



Recognition of a potential hereditary predisposition for breast and ovarian cancer allows the implementation of a specialized surveillance program to manage subsequent cancer risk.

James Rosenquist. *Shriek*, 1986. Monoprint/lithograph, 42½" × 71½". Courtesy of Graphicstudio/USE

Clinical Considerations in the Management of Individuals at Risk for Hereditary Breast and Ovarian Cancer

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Background: *Hereditary predisposition to breast and ovarian cancer; most commonly due to germline mutations in BRCA1 and BRCA2, has been recognized for many years. The optimal clinical management of individuals with such a predisposition is not yet completely defined.*

Methods: *The current literature regarding the clinical management of individuals at risk for hereditary breast and ovarian cancer was reviewed.*

Results: *Women with germline BRCA1 or BRCA2 mutations are at substantially increased risk for breast and ovarian cancer; although the risks may not be as high as originally reported. Current surveillance options are restricted in their effectiveness by both host and tumor factors as well as limitations of the techniques. Surgical prevention options, while effective, may be complicated by physical or psychological morbidity. Nonsurgical prevention options are under development.*

Conclusions: *The ability to define women as being at hereditary risk for breast and ovarian cancer facilitates the use of specialized surveillance and prevention strategies. Genetic testing, which plays a role in defining risk, requires careful pre- and post-test counseling to discuss the limitations of testing itself and available management strategies.*

Introduction

The American Cancer Society estimates that over 200,000 women will be diagnosed with breast cancer in the United States in 2002, and nearly 40,000 will die of the disease.¹ One of the strongest risk factors for the development of breast cancer is the presence of a family history of the disease, although only a minority of women with breast cancer report such a history.

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Aggregate analyses suggest that a woman with a family history of breast cancer has between 1.5 and 2.5 times the risk of a woman without such a history.² Women with multiple affected relatives, or relatives who are diagnosed at earlier ages, appear to be at higher risk.

The presence of two or more cases of breast cancer within a family is sufficient to diagnose "familial" breast cancer. Such familial clustering may result from a shared genetic predisposition, but it may also be a consequence of shared environmental exposures or sociocultural risk factors (such as later age at first child-birth) or even from the operation of chance. The presence of an apparent autosomal dominant pattern of breast cancer, however, suggests that a single predisposing allele is being transmitted through a family. In such families, which can truly be said to manifest "hereditary" breast cancer, the disease occurs in women of each generation, and approximately 50% of the female offspring of an affected woman are themselves affected. The predisposition may be transmitted by men, even if the male parent is not himself affected. Hereditary breast cancer generally occurs at a younger age than sporadic disease, and it is frequently diagnosed in both breasts, either synchronously or metachronously. Other types of cancer, particularly ovarian cancer, are often observed within hereditary breast cancer families. Although male breast cancer is not prominent in most pedigrees, an increased risk for this rare disorder is observed in certain kindreds.

Genetic Etiology of Hereditary Breast Cancer

Although an autosomal dominant predisposition to breast cancer was suspected for many years, formal demonstration of its existence was not provided until the segregation analysis of Newman et al³ in 1988. Subsequently, Hall and colleagues⁴ demonstrated that one associated locus was linked to chromosomal region 17q21, and the term *BRCA1* was coined to describe the putative gene. Other investigators demonstrated that the same region was linked to hereditary ovarian cancer, confirming the previous clinical observations of ovarian cancer in families with an apparent breast cancer predisposition. After an intense multinational effort, the *BRCA1* gene was isolated in October 1994, and germline mutations were detected in members of hereditary breast and breast-ovarian cancer families.⁵ However, a number of families could not be attributed to *BRCA1* by either linkage or direct mutation analysis. Further study of these kindreds demonstrated a second susceptibility locus, called *BRCA2*, on chromosome 13q12,⁶ and in December 1995 the gene was isolated and shown to be mutated in some, but not all, non-*BRCA1* families.⁷

