, testing should begin with an already affected family member. This is because the value of a negative test for predicting breast cancer is different depending on whether the family has a previously identified mutation. If a person with cancer has a particular germline mutation in a cancer susceptibility gene, testing then can be offered to other unaffected relatives who express an interest. Although initial testing may cost from several hundred to several thousand dollars for the first person tested, once a mutation is identified in a family, the cost of testing of subsequent individuals for this same mutation is significantly less. Testing of children under 18 years of age is generally discouraged for adult-onset disorders such as breast cancer.

### Choice of Laboratory and Test

Physicians are currently being bombarded with advertising and direct mailing regarding the availability of genetic testing. The array of choices is often daunting. With genetic technology moving at the current rapid pace and new cancer gene discoveries, the situation will become only more complex rather than less. Because the implications of genetic susceptibility testing are so profound, the highest standards of quality control should be maintained in testing. Although testing options are limited currently because of cumbersome technologies, the variety is certain to expand.

How does one choose a genetic testing laboratory? One consideration is quality. In the United States, "clinical laboratories performing an examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment . . . of human beings" must obtain certification from the Health Care Finance Administration under the Clinical Laboratory Improvement Act of 1988.<sup>31</sup>

Are you ordering the right genetic test? Genetic counselors and geneticists may be helpful in choosing a laboratory for susceptibility testing in two ways. First, not all tests are equal. There are different methods for different situations, each with its own strengths, limitations, costs, and weaknesses. For genetic testing to be informative, the correct genetic diagnosis must be made; the genetics professional can help to establish the correct genetic diagnosis on a patient. Ordering a genetic test for the wrong syndrome can be embarrassing, negligent, costly, and potentially dangerous if medical decisions are made based on these results. For that reason, we devote some attention to specific genetic syndromes.

### **Characteristics of Hereditary Syndrome**

The genetics of breast cancer are complex for various reasons. There is neither a single cancer syndrome, nor a single breast cancer gene. This is called genetic heterogeneity. Within the recognized genes, there is allelic heterogeneity (i.e., a variety of mutations are possible). Within each syndrome, a mutation confers risk for more than one manifestation, be it different types of cancer or the combination of cancer with benign features. This is known as pleiotropy. In addition only a proportion of individuals with a genetic mutation develop cancer. The proportion of affected individuals from among those who carry a given mutation is known as the penetrance. Finally, persons who develop physical manifestations may do so at different ages or in different organs, phenomena known as age-dependent penetrance or variable expressivity.

### **Breast Cancer Susceptibility Syndromes**

One of the hallmarks of genetic syndromes is that the risk associated with a given susceptibility gene hardly ever confers increased cancer risk for a single type of cancer. Rather, there is often a constellation of benign and malignant features, which often run together and are known as syndromes. For example, breast cancer associated with ovarian cancer may indicate hereditary breast-ovarian cancer, whereas breast and thyroid cancers typically occur in conjunction with Cowden syndrome. There exists considerable genetic heterogeneity in inherited breast cancer syndromes (i.e., a number of different genes can be responsible for different or even the same syndrome). This heterogeneity has serious implications not only for genetic testing but also for disease management.

Some hereditary syndromes that may predispose to breast cancer include hereditary breast-ovarian cancer, ataxia-telangiectasia (AT) heterozygosity, Carney syndrome, Cowden syndrome, Li-Fraumeni syndrome (LFS), Lynch II syndrome (HNPCC), Muir-Torre syndrome, Peutz-Jeghers syndrome, and Ruvacavva-Myhre-Smith syndrome.<sup>42,70</sup> In addition, undoubtedly other genes are associated with other syndromes yet to be dis-

covered. A discussion follows of some of the more well-studied of these syndromes for which genetic explanations have been found.

