Complete Summary

GUIDELINE TITLE

Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors.

BIBLIOGRAPHIC SOURCE(S)

Berliner JL, Fay AM, Familial Cancer Risk Special Interest Group of the National Society of Genetic Counselors. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2007 Jun;16(3):241-60. [110 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Hereditary breast and ovarian cancer

GUIDELINE CATEGORY

Counseling
Risk Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Medical Genetics
Oncology
Psychology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

To allow genetic counselors and other health care providers to identify clients who may benefit from cancer risk assessment and genetic counseling and to guide the practitioner in providing these services

TARGET POPULATION

Individuals who may benefit from cancer risk assessment and genetic counseling for hereditary breast and ovarian cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Genetic counseling, including education regarding the genetics of cancer, the likelihood of developing cancer as well as the likelihood of carrying a genetic susceptibility mutation, the benefits, risks and limitations of genetic susceptibility testing, and appropriate cancer screening and prevention strategies
2. Referral for cancer risk assessment and genetic counseling
3. Patient intake and taking of personal and family history, such as through a written questionnaire or during consultation
4. Thorough psychological assessment, including taking the patient's demographic and educational information and assessment of the patient's overall pre-test and psychological and emotional state
5. Use of cancer risk models and pedigree analysis to estimate a patient's absolute cancer risk or risk of carrying a genetic mutation related to increased cancer risk
6. Assessment of the potential impact of the risk estimate on the medical management and health behaviors of the client
7. Genetic susceptibility testing for hereditary breast and ovarian cancer (HBOC), including BRCA1 and BRCA2 testing and interpretation of results
8. Post-test genetic counseling and results disclosure

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of cancer risk assessment models and tests

- Accurate estimation of cancer risk or risk of carrying a genetic mutation related to increased cancer risk

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline authors searched via MEDLINE the relevant English language medical and psychosocial literature between 1992 and 2006, and incorporated information from several key seminal articles from earlier years. Key words included BRCA1, BRCA2, hereditary breast cancer, hereditary ovarian cancer, cancer genetic counseling, risk assessment, genetic susceptibility testing, family history, medical management and psychosocial assessment. Previously published guidelines and policy statements published by the American Society of Clinical Oncology (American Society of Clinical Oncology 1996, 2003), the American College of Medical Genetics Foundation (American College of Medical Genetics Foundation 1999), the National Comprehensive Cancer Network (NCCN), and the National Society of Genetic Counselors were also reviewed. This literature is based on clinical experience, descriptive studies and/or reports of expert committees.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

I. Evidence obtained from at least one properly designed randomized controlled trial

II-1. Evidence obtained from well-designed controlled trials without randomization

II-2. Evidence obtained from well-designed cohort or case-control-analytic studies, preferably from more than one center or research group

II-3. Evidence obtained from multiple time series with or without the intervention

III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventive Services Task Force ("See Rating Scheme for the Strength of Evidence").

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations were developed by genetic counselors who are members of the Practice Issues Subcommittee of the National Society of Genetic Counselors (NSGC) Familial Cancer Risk Counseling Special Interest Group. The information was derived from extensive review of the current literature on cancer genetic risk assessment as well as the professional expertise of genetic counselors with significant experience in the education and counseling of individuals at high risk for breast and ovarian cancer.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This document has been reviewed by additional cancer genetic counselors, members of the American College of Medical Genetics (ACMG) and the Oncology Nursing Society (ONS), consumer groups, National Society of Genetic Counselors (NSGC) general membership, and the Board of Directors and Genetic Services Committee of the NSGC.