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Linkage analysis of the hereditary breast and breast-ovarian cancer families participating in the Breast Cancer Linkage Consortium (BCLC), all of which had at least four cases of breast cancer either in women before age 60 years or in men, with or without cases of ovarian cancer, indicated that 87% of such families could be genetically linked to either *BRCA1* or *BRCA2*.⁸ Families with both breast and ovarian cancer were more likely to be attributable to *BRCA1*. Families with male breast cancer were more likely to be linked to *BRCA2*, although a significant minority were linked to *BRCA1* (Table 1). Although the predisposition in most families was attributable to either *BRCA1* or *BRCA2*, even in this highly selected group of families, a substantial proportion of kindreds with female breast cancer, but no male breast cancer or ovarian cancer, could not be linked to the known genes. Mutations in a number of genes other than *BRCA1* or *BRCA2* are known to predispose to breast cancer, including p53 (Li-Fraumeni syndrome), *PTEN* (Cowden's disease), *STK11* (Peutz-Jeghers syndrome), and possibly *ATM* and *CHK2*. To date, however, alterations in these genes do not appear to explain most families with an apparent isolated predisposition to female breast cancer.

Although considerable progress has been made since the discovery of *BRCA1* and *BRCA2*,⁹ the functions of the gene products remain incompletely defined. Although these proteins appear to have multiple functions, attention has been focused on their role in DNA damage repair. Recent experiments have demonstrated that both *BRCA1* and *BRCA2* may be critical to a process known as homology-directed DNA repair, a specific cellular mechanism for the resolution of double-stranded DNA breaks.^{10,11} Cells lacking normal *BRCA1* or *BRCA2* function may therefore be predisposed to acquire somatic mutations, accelerating the process of cancer development. The susceptibility conferred by a germline mutation has been thought to follow a classic tumor suppressor model, in that the normal copy of the gene appears to be mutated or lost

before the predisposition is expressed. However, unlike other tumor suppressor genes, somatic mutations in these genes are uncommon in nonhereditary breast cancer. Furthermore, some lines of evidence suggest that there may be phenotypic consequences of haplo-insufficiency, which may be relevant to the process of carcinogenesis in these families. These observations, as well as the restricted tissue expression of the cancer predisposition, have not yet been clearly explained by a single model.

Prevalence of *BRCA1* and *BRCA2* Mutations

Several series have examined the prevalence of germline *BRCA* mutations in population- or hospital-based samples of breast cancer patients. These studies are all likely to underestimate the true prevalence of such mutations, as current testing methodologies are incompletely sensitive. Bearing this limitation in mind, studies have demonstrated *BRCA1* mutations in 3.5% to 6.2% of women with early-onset breast cancer and *BRCA2* mutations in 2.1% to 3.4%.¹²⁻¹⁵ These studies have been conducted in populations of mainly European ancestry, and the prevalence of mutations in other groups has not been established. The available studies indicate that *BRCA1* mutations can be identified in approximately 4% to 5% of ovarian cancer patients and *BRCA2* mutations in 1% to 2%.¹⁶⁻¹⁸

Although *BRCA* mutations are relatively uncommon in women with breast or ovarian cancer, they may be observed with greater frequency in affected women who also have family histories of these diseases. A number of familial cancer risk assessment clinics around the world have identified mutations in either *BRCA1* or *BRCA2* in 21% to 73% of individuals undergoing testing.¹⁹ The ascertainment in these reports are extremely varied, including families from differing ethnic backgrounds with greater or lesser numbers of affected relatives at varying ages. As noted above, in the families whose pedigrees are most suggestive of a hereditary predisposition, such as those included in the BCLC, the probability that a predisposition may be linked to *BRCA1* or *BRCA2* may be as high as 87%. Lower average age at onset, bilateral breast cancer, ovarian cancer, or male breast cancer within the pedigree all increase the probability that the observed family history is the result of a *BRCA* mutation. General guidelines for family histories that are suggestive of a prior probability of detecting a *BRCA* mutation of 10% or greater, based on a reference laboratory experience testing 10,000 individuals, are outlined in Table 2.²⁰ These estimates are not applicable to populations in which specific founder mutations are segregating. The probability of detecting