### **Breast-Ovarian and *BRCA1* and *BRCA2* Mutations**

The major genes responsible for hereditary breast and ovarian cancer were discovered within the past decade.<sup>35,41,64</sup> A significant proportion of heritable breast-ovarian cancers involves mutations in either of these two genes. These are known as *BRCA1* and *BRCA2* (BReast CAncer genes 1 and 2). The risk of breast cancer is elevated with mutations in either gene. The risk for ovarian cancer is generally considered higher with *BRCA1* than *BRCA2* mutations. Wide variability exists, however, in disease penetrance for these genes when mutations occur in different populations. Some people with a mutation have a substantial risk (e.g., up to 85%) of developing breast cancer, whereas other people from different families may have a quite moderate risk increase (e.g., 35%–50%) with a mutation in the same genes. In all probability, selection bias, gene-gene, and environmental modifiers affect the disease penetrance. The practitioner should be cautious in counseling about cancer risk based on a genetic test and should present a range of cancer probability rather than a single figure, which may imply more precision than is currently warranted.

As a result of cultural and historical factors such as isolation and marriage within the group, certain mutations may be found in higher frequencies in specific ethnic groups.<sup>68a</sup> Such populations include Icelanders, Finns, and Ashkenazi Jews from Eastern and Central Europe.

Mutation detection is complicated for both *BRCA1* and *BRCA2* genes. The *BRCA1* and *BRCA2* genes are extremely large, thus full gene sequencing is laborious. Hundreds of mutations have been found in each, making targeted testing for specific mutations difficult outside of specific ethnic groups.

Finally, other loci may be implicated in hereditary breast and ovarian cancer. These include genes associated with LFS, AT, androgen receptor, Cowden disease, Muir-Torre syndrome, and Peutz-Jeghers syndrome. A brief synopsis of selected syndromes is presented next. If the family history reveals multiple types of cancer in addition to a breast or ovarian cancer, however, referral to a specialist with expertise in cancer genetics may be especially useful.

### **Li-Fraumeni Syndrome**

The *p53* gene plays a central role in normal cell growth, differentiation, and programmed cell death (apoptosis). More than half of human malignancies display *p53* mutations in the cancerous tissue, including breast cancers. These are known as somatic mutations and are not dis-

cussed further herein, although presence of *p53* mutations may have significant prognostic and treatment implications.

Germline *p53* mutations also account for a rare hereditary syndrome known as LFS.<sup>51,106</sup> LFS exists in both distinct and subtle forms. Classic LFS is defined by the following stringent criteria: (1) index case with sarcoma diagnosed before age 45, (2) first degree relative (FDR) with LFS-associated cancer before age 45, and (3) another FDR or second degree relative (SDR) with either a sarcoma diagnosed at any age or a component cancer diagnosed before age 45. The detection rate of germline *p53* mutations may approach 50% to 70% using stringent clinical definitions and meticulous mutation detection techniques, which are not generally available commercially.<sup>26,52</sup> In fact, most *p53* testing is probably still undertaken in research settings.

Hallmarks of LFS are usually young age at tumor onset and frequent multiple primary tumors. Bone sarcomas, soft tissue sarcomas, and brain tumors each account for approximately 12% of LFS-associated tumors. In one study, 57% of patients developed a second primary malignancy, 4% had three primaries, and 2% had four primary tumors within 30 years of the first.<sup>104</sup>

The risk for developing cancer in LFS is estimated to reach approximately 50% by age 30 and more than 90% by age 70. The lifetime penetrance of cancer is higher for women than men due to the high frequency of breast cancer in the syndrome.

Breast cancer is the most frequently observed cancer in LFS, accounting for one fourth to one third of all tumors, with an average age of onset of 36 years.<sup>40,49</sup> Breast cancer in the 20s, particularly the early 20s or in combination with other LFS features such as sarcoma or adrenocortical carcinoma, should prompt a consideration of LFS. In the absence of other LFS features the chance of a *p53* germline mutation is low, and germline *BRCA2* mutations are more likely.

## Cowden Syndrome

Cowden syndrome is a rare autosomal dominant cancer predisposing syndrome that involves characteristic mucocutaneous lesions and cancer of the breast, thyroid, and female genitourinary tract. Named for a patient with the condition, the alternate designation is the multiple hamartoma syndrome. Hamartomas are benign, disorganized, hyperplastic growths that may occur in any tissue. In Cowden syndrome, hamartomas are most commonly encountered in the skin, mucous membranes, breast, and thyroid, and hamartomatous polyps of the colon and small bowel are characteristic. Multiple trichilemmomas are pathognomonic. The cobblestone-like gingival and buccal mucosa papules, verrucous skin lesions of the face and limbs, acral keratoses, and papillomatous tongue should raise serious suspicions of Cowden syndrome. Lipomas and fibromas are also typical. Penetrance of the mucocutaneous features is nearly complete by age 20.