A draft of this document was made available to the 2,024 full members of the NSGC for comment in October, 2006. The revised document was reviewed by the

NSGC attorney and the NSGC Ethics Subcommittee. The NSGC Board of Directors reviewed and approved the final document on January 16, 2007.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The Cancer Risk Assessment and Genetic Counseling Process

Cancer risks in mutation carriers differ depending upon the syndrome, the specific mutation being carried in the family, age, and sometimes, gender. Cancer risk assessment involves the process of identifying individuals at risk for hereditary cancer. Pedigree analysis is used in conjunction with available risk assessment models to determine whether a family is suspected of having hereditary cancer, familial cancer, or sporadically occurring cancer (see table below). This classification can help in quantifying risks to individual family members and developing a plan for cancer screening, prevention, risk reduction and psychosocial support and counseling. Further, this classification helps in the determination of whether genetic testing is appropriate for the family, and if so, which relative(s) would be the appropriate individual(s) to test. Unfortunately, the separation of families into hereditary, familial, and sporadic cancer is often not precise. The features of these classifications are described in the table below.

Genetic counseling is a key component of the cancer risk assessment process and includes education regarding the genetics of cancer, the likelihood of developing cancer as well as the likelihood of carrying a genetic susceptibility mutation, the benefits, risks and limitations of genetic susceptibility testing, and appropriate cancer screening and prevention strategies. The goal is to empower the client to make informed decisions regarding screening, prevention and genetic testing by providing him or her with the necessary genetic, medical and psychosocial information. Attention to psychosocial issues is critical for effective genetic counseling.

Health care professionals should consider referring a client for cancer risk assessment and genetic counseling when the personal or family history is suggestive of familial or hereditary cancer. In order to meet all of the client's needs, cancer risk assessment ideally is offered in the context of a multidisciplinary team that includes expertise in both genetic counseling and oncology. The team may consist of a variety of different specialists including genetic counselors, medical geneticists, surgeons, oncologists, social workers, oncology nurses and psychologists.

Table: Characteristics of Hereditary, Familial, and Sporadic Cancer Syndromes

Classification of Family	Characteristics
Hereditary Cancer	• Apparently autosomal dominant transmission of specific cancer type(s) • Earlier age of onset of cancers than is typical

Classification of Family	Characteristics
	• Multiple primary cancers in an individual • Clustering of rare cancers • Bilateral or multifocal cancers • First degree relatives of mutation carriers are at 50% risk to have the same mutation • Incomplete penetrance and variable expressivity, such that obligate carriers of the family mutation may be cancer-free and the age of diagnosis of cancer among relatives will vary • Those who do not have the familial mutation have the general population risk for cancer
Familial Cancer	• More cases of a specific type(s) of cancer within a family than statistically expected, but no specific pattern of inheritance • Age of onset variable • May result from chance clustering of sporadic cases • May result from common genetic background, similar environment and/or lifestyle factors • Does not usually exhibit classical features of hereditary cancer syndromes
Sporadic Cancer	• Cancers in the family are likely due to nonhereditary causes • Typical age of onset • Even if there is more than one case in the family, there is no particular pattern of inheritance • Very low likelihood that genetic susceptibility testing will reveal a mutation; testing will likely not provide additional information about cancer risk

Referral for Cancer Risk Assessment and Genetic Counseling

There are many publications, policy statements, and organizational recommendations that propose criteria for when an individual should be referred for genetic counseling regarding hereditary risk of breast and/or ovarian cancer, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the U.S. Preventive Services Task Force (USPSTF), and the American College of Medical Genetics (ACMG).

Although the specific criteria for genetic counseling referral vary among organizations, they are consistently based on the recognition of clinical features that increase the likelihood of hereditary susceptibility to breast and/or ovarian cancer, including:

- Early-onset breast cancer, usually defined as before age 50

- Ovarian cancer
- Individuals with two or more primary breast cancers, or breast and ovarian cancer in the same individual
- Male breast cancer
- Two or more individuals in the family with breast and/ or ovarian cancer
- Ashkenazi Jewish ancestry

Health care professionals providing cancer genetic counseling services should evaluate the current professional society guidelines for referral, and determine which criteria they will provide to referring physicians to facilitate the identification of appropriate patients. It is important to recognize that criteria for genetic counseling referral do not necessarily equate to referral for germ-line genetic testing. Less restrictive referral criteria will allow for a larger number of clients to benefit from risk assessment, and may identify appropriate candidates for genetic testing who would be missed using stringent criteria.