Table 2. — Family Structures With a 10% or Greater Probability of Detecting a Germline *BRCA* Mutation

- Breast cancer diagnosed before age 50 in 2 or more related women
- Breast cancer diagnosed before age 50 in 1 woman, ovarian cancer at any age in 1 or more additional related women in family
- Breast cancer diagnosed after age 50 in 1 or more women, with ovarian cancer in 2 or more additional relatives
- Ovarian cancer in 2 or more relatives
- Male breast cancer with any family history of breast or ovarian cancer

a familial mutation is always greater when an affected woman is tested, but certain family structures may be sufficiently suggestive to warrant the offer of testing to unaffected individuals if no suitable living affected individual is available. In this circumstance, however, caution must be taken in the interpretation of a “negative” result. It is well established that currently available technology cannot identify mutations in all families whose histories are strongly suggestive of a *BRCA*-related predisposition. Specific mutations were detected in only 64% of the *BRCA1*-linked families in the BCLC who underwent direct mutation analysis, although this analysis was occasionally incomplete. A recent collaborative study of a test set of blinded samples containing 58 distinct *BRCA1* mutations demonstrated sensitivities of 60% to 91% with several different mutation analysis methodologies.²¹ As a result of this limited analytic sensitivity, it is critical that individuals in whom *BRCA* mutations are not detected remain aware of the possibility of hereditary risk and continue to perform surveillance as indicated by their family history. The exception to this injunction is in the situation where a deleterious mutation has already been identified in another family member. In this circumstance, individuals who do not carry the familial mutation are usually considered to have the same cancer risk as the general population, unless pedigree analysis suggests the possibility of a genetic predisposition transmitting from the other lineage than the one with the known mutation.

Individuals from certain ethnic groups may be more likely than members of the general population to carry specific *BRCA* mutations. Shortly after the identification of *BRCA1* and *BRCA2*, two specific *BRCA1* alterations (185delAG, also known as 187delAG, and 5382insC) and one *BRCA2* mutation (6174delT) were shown to be carried by approximately 1 in 40 individuals of Ashkenazi (Central and Eastern European Jewish) descent.²²⁻²⁵ One of these mutations may be identified in approximately 10% of unselected Ashkenazi women with breast cancer and in up to 30% to 40% of women with either early-onset breast cancer or ovarian cancer.²⁶⁻²⁹ It is important to note that mutations other

than the common founder alterations have been observed in Ashkenazi families,^{20,30,31} and thus Ashkenazi families with “negative” testing for the founder alleles cannot be reassured that they lack a detectable predisposition. It is also important to note that the Ashkenazim are not the only ethnic group in which *BRCA* founder mutations have been identified. Similar alterations have been noted in other groups, such as the Dutch and the population of Iceland.^{32,33} Although less well studied than the Ashkenazim, the contributions of these mutations to familial cancer in their respective populations may be significant.

Cancer Risks in Individuals With Deleterious *BRCA* Mutations

Current estimates of the cancer risks associated with germline mutations in *BRCA1* or *BRCA2* are presented in Table 3. All studies have demonstrated increased risks of female breast and ovarian cancer (including fallopian tube and primary peritoneal cancers), as well as prostate cancer, for both *BRCA1* and *BRCA2*. Mutations in *BRCA2* have also been associated with increased risks of a variety of other malignancies, including pancreatic cancer, stomach cancer, and various forms of head and neck cancer. *BRCA2* has been associated with a large increase in relative risk for male breast cancer, although the absolute risk remains low. Although there are no formal estimates of male breast cancer risk associated with *BRCA1*, it is noted that nearly 20% of families in the BCLC with both male and female breast cancer were linked to this gene rather than to *BRCA2*, indicating that germline mutations in this gene may also result in an increase in male breast cancer risk.