In addition to breast hamartomas, an array of benign breast findings may occur, including ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, fibroadenomas, and fibrocystic change as well as nipple and areolar malformations.<sup>7</sup> The risk of fibrocystic breast disease may be as high as 67%. Typical of this syndrome is the presence of a densely fibrotic hyalinized breast nodule. Ductal carcinoma in situ and invasive cancer are common, with a lifetime penetrance of 30% to 50% for breast tumors.

Thyroid disease, including multinodular goiter and adenomas, is seen in 50% to 75% of individuals with Cowden syndrome. There is a 3% to 10% chance of epithelial thyroid carcinoma, with follicular thyroid carcinoma being most typical. Multiple, early-onset uterine leiomyomas are characteristic, and brain tumors (meningiomas, glioblastomas multiforme) also can occur. A number of skin cancers have been reported, including primary neuroendocrine carcinoma of the skin (Merkel cell or trabecular carcinoma), squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Other malignancies occasionally associated include ovarian, renal cell, bladder, uterine, lung, colorectal, hepatocellular, pancreatic carcinomas, and liposarcoma.

Germline mutations in the *PTEN* gene in individuals with Cowden syndrome have been reported<sup>54,59,91</sup> since the gene was cloned.<sup>60</sup> *PTEN* (phosphatase and tensin homolog detected on chromosome 10) somatic mutations are not commonly observed in early-onset breast cancer, but *PTEN* somatic loss does appear to be important in the development of some common sporadic cancers, including breast, prostate, kidney, and brain cancers. Tensin interacts with focal adhesions; therefore, it is plausible that disruption of a tensin-like function in the *PTEN* protein could relate to metastasis and the observation of *PTEN* functional loss in advanced cancers. The loss of the tyrosine phosphatase function of *PTEN* conceivably might lead to unrestricted cell growth.

Because the breast and thyroid malignancies commonly associated with Cowden syndrome can be detected in early stages of surveillance, recognition of the syndrome is critical. The International Cowden Syndrome Consortium recently developed operational diagnostic criteria.<sup>53</sup> Eng<sup>20</sup> has pointed out the importance of instituting surveillance in families with mutations in this highly penetrant, autosomal dominant cancer predisposing gene. Because gene testing is still being conducted only as part of research studies and is not yet clinically available, management depends on disease recognition using the international diagnostic criteria. A team management approach with a surgeon, oncologist, primary care provider, geneticist, dermatologist, and neurologist is optimal. The earliest documented case of breast cancer in Cowden syndrome is age 14 years, but most breast cancer cases occur in the thirties and older. Physical examinations that focus on the skin and thyroid should begin in the teen years, and breast self-examination should be taught early. Annual mammography with or without breast ultrasonography should begin at age 30 or 5 years less than the youngest breast cancer diagnosed in the family, whichever is younger. Fibroadenomas may impair surveillance and cause

pain, disfigurement, and anxiety. They require tailored surveillance strategies with the option of bilateral prophylactic mastectomy offered as needed.

### **Ataxia-Telangiectasia**

There is debate in the scientific literature about whether female mutation carriers for the autosomal recessive disorder ataxia-telangiectasia are at increased risk of breast cancer. Evidence in favor of the AT heterozygote hypothesis is based mainly on epidemiologic studies and is supported by biologic plausibility.<sup>84</sup>

AT is an inherited disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, hypersensitivity to ionizing radiation, immunodeficiency, chromosomal instability, and a markedly increased frequency of malignancy, seen in one third of homozygotes (i.e., in individuals with the condition due to having mutations in both copies of the *ATM* gene).<sup>20</sup> The malignancies most often associated are lymphomas, chronic lymphatic leukemia, adenocarcinoma of the stomach, medulloblastoma, and glioma.<sup>7</sup> Breast cancer is usually not seen in homozygotes but may be seen more frequently in heterozygotes.<sup>30,99</sup>