Intake and History

An accurate personal and family history is essential to evaluate the possibility of hereditary cancer risk appropriately. This information may be obtained through a written questionnaire or during the consultation. (See the National Guideline Clearinghouse (NGC) summary of Genetic Cancer Risk Assessment and Counseling for further information on how to obtain such a history, including a list of specific questions to ask about the client and relatives.) When evaluating a client's personal and family history for breast and/or ovarian cancer risk, a few issues warrant particular attention:

1. Clients should be questioned about relevant environmental exposures and reproductive factors that may affect cancer risk. A list of risk factors for breast and ovarian cancer is provided in the table below. The impact of the risk factors on women with a positive family history of breast and/or ovarian cancer or those who carry a BRCA1 or BRCA2 mutation is an active area of research. Most reproductive and lifestyle risk factors lead to less than a two-fold increase in cancer risk, and therefore, may not have an effect sufficient to alter medical management in women with a high genetic risk. Pathologic markers of risk on breast biopsy such as atypia and lobular carcinoma in situ (LCIS) are important indicators of risk, and will lead to modified follow-up recommendations.

Table: Risk Factors for Breast and Ovarian Cancer

Risk Factors for Breast Cancer	Risk Factors for Ovarian Cancer
• Menarche before age 12 • First live birth after age 30 • Nulliparity • Menopause after age 55 • Atypical hyperplasia or lobular carcinoma in situ (LCIS) diagnosed by breast biopsy • Postmenopausal obesity	• Nulliparity • Family history of ovarian cancer

Risk Factors for Breast Cancer	Risk Factors for Ovarian Cancer
• Hormone replacement therapy • Alcohol use (more than 2 drinks per day) • Previous therapeutic radiation to chest or upper body • Family history of breast cancer	

2. For the purpose of family history evaluation, surgeries that significantly reduce the risk of breast and/or ovarian cancer should be documented, as they may obscure an obvious pattern of hereditary cancer in the pedigree. Therefore, clients should be asked about surgical removal of the ovaries, fallopian tubes, and breast tissue, both in themselves and their relatives. Similarly, deaths at young ages due to other causes may lead to fewer cancers in the family than may be expected in a family with hereditary cancer risk.
3. Medical record confirmation of cancer diagnoses is ideal for accurate risk assessment, when possible. In clinical practice, it may be logistically difficult for clients to obtain medical records on their relatives' cancer diagnoses. Clients should be advised that their risk assessments are based on the personal and medical histories they provide, and may change dramatically should any of the reported information prove to be inaccurate. Reports of breast cancer are often accurate, while reports of ovarian cancer are more likely to be erroneous. If the risk assessment depends on a particular family member's specific diagnosis, medical records should be pursued. For example, the presence or absence of ovarian cancer in a family can significantly affect the estimated likelihood of a BRCA1 or BRCA2 mutation. Therefore, the primary site of reported "abdominal" or "female" cancer in a close female family member should be confirmed, if possible.

Psychosocial Assessment

Risk assessment for cancer can raise a number of psychosocial issues. Clients will need to contend with an enhanced understanding of their specific cancer risks, potentially difficult decisions for managing their cancer risks, concerns about discrimination and worry about potential risks for their children and other family members. Thus, when providing genetic counseling for hereditary breast and ovarian cancer (HBOC), a thorough evaluation is essential to understand better how genetic information will impact the individual and his or her family. Professionals performing cancer risk assessment and genetic counseling require proficiency in communication and counseling, psychosocial assessment and crisis intervention as well as the genetics of cancer and risk assessment. Psychosocial issues can be addressed by utilizing the principles and practices of genetic counseling as well as psychology and psycho-oncology.

Even when presented with numerical risks, clients' cancer risk perceptions remain largely based on the emotional responses and psychosocial outcomes of their previous cancer experiences. These experiences ultimately drive behaviors related to cancer screening, genetic counseling and testing, and medical management.

Although a thorough psychosocial analysis may be difficult, there are several key factors which can provide a better understanding of the client's overall psychological state. An awareness of the client's socioeconomic, ethnic, educational, and religious backgrounds may provide information about how he or she will interpret and utilize the genetic information. This information can be gained either through completion of an intake form prior to the counseling session or through informal questioning during the session.