Risk estimates have varied widely among series, in part due to different methods of ascertainment and penetrance calculation. In general, higher risk estimates have been generated by studies of families ascertained on the basis of multiple cases of early-onset

breast cancer (and ovarian cancer), while lower penetrance figures are derived from the study of less highly selected families. Genetic or environmental factors not yet unidentified may also influence the penetrance of the inherited predisposition, and these factors may be distributed differently in the reported study populations. Finally, there may be gene-specific and even mutation-specific differences in risk. For example, it appears that both breast and ovarian cancer risk may be lower among *BRCA2* carriers than among *BRCA1* carriers, these cancers may occur at later ages, on average, in *BRCA2* carriers, and risk may also vary with the location of the mutation within the gene.^{34,35}

Clinical aspects of *BRCA*-Associated Breast and Ovarian Cancer

The most striking clinical feature of *BRCA*-associated breast cancer is its propensity to strike younger women. In the BCLC dataset, the risk of breast cancer by age 50 was 49% for *BRCA1* mutation carriers and 28% for *BRCA2* mutation carriers.⁸ Among unselected Ashkenazi female breast cancer patients with one of the specific *BRCA* founder mutations that are common in that population, 27 (79%) of 34 of patients with *BRCA1*-associated breast cancer were diagnosed before the age of 50, as were 10 (67%) of 15 of patients with *BRCA2*-associated disease.²⁹ A similar but less dramatic predilection for early-onset disease is noted in women with *BRCA*-associated ovarian cancer. In the BCLC families, the *BRCA1*-associated ovarian cancer risk was 23% to 29% by age 50 compared with 0.4% to 3.3% by the same age among women with a *BRCA2* mutation.^{8,36} In a population-based series of women with ovarian cancer, 24 (61%) of 39 affected *BRCA1* mutation carriers were diagnosed before the age of 50, as were 5 (24%) of 21 women with *BRCA2*-associated disease.³⁷ Similarly, in a study of Ashkenazi women with ovarian cancer, 31 (54%) of 57 affected *BRCA1* carriers and 3 (10%) of 29 affected *BRCA2* carriers were diagnosed before age 50.²⁷

BRCA-associated breast cancers are usually infiltrating ductal carcinomas, with some authors reporting an increased frequency of medullary and atypical medullary types. The tumors are often poorly differentiated, although there may be subtle differences between *BRCA1* and *BRCA2*-associated disease in this regard. *BRCA*-associated cancers are often aneuploid, with high proliferative rates by flow cytometry or Ki-67 staining. *BRCA1*-associated cancers are usually, but not always, hormone receptor-negative, as opposed to *BRCA2*-associated tumors, which

Table 3. — Range of Cancer Risk Estimates (to Age 70) Associated With Deleterious Germline *BRCA* Mutations

Site	<i>BRCA1</i>	<i>BRCA2</i>
Female breast	46-85%	23-85%
Ovary	16-63%	9-27%
Male breast	No estimate available	~6%
Prostate	Up to 25%	5-7.5%
Pancreas	No increase suggested	1.5-2%
Other cancers (suggested, not proven)	Colon	Stomach, head and neck

often express these receptors. *HER-2/neu* overexpression appears to be uncommon, particularly in *BRCA1*, but p53 mutations are common and may be directly relevant to the pathogenesis of *BRCA*-associated cancer.³⁸⁻⁴⁰

BRCA-associated ovarian cancers have not been as thoroughly studied as breast cancers. High-grade disease appears to predominate, and serous or endometrioid histologies are most common. Mucinous tumors are distinctly underrepresented, as are tumors of borderline malignant potential.^{27,37} As for breast cancer, somatic p53 mutations are frequently observed.