The gene responsible for AT was cloned in 1995 and named the *ATM* gene (ataxia-telangiectasia mutated).<sup>98</sup> Generally it is believed that cells from AT patients are abnormally sensitive to induction of chromosomal breakage and killing by ionizing radiation, paralleled clinically by radiation necrosis seen in homozygotes when given conventional treatment doses for malignancy. The AT heterozygote hypothesis is that individuals with one mutated copy of the *ATM* gene and one normal *ATM* gene do not possess enough intrinsic ability to guard against the carcinogenic effects of radiation and develop cancer at a higher rate than individuals with two working copies of the *ATM* gene. Based on estimated AT homozygote frequency, it has been estimated that 1% of people are carriers of AT mutations. Although the extent of increase in breast cancer risk may be small for an individual woman, the cumulative effect of these small increases in 1% of the population creates a significant proportion of breast cancer attributable, at least in part, to *ATM* carrier status. If so, then identification of these at-risk individuals and minimization of radiation exposure might impact favorably on the incidence of breast cancer.

### **Male Breast Cancer**

Although much remains to be understood about the cause of male breast cancer, a number of cases are due to genetic causes. Klinefelter syndrome (47,XXY karyotype) is associated with approximately a 3% lifetime risk of male breast cancer, perhaps due to circulating endogenous estrogens. Male breast cancer in androgen insensitivity (AI) syndrome, due to mutations in the androgen receptor gene, has been described. Both

Klinefelter syndrome and AI syndrome are evident on history and physical examination.

Germline mutations in *BRCA1* and *BRCA2* genes are also responsible for male breast cancer in some families. *BRCA2* mutations cause more of a risk than *BRCA1*. In an Icelandic population-based study, one particular *BRCA2* mutation—999del5—accounts for 40% (12/30 cases) of male breast cancer in the country.<sup>23</sup> In a US study of high-risk patients, 14% (7/50) of male breast cancer cases had *BRCA2* mutations. The three Ashkenazi Jewish individuals had the same 6174delT *BRCA2* mutation.<sup>85</sup> Eighty percent of men with breast cancer had a family history of breast cancer, with 85% of mutation-identified cases having a positive family history. Ascertainment bias may have led to the elevated estimates of attributable risk of *BRC2* to male breast cancer. In another population-based study, Friedman et al<sup>27</sup> found *BRCA2* mutations in 4% (2/54 cases) of men with breast cancer, one of which had no family history of breast or ovarian cancer.

Men with germline *BRCA2* mutations have approximately a 6% lifetime risk of breast cancer, far less than female carriers, but far more than average-risk men. Breast self-examination and awareness may lead to early detection, which would be expected to improve prognosis.<sup>27</sup>

### Low Penetrance Genes

The search for genetic markers for breast cancer susceptibility has led to an increasing number of epidemiologic studies of relatively common genetic markers, referred to collectively as genetic polymorphisms, in genes that often code for enzymes that may have a role in the metabolism of estrogens or detoxification of drugs and environmental carcinogens. Although the clinical significance and causality of associations with breast cancer reported to date is unclear, genetic polymorphism may account for why some women are more sensitive than others to environmental carcinogens such as hormones, chemicals, or radiation.

One category of genetic polymorphisms that causes breast cancer susceptibility and has received the most attention is the cytochrome p450 enzymes (CYP).<sup>16</sup> These have a role in steroidogenesis and detoxification of polycyclic aromatic hydrocarbons, benzopyrenes, arylamines, and heterocyclic amines and as such normally provide a line of defense against these exposures to varying degrees. Certain genotypes such as CYP1A1, CYP2D6, and CYP17, which lead to different forms of these enzymes, have been associated with certain cancers such as breast, lung, colon, and bladder.

*N*-Acetyl transferase (NAT) 1 and 2 genes detoxify or activate aromatic amines found in tobacco smoke and well-done meats. Both phenotypic assays and genotypic assays for *NAT2* can be used to classify individuals as rapid or slow acetylators. Studies of the *NAT2* genotype and breast cancer susceptibility have had inconsistent results.

