Genetic testing of younger women with family history of breast cancer flashcard

The recent characterization of two genes associated with susceptibility to breast cancer makes it technically possible to identify a subset of individuals with an increased danger of developing such malignancies. However, the clinical utility of DNA-based susceptibility testing has not yet been fully established. Each year, close to 200, 000 cases of breast cancer are diagnosed. While the majority of breast cancers are not caused by inherited risk factors, researchhasshown that about 10 percent of these cases are hereditary. Two genes in particular, BRCA1 and BRCA2, normally work to prevent breast cancer. But in some cases, we can inherit a BRCA1 or BRCA2 alteration from either parent.

This alteration or mutation interferes with the normal activity of the gene, making us more susceptible to breast and ovarian cancer. A person with one of these gene mutations has a higher risk of developing these cancers and also may pass that gene mutation on to his or her children. These Guidelines have been formulated to assist the health care professional in identifying individuals at increased heritable risk for breast cancer and to address their needs and concerns.

Specific aims Women with certain specific family history patterns (increased-risk family history) have an increased risk for developing breast or ovarian cancer associated with BRCA1 or BRCA2 mutations.

It has been determined that these women would benefit from genetic counseling that allows informed decision making about testing and further prophylactic treatment. This counseling should be done by suitably trained health care providers. There is insufficient evidence to determine the

benefits of chemoprevention or intensive screening in improving health outcomes in these women if they test positive for deleterious BRCA1 or BRCA2 mutations. However, there is fair evidence that prophylactic surgery for these women significantly decreases breast and ovarian cancer incidence. Thus, the potential benefits of referral and discussion of testing and prophylactic treatment for these women may be crucial.

Background & Significance The provider should determine which individuals among those in his/her practice are at ‘ increased genetic risk’ by depicting an appropriate personal and family history on all patients. The health care provider is not expected to calculate an exact quantitative risk, but rather to ascertain whether the patient is in an increased risk domain. This qualitative risk should be derived through a complete personal and family cancer history, including multiple generations on both maternal and paternal sides of the family.

The assignment to a risk category is based on the number of first degree relatives (including parents, siblings, and children) and second degree relatives (including grandparents, grandchildren, aunts and uncles, half-siblings and nieces and nephews) with breast, or other relevant cancers such as ovaries, prostate and colon, ages at diagnosis in affected family members, and some other factors such as ethnic background.

There is much research that has been conducted into the same as well. “ Clinicians should offer genetic counseling and DNA testing to breast cancer patients from families with breast and ovarian cancer, and to patients who are younger than 45 years when they are diagnosed with breast cancer.”

(Ausems et al, 2005). “ The differences in clinical aspects of BRCA carriers with bilateral BC should be considered in clinical management.” (Maka, et al 2004).

“ A family history of breast cancer is associated with an increased risk of DCIS and LCIS, particularly among women with multiple relatives affected at early ages. Statistical risk models predict a low prevalence rate of BRCA1 and BRCA2 in DCIS; these estimates await confirmation through laboratory testing.” (Carter, et al, 2003). “ There is some evidence that other, undiscovered genes may be important in explaining familial breast cancer.” (Aguilar, et al, 1998). “ Risk assessment including test result interpretation and counselling can be appropriately provided directly to the patient by physicians and genetic counsellors in a coordinated genetic counselling setting.” (Kurth, et al, 1995).

Detecting a mutation is unlikely if the family has fewer than three affected close (first- and/or second-degree) relatives on the same side of the family unless extraordinary features are present. These special features (justifying exception to the requirement for three affected relatives) include:

• A family member has been recognized with a detectable mutation • Early age at breast cancer identification (especially before 45 years) in the patient or any close (first- and/or second-degree) relative • One or more cases of cancer at any age, in accumulation with one or more individuals on the same side of the family with breast cancer at any age • Multiple primary or bilateral breast cancers in one person • Breast cancer in a masculine first- or second-degree relative Risk assessment may be an intricate process.

Many patients, when inquired about family history of cancer, will have a single distant relative with a diagnosis of late-onset breast cancer. Such individuals do not fall into an increased risk category as explained here. They should be reassured that their risk is not significantly different than the general population risk and provided with a review of standard recommended surveillance measures based on their age. Given the associated risks, burdens and limitations, genetic testing is not indicated where increased risk has not been shown.