The prognosis of *BRCA*-associated cancer has been a matter of some controversy. Despite the adverse histopathologic features associated with *BRCA*-associated breast cancer, most series have not shown that breast cancer patients with germline mutations have a worse survival than those who do not.⁴¹⁻⁴⁵ However, most of the published reports may have been subject to a systematic survival bias in that only living women were tested, which could have obscured a clinically relevant effect of mutation status on outcome. In support of this hypothesis are studies of unselected Ashkenazi women with breast cancer performed with an anonymized design that allowed linkage of clinical data to genotype without regard to survival. In these series, women with mutations experienced a worse survival than women without mutations.^{28,46,47} A similar design has been applied to the study of Ashkenazi women with ovarian cancer. In contrast to breast cancer patients, women with *BRCA*-associated ovarian cancer had an improved survival compared to those without mutations.⁴⁸

Based on the above data, there is no clear indication that systemic adjuvant therapy should be modified on the basis of germline *BRCA* status, although the threshold for treatment may be lowered for women with *BRCA*-associated breast disease. However, questions have arisen as to whether women with *BRCA* mutations should be offered breast-conserving therapy. One study has demonstrated an apparent increased risk of metachronous ipsilateral disease among mutation carriers surviving for a prolonged period after their initial breast cancer, apparently related to an increased risk of new primary lesions within the treated breast.^{49,50} Studies with generally shorter follow-up, however, have not clearly identified a dramatically elevated risk when the influence of young age is taken into account.^{28,51} The apparent contradiction may be resolved by a model wherein a breast lesion is as likely to be controlled by radiotherapy in women with

BRCA mutations as in those without such mutations, but that the breast tissue of mutation carriers remains at risk for the development of new primary malignancies, which may not manifest until many years later. This hypothesis is consistent with the observation of a significant risk of metachronous contralateral breast cancer in women with mutations. This risk has been reported to be between 25% and 30% at 10 years after the first breast cancer, with some suggestion that the risk may decrease with increasing age at the initial diagnosis.^{28,51,52} Whether scattered radiation from adjuvant radiotherapy increases contralateral breast cancer risk is currently unknown, but there has been no indication as yet of a substantial increase in contralateral risk among women receiving breast conserving treatment compared to those undergoing mastectomy of the affected breast. Thus, while women with germline *BRCA* mutations should not be precluded from undergoing breast-conserving therapy, those who would consider bilateral risk-reducing mastectomy should be made aware that their future reconstruction options may be affected by adjuvant radiotherapy.

Surveillance Options for Women With *BRCA1* or *BRCA2* Mutations

Surveillance recommendations for women with germline *BRCA* mutations are necessarily founded upon expert opinion. As yet, there has been no prospective study demonstrating an impact of surveillance on cancer-specific mortality in this population. Nonetheless, specialized screening programs have been developed by consensus in both the United States and Europe.^{53,54} The program currently recommended by the National Cancer Center Network is presented in Table 4. For management of female

Table 4. — Suggested Surveillance Program for Individuals at Risk for Hereditary Breast and Ovarian Cancer

Site	Modality	Frequency	Age to Begin
Breast	Breast self-examination	Monthly	18
	Clinical examination	q6 months	25
	Mammogram	Yearly	25
Male breast	Breast self-examination	Monthly	Not defined
	Clinical examination	Not defined	Not defined
	Mammogram	Consider annual	Not defined
Ovary	Transvaginal ultrasound	q6-12 months	30-35
	CA125	q6-12 months	30-35

Daly MB, et al. The NCCN 2002 genetic/familial high-risk assessment clinical practice guidelines in oncology, version 1.2002. Available at http://www.nccn.org/physician_gls/index.html. Accessed October 22, 2002. Adapted with permission from the National Comprehensive Cancer Network. To view the most recent version of the guideline, go online to www.nccn.org.