There is a family of glutathione S-transferase (GST) genes, *GSTM1*, *GSTT1*, and *GSTP1*. The transferases produced by these genes detoxify various carcinogens and cytotoxic drugs. Having certain genotypes may confer higher risk of breast and other cancers because of their impaired ability to metabolize and eliminate carcinogens. The *GST* genotypes also may have a relationship to age at breast cancer diagnosis in women with a positive family history.<sup>82</sup>

## **MEDICAL MANAGEMENT OF FAMILIAL AND HEREDITARY CANCERS**

There are few data on the outcomes of interventions to reduce risk in people with a genetic susceptibility to breast or ovarian cancer. Recommendations for management are based primarily on expert opinion and personal preferences. The interventions generally fall into categories of early detection, chemoprevention, surgical prevention, and altered treatments.

### **Breast Cancer Screening and Early Detection**

Decision analysis may help optimize breast cancer screening for young women at increased risk for breast cancer. The frequency of germline *BRCA1* and *BRCA2* mutations is approximated at 1 in 800 in the general population, unselected for family history of cancer.<sup>93</sup> Thousands of US women aged 25 to 49 are at exceptionally high risk of developing breast cancer, with incidence rates reaching 21 to 27 per 1000 in the fifth decade. These women need targeted surveillance.

Early detection methods currently available for breast cancer include breast self-examination, clinical breast examination, mammography, ultrasound, and other imaging techniques. These all have limitations in the younger population at risk.

The efficacy of breast self-examination in female carriers of *BRCA1/BRCA2* mutations has not been studied. A task force convened by the Cancer Genetics Studies Consortium has recommended monthly breast self-examination beginning during early adulthood to establish a regular habit and allow familiarity with the normal characteristics of one's own breast tissue. Education and instruction in breast self-examination were recommended.<sup>68</sup> In the general population, clinical breast examination is used as a supplemental screening method for breast cancer, but again there are few prospective data regarding clinical breast examination among male or female carriers of *BRCA1/BRCA2* mutations. The Cancer Genetics Studies Consortium task force conclusions about clinical breast examination were similar to those for breast self-examination, namely, begin annual or semi-annual clinical breast examination beginning at age 25 to 35 years.<sup>68</sup>

Mammography has been shown to reduce breast cancer mortality by 25% to 30% in women aged 50 to 59 and by 17% in women aged 40 to 49, occurring 15 years after the start of screening. There are no data regarding relative benefits or risks to screening mammography among female or male carriers of a *BRCA1/BRCA2* mutation. The Cancer Genetics Studies Consortium task force has recommended annual mammography beginning at age 25 to 35 for female *BRCA1/BRCA2* carriers based largely on expert opinion.<sup>68</sup> They advise that mammograms be done at a consistent location when possible, with prior films available for comparison.

Psychosocial issues appear to influence breast cancer screening behaviors and decisions. Kash et al<sup>47</sup> demonstrated that one group of high-risk women showed an inverse relationship between level of anxiety and frequency of breast self-examination.

Newer methods of breast imaging ideally would be targeted at the population of young women at increased risk for breast cancer on a genetic basis. The sensitivity of contrast-enhanced breast MR imaging for breast cancer detection has been reported as high with specificities more variable. Available data indicate that MR imaging and mammography are complementary tests; however, trials in high-risk women are pending.

## **Surgical Prevention of Breast Cancer**

### *Prophylactic Mastectomy*

In the general population, both subcutaneous mastectomy and simple (total) mastectomy have been used to prevent breast cancer for various indications. Whereas more vulnerable breast tissue is removed with the total mastectomy and removal of the nipple-areolar complex, only 90% to 95% of the breast tissue is removed with subcutaneous mastectomy.<sup>2</sup>

One recent retrospective cohort study was conducted at the Mayo Clinic to examine the outcome of prophylactic mastectomy.<sup>39</sup> Median follow-up after surgery was 14 years. All women included in the report had some family history of cancer and were classified as high risk or moderate risk for breast cancer based on the pattern of breast cancer in the family. Over a 30-year period, the expected number of cancers was calculated from the Gail model for the women at moderately high risk and compared to the observed number of cancers in sisters of the high-risk women. Hartmann et al<sup>39</sup> observed that a history of prophylactic mastectomy was associated with a 90% risk reduction of breast cancer in the surgical cases as compared to expected number. Information of *BRCA1/BRCA2* mutation status was not known. Although this study provides the best evidence available to date that prophylactic surgery offers benefits despite the fact that some breast tissue remains after surgery, the results may have been biased by several factors. Misclassification of women at high risk when they did not inherit a deleterious mutation would lead to an overestimation of the benefits of surgery because these women would never have

gone on to develop breast cancer anyway. It is possible that many women may have received unnecessary surgery to prevent few cancers.