However, factors such as level of patient concern and clinical judgment may influence the decision as to whether more comprehensive genetic counseling is indicated and the possibility of genetic testing be considered. The focus of the health care provider is to utilize the personal and family cancer history information to delineate individuals at increased danger. Admittedly, those at increased risk do not constitute a clearly discrete category, but rather lie toward one end of a continuous distribution, so that it may be difficult to demarcate an exact cut off or testing limit. Some patients may appear to approach the level of the increased risk group; others may appear to have a risk only slightly higher than the general population hazard.

An example of the former would be a woman with two relatives (on the same side of her family) with breast cancer found in their 50’s. An example of the latter is a woman who, by chance, has only some female relatives, one of whom has breast cancer. In such instances, more thorough risk assessment, appropriate counseling, and a full elaboration of the benefits and burdens of testing would be helpful.

Those patients identified as high-risk by the health care provider may be presented comprehensive information concerning the benefits, burdens and limitations of each of the available options, including DNA-based mutation detection or heightened surveillance without genetic testing. Moreover, it may be essential to provide a more exact risk figure to enhance the patient's decision-making process. In such instances, consultation with or referral to a specialist with expertise in cancer genetics, clinical genetics or genetic counseling may be important.

Genetic testing is not considered appropriate for individuals below 18 years of age, since there is no recommended preventive intervention in childhood for those known to have BRCA1 or BRCA2 mutations, and breast cancer rarely manifest in this age group. An individual who is identified to be at increased risk and wants to consider genetic testing may benefit from consultation with an expert in cancer genetic therapy. Additional information about the personal and family history should be elicited, if required. Because individuals are often not fully informed about cancer diagnoses in the family, it is important to document, where possible, primary site, age at diagnosis and other information through retrieval of appropriate medical data. Based on all available information, the practitioner should assign an approximate danger (average vs. increased) for the patient to have a breast/ cancer-predisposing gene mutation.

The patient should be encouraged to consider how her or his behavior would change depending on the test outcome. However, making such decisions in the abstract may not always be predictive of actual behavior when faced with test results. The patient must be educated as to the potential benefits

and burdens of genetic testing in order to make an informed decision about whether or not DNA-based mutation testing would be appropriate for the subject. Gene testing can confer both benefits and burdens in the same case. Benefits of detecting a mutation can include:

• the reduction of uncertainty and the often linked anxiety of " not knowing"; • the potential for reduced morbidity and mortality due either to enhanced surveillance, or to preventive issues such as chemoprophylaxis regimens and/or prophylactic surgery; • the opportunity to alert relatives to their potential hazard and available services; • the opportunity to participate in clinical trials and associated research. Benefits of not detecting a gene mutation (when an affected relative has been found to have one) include: • reassurance and removal of anxiety; and • evasion of unnecessary intensive monitoring strategies and prophylactic surgical measures and their attendant risks and costs.

Burdens can also be caused by a positive, negative, or uncertain test result. These are expensive tests which may or may not be facilitated by third party payers. Burdens of detecting a mutation can include:

• anxiety; • depression; • reduced self-esteem; • frustration associated with the unverified effectiveness of available interventions; • the risks and costs of added surveillance or prophylaxis, which may or may not be covered by insurance policies; • stressed relationships with a partner or with relatives; • guilt about probable transmission to children; • stigmatization; • possible bias by health, life or disability insurance companies, by employers, or by

others; and • the possible (but as yet unproven) hazards of more frequent and earlier mammograms in BRCA1 and/or BRCA2 mutation carriers.

Burdens of not detecting a mutation include: • potential for disregard of routine surveillance due to the mistaken belief that risk is zero in the absence of a detected mutation; • survivor guilt, i. e., sentiments of undeserving of negative test results when other family members test positive and are suffering because of present or potential disease. Burdens of a test result of “ uncertain significance” include: • the need to assess other family members to determine its significance; • the need to uphold intensive surveillance until the significance of the genetic alteration is known; and • anxiety, frustration, and other unfavorable psychological sequelae associated with uncertainty.

Due to the complexity of the material covered in the pre-test education component, it is unlikely that many individuals can process the information and make a decision about whether or not to proceed with testing during the same visit. Accordingly, it is recommended that testing be deferred to a second or subsequent visit. Pre-test education and time to review the written materials should be provided.