Prevention Options for Women With *BRCA* Mutations

breast cancer risk, women are encouraged to learn and practice breast self-examination beginning at age 18 and to begin annual mammogram screening at age 25. At present, there is no clear preclinical or clinical evidence to support theoretical concerns that radiation exposure consequent to mammography may increase cancer risk. However, breast density may preclude satisfactory examination in the younger women, and the high-grade nature of *BRCA*-associated breast cancer may predispose to the development of disease in the intervals between mammographic examinations. In two relatively small prospective follow-up series of women with *BRCA* mutations, approximately half of incident breast cancers presented symptomatically in the intervals between screening.^{55,56} Improvements in surveillance technologies are needed, and a number of centers have begun investigating the utility of breast ultrasound or magnetic resonance imaging (MRI). Although the exact role of these modalities has not been defined, early studies have suggested that breast MRI may be more sensitive in this population, with acceptable specificity.⁵⁷⁻⁵⁹ There are no established guidelines for screening of men at risk for hereditary breast cancer. It is reasonable to suggest periodic self-examination and evaluation by a provider experienced in clinical breast examination. The utility of screening mammography in men is unknown, although it is technically possible in at least some individuals.

Transvaginal ultrasonography and CA125 measurement is recommended twice a year in women at risk for hereditary ovarian cancer. Screening can begin slightly later than breast cancer screening, as most hereditary ovarian cancers appear to be diagnosed after the age of 35. The effectiveness of this program in reducing ovarian cancer mortality in this population has not been established, although in one small experience, the approach was able to detect early-stage hereditary ovarian cancers with acceptable specificity.⁵⁶ In another, multi-institution experience, transvaginal sonography and CA125 measurement was less useful in women at risk for hereditary gynecologic malignancy.⁶⁰ CA125 measurement was insensitive in this series, and ultrasound, while able to detect primary ovarian and fallopian tube malignancy, failed to identify malignancies arising from the peritoneal surface, which constituted a significant fraction of the total number of gynecologic cancers.

Individuals at risk should undergo population screening for other malignancies, especially prostate and colon cancer. While it is reasonable to initiate this screening slightly earlier than in the general population, there is no clear evidence that there is a predilection for these cancers to occur at a younger age.

As the screening programs recommended to women at risk for hereditary breast and ovarian cancer are of uncertain effectiveness, a number of women with *BRCA* mutations consider undergoing surgical procedures in an attempt to reduce their risk. Bilateral risk-reducing mastectomy has been reported to be at least 90% effective in reducing breast cancer incidence and mortality in women with a family history of breast cancer, and this approach appears to be effective in women with *BRCA* mutations.^{61,62} The procedure is not completely protective because of the risk of developing cancer in microscopic rests of breast tissue that are not removed at the time of surgery. Despite the evident effectiveness of the procedure, the uptake of risk-reducing mastectomy has been modest, presumably because of the significant physical and psychological morbidity attendant on the procedure.

Risk-reducing salpingo-oophorectomy is more frequently employed, particularly in women who have completed childbearing and are nearing menopause. When performed laparoscopically, the acute morbidity of the procedure is modest, although the quality-of-life consequences and long-term health risks of premature estrogen deprivation have not been defined. *BRCA* mutations are associated with an increased risk of fallopian tube carcinoma, and complete removal of both tubes and ovaries is indicated. However, there is no clear evidence of an increased risk of uterine cancer in *BRCA* heterozygotes, and thus hysterectomy is not necessary in the absence of another gynecologic indication. Two studies have now demonstrated a significant reduction in ovarian cancer risk after risk-reducing oophorectomy.^{63,64} These studies and others have also noted a significant reduction in breast cancer risk in women undergoing oophorectomy, which constitutes a substantial collateral benefit to the procedure.⁶⁵

A number of decision analyses have been performed in an attempt to compare the relative benefits of surveillance and preventive surgery in women with *BRCA* mutations.^{66,67} While these analyses are uniformly supportive of surgical approaches, they can easily be misinterpreted and should not be used for counseling of individuals considering surgery. These studies project life-expectancy gains for women undergoing specific interventions, using a series of assumptions that may not be robust, depending on the amount of data underpinning them. As these studies report anticipated benefits as average gains distributed across a population, they may markedly underestimate (or overestimate) the benefit that will be experienced by a particular individual.