In addition to the patient's demographic and educational information, it is valuable to assess briefly the patient's overall pre-test psychological and emotional state. It is important to remember that genetic counselors are not trained to perform a full psychological analysis or provide psychological counseling and should refer to appropriate mental health professionals when necessary. Having a broad understanding of the following components may be useful in identifying those patients who would benefit from contact with a mental health professional.

- *Current emotional well-being*: The perception of being at increased cancer risk can result in a range of emotional responses which can influence many areas of the individual's life. It may be useful to evaluate for signs of depression or anxiety by asking about any recent changes in eating, sleeping or overall emotional state.
- *Mental health history*: An individual with a history of mental health issues may be more emotionally vulnerable to a genetic test result, particularly a positive test result confirming the perception of increased cancer risk. It may be valuable to integrate direct questions about the client's mental health history and previous therapeutic interventions. These questions may help pave the way to recommending counseling intervention if necessary.
- *Emotional response to family history of cancer*: It is important during the counseling session to understand not only the genetic impact, but also the psychological impact of a cancer family history on the client. It may be useful for both client and counselor to address questions about the impact of a family member's illness and how the client views his or her increased risk status.
- *Coping strategies*: Clients will have developed different coping methods for dealing with their increased risk (real or perceived) of developing cancer. To understand these coping strategies better so that they can work to their best advantage, it is important both to ask clients how they perceive themselves coping with the cancer in the family, and to observe their reactions and coping skills directly throughout the session.
- *Reactions/responses during the counseling session*: HBOC counseling sessions typically include discussions about family cancer history and estimates of cancer and mutation risks. These discussions have the potential to bring out unpleasant emotions, making it essential that the counselor continually monitor the client's reactions and adjust the focus and content of the session accordingly.

In addition to having an understanding of the psychological and emotional state of a patient, it may be valuable in a pre-test counseling session to identify any potential psychological barriers to testing that the client may be experiencing. These barriers might include any of the following: fear of a positive result in an unaffected individual, guilt associated with passing a mutation to children,

survivor guilt, fear of discrimination/stigmatization due to a positive result, fear of insurance discrimination, or avoidance of the medical management decisions that would be necessary with a positive result. In addition to the discussion of psychological barriers to testing, it is important to ask the client about his or her perceived benefits of or motivations for testing. These potential benefits might include relieving the anxiety of not knowing, allowing mental focus on proactive medical management, and the potential to inform and educate other at-risk family members. The following pre-test questions may help both the counselor and client identify and process any potential psychological factors related to testing:

- Do you want to know more about your risk of developing breast/ovarian cancer? If so, how will the results of the test affect you?
- If a mutation is detected, how will you cope with knowing that you have an increased risk of developing cancer?
- Will you change your surveillance practices? Will you consider prophylactic surgery?
- If you test positive for a mutation, how will you feel about sharing this information with family members who may be at risk?
- What plans might you make in light of a negative/positive test result?
- Do you want to pursue this testing? Now? Perhaps in the future?

Cancer Risk Assessment

Risk assessment models have improved since genetic testing became available in 1996. Which model(s) a practitioner uses depends upon the personal and family characteristics of the individual(s) seeking the information, and available information about the family. Many families who present for cancer risk assessment exhibit some features of a hereditary cancer syndrome without clear evidence of single-gene dominant inheritance. Several factors can make it difficult to assess hereditary risk from a pedigree, including small family size, reduced penetrance, a paucity of individuals of the susceptible gender for sex-influenced or sex-limited cancers, prior prophylactic surgeries in at-risk individuals, and inaccurate or incomplete information on family members. It is important for clients to report any new cancer diagnoses or newly gathered information on former diagnoses so that the pedigree can be reassessed over time.