Practice guidelines for performing prophylactic mastectomy appear to vary by profession. Stefanek et al<sup>92</sup> found that plastic surgeons recommend prophylactic mastectomy much more frequently and with less serious genetic indications than do general surgeons. Both plastic and general surgeons recommend prophylactic mastectomy more frequently than do gynecologists. One should be conscious of the unconscious biases introduced by one's professional training and affiliations.

Although it may seem to the surgeon that use of prophylactic mastectomy for breast cancer prevention is high among women at increased genetic risk, instances of actually having the surgery are quite rare.<sup>86,92</sup> Interest in discussing the procedure may be significant in women who attend high-risk breast clinics, however.

Stefanek et al<sup>92</sup> found the following characteristics predictive of interest in prophylactic mastectomy in a high-risk cancer clinic setting: high perceived cancer risk, history of breast biopsy, frequent breast screening, breast cancer-related worry, and cognitive intrusive thoughts about breast cancer. Women who indicated a significant level of cognitive intrusion about breast cancer more often opted for surgery than those with fewer intrusive thoughts. Although a recent stressful life event often prompted women to attend a high-risk breast service, it was not a predictor of interest in prophylactic mastectomy. Satisfaction with the decision to undergo surgery was related to the supportiveness of family members and friends as well as the extensive counseling that accompanied the procedure.

Decision analyses of surgical prophylaxis in theoretical *BRCA* mutation carriers have provided evidence that many years of life would be added for women who undergo prophylactic mastectomy and oophorectomy in their 30s.<sup>34,87</sup> When quality of life is considered, however, the benefit may be considerably less.

The decision to have prophylactic mastectomy is a personal one that is based on various cognitive and emotional factors. Prophylactic surgery is rarely an emergency because the risk of cancer is generally a statistical one for some time in the future, although patients who request the procedure often express a poignant sense of urgency due to their anxiety about developing cancer. We recommend that these requests be handled by a multidisciplinary team of breast cancer specialists. The option should be presented neutrally and with respect for the multiple personal issues it raises.

At minimum, all patients who inquire about prophylactic surgery should have a quantitative risk assessment performed by a qualified genetics professional in the context of cancer genetic counseling. Genetic testing often can be helpful in clarifying cancer risk for those women who consider themselves to be at high risk. With the help of genetic information such as predictions from risk models or genetic test results, the decision can be made with consideration of the age-dependent penetrance of breast and ovarian cancer in *BRCA*-associated syndromes. The risk for

breast cancer rises early for *BRCA1* and is 3.6% by age 30 and 18% by age 40.<sup>24</sup> For *BRCA2*, the cumulative breast cancer incidence is slightly lower: 0.6% by age 30 and 12% by age 40. The optimal benefit of prophylactic mastectomy is obtained by acting on the decision while in one's 30s or 40s.

Because the surgery can raise a number of issues about sexual function, body image, female identity, and marital and family relationships, it is also helpful to have various psychosocial options to offer, including the opportunity to speak with a trained psychotherapist, attend a support group for high-risk individuals, and be offered introductions to (or readings from) other women who are considering or have undergone prophylactic mastectomy.

There has been a recent report of a 6-week psychosocial support group for women at high genetic risk for breast cancer who were considering prophylactic mastectomy.<sup>46</sup> The themes of the group sessions included overestimation of and anxiety about risk; desire for hard data; the emotional impact of watching a mother die of breast cancer; concerns about spouse reactions; self-image and body image; the decision-making process; and confusion over whom to trust in decision making. The authors concluded that the support group was beneficial and cost effective as a supplement to individual counseling in high-risk women who had difficulty in making decisions about surgery.