Nonsurgical options for the prevention of hereditary breast cancer are currently limited. Tamoxifen was shown in a case-control study to reduce the risk of new contralateral breast primaries in women taking the drug for their initial breast cancer diagnosis.⁶⁸ However, a subset analysis of the prospective Breast Cancer Prevention Trial, carried out in unaffected women at risk, failed to demonstrate a significant risk reduction in *BRCA* mutation carriers.⁶⁹ The lack of statistical significance may have resulted from the limited power of the small subset analysis. Alternatively, selective estrogen receptor modulators such as tamoxifen or raloxifene do not appear to reduce the incidence of estrogen receptor-negative tumors, which *BRCA1* heterozygotes, in particular, are at risk to develop. Until further data become available, the use of tamoxifen and similar drugs for the prevention of *BRCA*-associated breast cancer should be considered investigational. Tamoxifen is still appropriate and clearly indicated as adjuvant therapy for women with hormone receptor-positive tumors, whether or not a germline *BRCA* mutation is present.

Oral contraceptives may be considered for the reduction of ovarian cancer risk in *BRCA* heterozygotes,⁷⁰ although not all studies have demonstrated effectiveness.⁷¹ It is important to note that the impact of oral contraceptives on *BRCA*-associated breast cancer risk has not yet been defined, and young women with documented mutations should probably not take the drugs indefinitely as the incremental benefit in ovarian cancer risk reduction is likely to be modest after approximately 5 years of exposure.

Finally, although not a nonsurgical option, it is worth noting that one study has demonstrated a reduction in ovarian cancer risk among *BRCA* heterozygotes in women who have undergone tubal ligation.⁷²

Conclusions and the Role of Genetic Testing

The currently available studies demonstrate that women with *BRCA*-associated breast or ovarian cancer may experience different outcomes than women without germline mutations. Neither the magnitude nor the certainty of these differences is sufficient to justify modification of treatment of the primary malignancy in women with suspected hereditary disease. However, recognition of a potential hereditary predisposition allows the patient and her physician to develop a specialized program of surveillance to manage her subsequent cancer risk and that of her female relatives. She and her relatives may also wish to consider surgical or nonsurgical risk-reduction strategies. Men in the kindred may also be made aware of the increased risk of

prostate, breast, and possibly colon cancer, so they may also take appropriate action.

The choice of whether to undergo genetic testing is a difficult one and should be made only after extensive consultation with a professional who is well versed in the counseling and management of families at hereditary risk. Such professionals can assess whether a particular family history is likely to reflect a hereditary predisposition, determine whether such a predisposition (if present) is likely to result from a *BRCA* mutation or from an alteration in another gene, and provide an empiric estimate of the likelihood that a mutation will be detected, if genetic testing is performed. Furthermore, these providers can address the unique psychosocial concerns of individuals seeking cancer risk assessment and genetic testing. Health insurance discrimination as a result of undergoing genetic testing has not arisen in any systematic way, but the psychological consequences of testing and the potential impact on family dynamics are important considerations that must be individually addressed. Finally, these professionals should also be involved in the interpretation and transmission of genetic test results. In addition to providing necessary psychological support, the integration of test results into a cancer risk assessment may be a complex endeavor, particularly if the results are "negative" in the setting of a strong family history or if the test identifies a genetic variant of uncertain significance.

The management of individuals at hereditary risk for breast and ovarian cancer is being rapidly and continuously refined. We are at the threshold of a new area of genetically targeted risk management, and considerable work remains to maximize the benefits of this technology for families at risk.

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