Risk can be assessed in many ways, and clients may be presented with several risk estimates, including the likelihood of developing certain types of cancers or the probability of carrying a genetic mutation related to increased cancer risk. Because individuals differ in their experiences and educational background, it is important to assess the client's understanding of the information being presented, and if necessary, explain it in different ways. Since data can vary from one study to another, presenting the range of risks along with how those risks were derived is illustrative and may help the client understand that a specific numerical risk is not usually available. Pointing out how the client's risk compares with that of the general population may also be helpful. Finally, assessing the potential impact of the risk estimate on the medical management and health behaviors of the client is essential.

Population estimates of the likelihood of having a mutation within the BRCA1 or BRCA2 genes can help determine who might benefit most from a referral to a cancer genetic counselor and consideration of genetic susceptibility testing.

Personalized risk assessment based on the individual's medical and family history characteristics will provide a more accurate estimate of the likelihood that a client is carrying a BRCA mutation.

Determining cancer risk involves two processes. One is the estimation of the absolute risk that the client will develop cancer based on the family history (see the NGC summary of Genetic Cancer Risk Assessment and Counseling for detailed explanations of the models available for estimating cancer risk in the absence of a known heritable genetic mutation) and the assessment of whether the history is indicative of a hereditary, familial or sporadic pattern. The genetic counselor can be instrumental in sorting out families who fall into these categories through careful pedigree assessment. In general, a pedigree that shows an autosomal dominant pattern of inheritance of a specific constellation of tumors, especially at earlier ages of onset, may suggest an inherited cancer syndrome. However, because most hereditary cancer syndromes demonstrate incomplete penetrance, a family that does not show a typical autosomal dominant transmission pattern may still have a single cancer predisposing mutation. Familial cancers are those that do not generally exhibit the features of hereditary cancers as far as inheritance patterns or onset age, but occur in more individuals in the family than statistically expected. These may be the result of several factors, such as shared environment, chance clustering, small family size, and many others. Finally, sporadic cancers are those that can be defined by lack of (or limited) family history of cancer, older ages of onset, and a lack of an autosomal dominant pattern of inheritance. Most of the time clients with sporadic cancers will not benefit from molecular genetic testing for hereditary cancer syndromes. The exceptions include those cancers that are rare and/or may have a fairly high de novo mutation rate. The genetic counselor or other trained health professional can be instrumental in identifying these types of syndromes in an otherwise sporadic looking family, which could have important ramifications for the client and his/her family members.

The second part of the risk assessment process is estimating the probability that there is a heritable genetic mutation (or family-specific mutation) in the family that the client may have inherited. The most effective models to determine this probability are compared in Table III in the original guideline document. Models for determining the probability of a BRCA1 or BRCA2 mutation in a family take into account some or all of the following factors:

- Age of onset of cancer or age achieved cancer-free
- Number of affected relatives
- Degree of biological relationships of affected relatives
- Ratio of affected to unaffected relatives
- Presence/absence of associated malignancies
- Ethnic background

Given that each risk assessment model takes different factors into account, accurately assessing a client's probability requires knowledge of which model(s) applies most closely to the personal and family characteristics. Because many people overestimate their risks, knowing the probability that genetic testing will reveal a mutation is often useful for those considering testing. It is important to recognize that risk assessment models are tools to enhance the clinician's risk assessment, but should not be used in place of clinical judgment. The use of the

appropriate model(s) and the interpretation of the results for the client are important.

See the original guideline document for a discussion of "Other Risk Factors," "Limitations of Risk Assessment Models," and "Other Hereditary Syndromes with Breast and/or Ovarian Cancer."

Genetic Susceptibility Testing for HBOC

The American Society of Clinical Oncology (ASCO) recommends that genetic testing be offered when:

- The individual has personal or family history features suggestive of a genetic susceptibility condition
- The genetic test can be adequately interpreted
- The test results will aid in diagnosis or influence the medical management of the patient or family members at hereditary risk of cancer

Initially, genetic testing of the BRCA1 and BRCA2 genes was only offered to clients with a high probability of testing positive. In such families, genetic test results often confirm the underlying molecular cause of cancer risk in the family, so that high-risk and average-risk relatives can be distinguished by testing for the family-specific mutation. However, clients with less significant personal or family histories of cancer may also be appropriate candidates for genetic testing, such as a woman diagnosed with breast cancer at age 40 with no family history of cancer. In fact, a positive genetic test result may alter the course of medical management more dramatically for a client who presents with a moderate clinical history. In its 2003 policy statement on genetic testing for cancer susceptibility, ASCO suggested that the clinical judgment of a healthcare provider experienced in cancer genetics should be relied upon to determine the appropriateness of genetic testing, as opposed to a numerical threshold. This is consistent with the guidelines of other professional organizations, most of which provide criteria for outlining which clients should be offered further education and counseling, so that they can make informed decisions about genetic testing.