### *Breast Cancer Chemoprevention*

Tamoxifen, used for decades to treat women with breast cancer, recently has been demonstrated to be effective in preventing primary breast cancers in unaffected women. In a recent, prospective, randomized, double-blind trial comparing tamoxifen to placebo for 5 years, tamoxifen was shown to reduce the risk of invasive breast cancer by 49%<sup>22</sup> and of preinvasive breast cancer to a similar degree. Reductions in breast cancer risk were noted among women with a family history of breast cancer as well as those without. Interim data from two European tamoxifen prevention trials did not show a similar reduction after a median follow-up of 48 months. These trials varied considerably in study design and populations. There are no specific data regarding effectiveness in women carrying *BRCA1/BRCA2* mutations; however, these studies are pending.

### **Ovarian Cancer Surveillance**

A practice oversight sometimes made by people unfamiliar with hereditary cancer susceptibility syndromes is that of overlooking the need for surveillance of organs other than breast. Determination of which organs to monitor depends on what hereditary syndrome is involved in a given family. For Cowden disease, typically the screening involves breast, thyroid, and skin. Persons with susceptibility based on *BRCA1* or *BRCA2* mutations require ovarian as well as breast cancer surveillance.

Patients with *BRCA1/BRCA2* mutations are at increased risk for ovarian cancer. Limited data are available on the potential benefit of screening with serum CA-125 levels or transvaginal ultrasound in women with inherited risk for ovarian cancer. Although the 1994 NIH Consensus Statement on Ovarian Cancer recommended against routine ovarian screening of the general population, they did recommend that women at inherited risk for ovarian cancer undergo annual or semi-annual screening for ovarian cancer with transvaginal ultrasound and serum CA-125.<sup>69</sup> The Cancer Genetics Consortium task force also recommended beginning ovarian cancer screening in known *BRCA1/BRCA2* mutation carriers annually or semi-annually beginning at age 25 to 35.<sup>8</sup>

### Ovarian and Breast Cancer Prevention

It has been suggested that repeated ovulation may increase the risk of ovarian cancer. This view is supported by studies that show that physiologic states that prevent ovulation have been associated with decreased risk of ovarian cancer. For example, oral contraceptive use is associated with decreased ovarian cancer risk in the general population. There are limited data regarding the impact of oral contraceptive use on risk of ovarian cancer among women with *BRCA1/BRCA2* mutations. In the Gilda Radner Ovarian Cancer Registry, users of oral contraceptives had a lower incidence of ovarian cancer than those who did not use contraceptives.<sup>80</sup> In a case-control study of 207 carriers of *BRCA1/BRCA2* mutations and ovarian cancer versus 161 of their sisters without ovarian cancer, Narod et al<sup>67</sup> evaluated oral contraceptive use. After adjustment for year of birth, parity, and age at delivery of first child, there appeared to be an association between oral contraceptive use and decreased risk of ovarian cancer. The effect reached 60% risk reduction in women who took oral contraceptives for more than 6 years. The main risk from oral contraceptive use is possible increased breast cancer risk.

### Prophylactic Oophorectomy for Breast and Ovarian Cancer Prevention

In the general population, removal of both ovaries has been associated with a reduction in breast cancer risk of up to 75%, depending on parity, weight, and age at time of artificial menopause.<sup>45,102</sup> The effects of abrupt surgical menopause are significant, and this method is not in common use currently, given the various other options.

Struewing et al<sup>94</sup> analyzed the incidence of breast and ovarian cancers during 1600 person-years of observations among 12 families with breast or ovarian cancer. They compared the observed number of cases to the expected based on adjusted data from the Connecticut Tumor Registry. Among women who underwent oophorectomy, three breast cancers occurred during 484 person-years of observation. The ratio of observed to

expected cases was 2.7 (CI = 0.5–8). For those women who did not undergo oophorectomy, 14 breast cancers were observed during 1587 person-years of observation. The ratio of observed to expected cases was 7 (CI = 4–12).