Approach to BRCA1 and BRCA2 Testing

Once a client has been identified as an appropriate candidate for BRCA testing, the testing options should be explained in more detail. It is imperative for the genetics professional to explain why the test is being offered, how the results might affect the client's risk for cancer, and what medical management options may be offered depending upon the results. At a minimum, discussion of the following elements would constitute informed consent:

- Details of the genetics of cancer in general
- The medical and family history of the client and the specific syndromes being considered (if any)
- The likelihood of a mutation being present in the family
- Possible test outcomes and the implications of these outcomes
- Medical management options

It is most informative for testing of the BRCA1 and BRCA2 genes to begin with the relative who is most likely to test positive, typically an individual who had breast cancer at a young age or ovarian cancer. For individuals who are not of Ashkenazi Jewish descent, the first individual tested will need to undergo comprehensive analysis of both genes, in order to determine if a mutation can be identified. At present, this analysis generally involves full sequencing of both genes and analysis of common large rearrangements in BRCA1. Clients who are of Ashkenazi Jewish ancestry should initially be offered testing for three founder mutations, 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2, that are most common in that ethnic group. Testing for these three mutations is offered as a panel, and is far less expensive than comprehensive sequencing. Some individuals of Ashkenazi Jewish ancestry carry a different BRCA1 or BRCA2 mutation, which will only be detected by comprehensive analysis of the genes. Further testing may be indicated based on family cancer history and high pre-test probability.

Once a specific mutation has been identified, at-risk relatives may be offered testing for the family-specific mutation only. Exceptions to this strategy include individuals who present with a significant family history of breast and/or ovarian cancer on both sides of the family. For these clients, the potential of a different mutation on the opposite side of the family should be addressed, either by offering comprehensive analysis of BRCA1 and BRCA2 to the client or the most appropriate affected relative from the opposite side of the family. Similarly, in Ashkenazi Jewish families in which one of the three founder mutations has been identified, relatives pursuing genetic testing should be tested for all three founder mutations based on the high prevalence of all three mutations in this population.

Interpretation of BRCA1 and BRCA2 Test Results

Positive Result

A positive test result means that a deleterious mutation was found in either the BRCA1 or BRCA2 gene, indicating an increased risk for breast, ovarian and other cancers. If the client has already been diagnosed with cancer, a positive result indicates an increased risk for a second primary cancer. Published literature provides recommendations for medical management for clients found to carry a BRCA1 or BRCA2 mutation (see "Medical Management Options for Patients" in the original guideline document).

In order to determine which side of the patient's family is at risk for carrying the mutation, the parents or other relatives, particularly women affected with cancer or offspring of women with breast or ovarian cancers, should be offered testing for the familial mutation to determine their status. For many clients, it may be possible to assume which side of the family is at risk, based on the history of cancer in the family. Whenever possible, the suspected parent's carrier status should be confirmed through genetic testing.

No Mutation Detected -- No Mutation Previously Identified in Family

When a mutation has not been previously identified in the family, a "no mutation detected" result in an affected patient means that the current technology did not find a mutation in BRCA1 or BRCA2. The cause of the pattern of cancer in the

client and the family is still undetermined, and the risk assessment must be based on the clinical history.

There are three possible explanations for a "no mutation detected" result; for an individual patient, it is necessary to consider which is most likely by reviewing the patient's personal and family histories of cancer, and considering the pre-test probability of detecting a mutation in BRCA1 or BRCA2. First, the cancer history may be due to the combined effects of chance, environmental factors, and lifestyle factors, as opposed to a mutation in a single gene.

Second, a BRCA1 or BRCA2 mutation is present, but current technology is not able to detect such a change. When interpreting a "no mutation detected" test result, it is important for the healthcare provider to have an understanding of the testing methodology used by the laboratory and its estimated sensitivity. For clients that meet defined clinical criteria, it may be appropriate to request additional analysis to detect large genomic rearrangements in both BRCA1 and BRCA2 genes. Research opportunities may be available for families with a significant history of breast and ovarian cancer, in whom no mutation was found through clinical testing. Such families should be encouraged to contact their genetic counselor on a regular basis, to determine if additional technology has been added to the clinically available testing methods that may find a previously undetectable mutation.

Third, the cancer history in the client or family may be due to a mutation in a different set of genes. Mutations in BRCA1 or BRCA2 are responsible for the majority of strong family histories of early-onset breast cancer and ovarian cancer. Among families with a clustering of only breast cancer, a smaller, but still significant, proportion is due to a BRCA1 or BRCA2 mutation. Other genes for breast and ovarian cancer susceptibility remain the subject of research, but are not available for testing at this time. If other specific cancers or clinical findings are present in the patient or family, consideration of a different hereditary cancer syndrome may be warranted, as described above.

If a patient is affected with breast cancer or ovarian cancer and receives a "no mutation detected" result, it may be worthwhile for another family member to undergo genetic testing, as the patient may be a phenocopy. This possibility is more likely if the patient was diagnosed with breast cancer at a later age than is typical for hereditary cancer, or if the patient had a type of cancer other than breast or ovarian.

It is most informative to test a family member who has had breast cancer at a young age or ovarian cancer first. If a patient who has not had cancer receives a "no mutation detected" result, the most closely related affected family member should undergo comprehensive genetic testing. In the absence of a positive test result in the family, a "no mutation detected" result in an unaffected patient is uninformative.

No Mutation Detected -- Known Mutation in Family

If a mutation in BRCA1 or BRCA2 is known to be the cause of cancer risk in a family, a negative result means that the client's risk of developing breast or ovarian cancer is similar to that of the general population, assuming that there is

no history on the other side of the family that might be suggestive of a hereditary cancer syndrome and that there are no other risk factors such as atypia.

Genetic Variant of Uncertain Clinical Significance

Genetic variants of uncertain significance are typically missense mutations of unknown functional significance. In the immediate sense, the client's medical management should be based on the strength of her personal and family history of cancer, similar to the approach for a "no mutation detected" result in the absence of a known mutation in other relatives. Further research on the segregation of the variant with cancer in the family, or laboratory studies of a variant's functional impact, may elucidate its clinical significance in the future. Past studies show that many genetic variants in BRCA1 and BRCA2 have been reclassified as harmless polymorphisms. However, a small number of uncertain variants have later been shown to be deleterious.

Some variants are classified at the outset as "favor polymorphism" or "suspected deleterious," such that based on the position and type of the alteration within the DNA, certain assumptions about the effect on the ultimate protein can be made. When an alteration is classified as "favor polymorphism," it can generally be treated as a negative result, although not technically considered as such. No change in the client's medical management would usually be warranted. Alternatively, a "suspected deleterious" result may warrant medical management recommendations similar to those for someone found to have a mutation, keeping in mind the personal and family history of cancer, the client's position in the family, whether the client may have already had risk reducing surgeries, etc.

Post-Test Genetic Counseling and Results Disclosure

Once a client opts to pursue genetic susceptibility testing and the sample is sent to the laboratory, the client's anxiety regarding the test results may climb. Explaining the protocol for results disclosure at the time of testing can help to reduce the anxiety of receiving the phone call that the results are available. By scheduling a result appointment either in person or on the telephone, clients can arrange to have a support person (e.g., spouse, family member or close friend) if desired. Once the client has agreed to have the information and the results are given, a discussion of the significance of the results should ensue. This should include a review of the specificity and sensitivity of the testing, impact of the results on cancer risk and emotional state, medical management options (see Table IV in the original guideline document), referrals to other health professionals, and assistance in informing other family members if applicable. A discussion of the carrier risks for other family members and potential cancer medical management issues may also be helpful. Supportive counseling should be provided throughout, with referral to other health care professionals when indicated. Some clients who test positive find it helpful to speak with another individual in a similar circumstance, and can greatly benefit from being provided a contact. If a high-risk client tests negative in the absence of a known familial mutation, he or she should be encouraged to maintain contact with the healthcare provider in the event that a new gene is discovered or new family history information comes to light.