The NIH Consensus Statement on Ovarian Cancer recommended that women at inherited risk of ovarian cancer undergo prophylactic oophorectomy after completion of child-bearing or at age 35.<sup>69</sup> The Cancer Genetic Studies Consortium concluded that there was insufficient evidence to recommend for or against prophylactic oophorectomy as a measure for reducing ovarian cancer risk.<sup>8</sup>

Prophylactic oophorectomy decreases the risk of ovarian cancer; however, the peritoneum appears to remain at risk for the development of a mullerian-type adenocarcinoma, even after oophorectomy.<sup>9,94</sup> There is some indication that the risk for subsequent malignancy after prophylactic oophorectomy is high for women from cancer-prone families.<sup>56,101,103</sup>

As with prophylactic mastectomy, decisions about prophylactic oophorectomy should be made by the woman in consultation with a multidisciplinary team. The genetic analysis may help with decision making, such as the timing of surgery, depending on age-specific penetrance figures. Generally, ovarian cancer risk is less with *BRCA2* mutations than with *BRCA1*. There is some debate about mutations in certain regions of the gene being more or less likely to predispose to ovarian cancer. The age distribution of cancers also may differ. The ovarian cancer risk for *BRCA2* mutations is relatively low at younger ages (e.g., 0.4% by age 50 and 7% by age 60).<sup>24</sup> This suggests possibly marginal benefit of prophylactic oophorectomy in *BRCA2* carriers before the perimenopausal years. The age-dependent penetrance of *BRCA1* for ovarian cancer is less than 1% by age 40, 23% by age 50, and 30% by age 60 years.<sup>17</sup> Whereas the ovarian cancer risk for *BRCA1* carriers is much greater than for the average women, most cases occur after age 40; therefore, prophylactic oophorectomy after completion of child-bearing is a surgical option available to women with *BRCA1* mutations.

### **Cancer Genetic Counseling in Breast Cancer Treatment Planning Conference**

What mutual benefits become possible with the inclusion of a medical genetics professional in the treatment planning conference? First, there is networking among the team so that patients receive concordant messages from various team members. Also, the genetics professionals may become more familiar with the range and flow of services at a given institution to expedite referrals to your practice. Additionally, the presence of the genetics professionals generally leads to inclusion of more family history information during the presentation. If there is a positive family history of female or male breast cancer, ovarian, or other cancers, an ad hoc consultation is readily available to determine whether further exploration into the family history is necessary. For cases in which the likelihood of a hereditary syndrome is increased, referrals may be made efficiently. The

consideration of a hereditary syndrome with its increased risk for bilateral disease and multiple primary sites in various organs may influence a decision about breast-sparing surgery. Although treatment decisions about adjuvant radiation therapy are not yet being made on the basis of the patient's genotype, this hypothetical possibility exists as more becomes known about the role of *BRCA1* and *BRCA2* genes in recognizing and repairing radiation-induced DNA damage.

## SUMMARY

There are a number of benefits of providing familial cancer risk assessment, education, and counseling in the context of the multidisciplinary breast center. The following are some examples:

- Early identification for those at increased risk through systematic risk assessment.
- Prevention, early detection, and early treatment in high-risk cohort.
- Identification of cancer risks beyond the obvious (e.g., ovarian and pancreatic cancer as well as breast in *BRCA2* mutation carriers).
- Genetic susceptibility testing for high-risk relatives.
- Avoidance of unnecessary medical surveillance in relatives who did not inherit a deleterious genetic mutation.
- Opportunity to address individual and family concerns.
- Establishment of high-risk registries for future research participation.

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## ADDENDUM

The Society of Surgical Oncology (SSO) recently issued a statement on genetic testing for cancer susceptibility. This statement endorses reform in four important areas in which genetic testing poses potential dilemmas and risks: (1) clinical patient care, (2) medical evaluation, (3) research, and (4) patient rights or advocacy. In terms of clinical care, SSO endorses use of written and informed consent, becoming clear about indications for genetic testing, choice of testing laboratory, use of pre- and post-test genetic counseling from a genetic counselor, and medical management after testing. The SSO supports guideline development, CME accredited cancer genetic courses, resident education and patient education. They recognize that the benefits of genetic testing will not be realized and patients will not participate in clinical trials if they fear insurance or employment discrimination as a result of testing and therefore support long-term outcome studies and the design and implementation of national cooperative registries that preserve confidentiality. Finally, the SSO endorses passage of state and federal legislation to strengthen regulatory authority over genetic testing laboratories, prohibit genetic discrimination, cover access of genetic services, and define the rights of individuals regarding privacy and confidentiality of genetic information.

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*Address reprint requests to*

June A. Peters, MS, CGC  
Department of Human Genetics  
Graduate School of Public Health  
University of Pittsburgh  
130 Desoto Street, Crabtree A-300  
Pittsburgh, PA 15261