Support resources should also be provided as appropriate (see Table V in the original guideline document). A follow-up letter to the client is always helpful, as it can be used as a permanent reference and a summary of the cancer risk assessment and genetic testing process. This written summary can then be shared with other family members to help relay information about the significance of their family history and outcome of the assessment. Clients should provide written permission for copies of the letter or a separate consultation summary to be sent to other healthcare providers.

Medical Management Options for Patients

See "Medical Management Options for Patients" in the original guideline document.

Ethical and Legal Implications

See "Ethical and Legal Implications" in the original guideline document.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation. In general, the recommendations are based on clinical experience, descriptive studies, and/or reports of expert committees. The rating of supporting literature for the recommendations includes:

- II-2. Evidence obtained from well-designed cohort or case-control-analytic studies, preferably from more than one center or research group
- II-3. Evidence obtained from multiple time series with or without the intervention
- III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of risk assessment and genetic counseling for hereditary breast and ovarian cancer to inform medical management of individuals at increased risk for breast or ovarian cancer

POTENTIAL HARMS

- Risk assessment for cancer can raise a number of psychosocial issues, including understanding of their specific cancer risks, potentially difficult

decisions for managing their cancer risks, concerns about discrimination, and worry about potential risks for their children and other family members.

- As with all genetic testing, hereditary breast and ovarian cancer (HBOC) testing has the potential to raise ethical and legal issues both within a family and for society as a whole. Concerns include:
    - Predisposition testing for a less than fully penetrant gene
    - The potential for prenatal testing or testing of minors for an adult onset condition
    - Concern for the potential of genetic discrimination, particularly with regard to health and life insurance in the event of a positive test result
- Given the nature of genetic testing within families, it is possible that ethical dilemmas may arise surrounding the issue of confidentiality. This may be particularly true for cases in which multiple family members are seen at the same clinic. The principle of confidentiality can expand to the social level as well, given the potential for genetic discrimination. See the section "Ethical and Legal Implications" in the original guideline document for further discussion of these issues.

QUALIFYING STATEMENTS

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- Genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist practitioners and patients in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the submission date and are subject to change as advances in diagnostic techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient.
- There are some global limitations to all of the available models, based on the fact that the studies are largely based on Caucasian women from North America and Northern Europe. Probability estimates for other populations are difficult to determine. It can also be difficult to assess risk if there is a lack of family history information, a small family size, deaths at young ages in at-risk individuals, a dearth of women in the family or a lack of verifiable cancer diagnoses in the family. It is imperative to tell the family that the risk assessment information provided is only as accurate as the family history data provided. Each risk model has its optimal applications, based on the methods by which it was developed, the populations studied, and the characteristics of the family being assessed. Therefore, the clinical judgment of the health care provider is critical.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Berliner JL, Fay AM, Familial Cancer Risk Special Interest Group of the National Society of Genetic Counselors. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2007 Jun;16(3):241-60. [110 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

National Society of Genetic Counselors - Medical Specialty Society

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GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Janice L. Berliner, Saint Barnabas Medical Center, Livingston, NJ and Angela Musial Fay, Meridian Health, Brick, NJ

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

While the above National Society of Genetic Counselors (NSGC) recommendations do not necessarily reflect the opinions or policies of any corporate entity, the authors acknowledge the potential for the appearance of a conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies available from: the National Society of Genetic Counselors Web site.

Print copies: Available from the National Society of Genetic Counselors, 233 Canterbury Drive, Wallingford, PA 19086-7608; Web site: http://www.nsgc.org/.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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