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ORIGINAL ARTICLE – BREAST ONCOLOGY

Assessing, Counseling, and Treating Patients at High Risk for Breast Cancer

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ABSTRACT Identifying patients at high risk of carrying pathogenic variants in genes is a crucial part of providing both accurate counseling and evidence-based treatment recommendations. Current risk assessment models have strengths and weaknesses that may limit their applicability to specific clinical circumstances. Clinicians must have knowledge regarding variations in available models, how they should be used, and what data they can expect from specific models. In addition, indications for genetic testing are expanding, and the adoption of next-generation sequencing has allowed the creation of multigene testing panels. Complex consequences of panel testing have included an increase in the incidence of identifying variants of uncertain significance and the identification of pathogenic variants in genes for which treatment guidelines are not available. Women diagnosed with breast cancer who carry pathogenic variants in genes with proven associations with breast cancer (*BRCA1/2*) or highly likely associations (*PTEN, PALB2*) require additional risk assessment to facilitate treatment decisions that will limit in-breast tumor recurrence and contralateral breast cancer.

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Assessing, counseling, and treating breast cancer patients at risk for harboring a pathogenic variant is a complex but crucial task best performed in a collaborative manner among clinicians and those with genetics expertise. Established risk assessment models provide a framework for determining risk but are not always consistent in input variables or determined risk. In addition, there have been vast changes in genetic testing since the United States Supreme Court ruled that substances existing in nature (genes) cannot be patented. While the American Cancer Society and the National Comprehensive Cancer Network (NCCN) provide screening and treatment guidelines for some genes, these do not cover all situations encountered in clinical practice.[1,2] Frequently, a variant of uncertain significance (VUS) can be troubling for both patient and clinician, as are pathogenic variants in a low-penetrance gene or a gene not associated with the patient's phenotype. Counseling and treatment recommendations in these situations can be challenging. Furthermore, women diagnosed with breast cancer who carry a pathogenic variant known to predispose them to breast cancer require specific counseling regarding their risk of ipsilateral recurrence and contralateral breast cancer (CBC). Herein we address some of these common challenges breast surgeons face on a daily basis and provide guidance in counseling and decision making.

NAVIGATING RISK ASSESSMENT MODELS: WHAT DATA TO EXPECT

Surgeons need to estimate the breast cancer risk for every patient in order to determine screening, diagnosis, and treatment approaches. Risk models allow an evidence-based approach to risk assessment by estimating the risk of breast cancer over time and aid in determining the risk of

testing positive for a pathogenic *BRCA1* or *BRCA2* variant. Risk models provide estimates of breast cancer risk in the short (5-year risk) and long term (lifetime risk).

Risk models use combinations of family history (*BRCA*PRO, Myriad, Claus, Boadicea, or Tyrer Cuzick), hormonal risk factors (Tyrer Cuzick or Gail), and pathologic factors such as atypical hyperplasia (Gail) or atypical hyperplasia/lobular carcinoma-in-situ (Tyrer Cuzick).[3–7] Models assign a weight to each factor, then use an algorithm to estimate overall risk on the basis of the constellation of factors present. In determining which model to use, one must think about the outcome desired. For example, eligibility for screening magnetic resonance imaging (MRI) is best suited to using the Tyrer Cuzick model, followed by *BRCA*PRO and Claus. When determining the need for genetic testing, *BRCA*PRO, Tyrer Cuzick, and Myriad are the best models, while NCCN offers the most comprehensive guidelines. The Gail model is not appropriate for identifying patients at high risk of hereditary disease, as it only accounts for first-degree female relatives with breast cancer, thereby ignoring male breast cancer, second-degree relatives, ovarian cancer, and paternal family history, all of which are critical in identifying patients for genetic testing. Further, while running the Gail model is easy, it lacks credibility in determining the need for MRI and genetic testing, the two major interventions providers need to discuss with each patient. However, this model can be useful in stratifying patients for chemoprevention, though the uptake of chemoprevention has not gained traction beyond its use in women with atypia or lobular carcinoma-in-situ.[8,9]

Preferably, women should undergo breast cancer risk assessment as early as possible. The lifetime risk of breast cancer tends to be higher for younger patients (longer time at risk) and helps inform the need for MRI. Those with a 20 % or greater lifetime risk should be offered MRI and mammography annually after the age of 30 according to current guidelines.[1,2] Models can be run through a variety of software packages, including but not limited to the ASBS Mastery of Surgery, Hughes RiskApps Express, and CancerGene.[5,7,10] Finally, risk models can help in determining one's risk of testing positive for a pathogenic *BRCA1* or *BRCA2* variant, which informs the need for formal genetic evaluation and subsequent testing. Customarily, patients found to have a 5 to 10 % or greater chance for testing positive for a pathogenic *BRCA1* or *BRCA2* variant or those who meet the NCCN guidelines should be offered genetic testing. Clinicians must understand the consequences of genetic testing, as contemporary results can be complex and provide unexpected information. For this reason, national guidelines and many hospital systems suggest patient's proceeding with genetic testing should complete both pre- and posttest counseling for discussion of results and consequences, as two clinical scenarios may occur. First, the identified mutation does not match the patient's clinical history; second, and perhaps more commonly, the testing identifies a VUS.

WHEN THE MUTATION DOES NOT FIT THE FAMILY HISTORY

In the era of next-generation sequencing and multigene cancer panels, healthcare providers can provide patients valuable information beyond *BRCA1* and *BRCA2* evaluations. However, with the utilization of this type of testing, clinicians are frequently faced with having to interpret complicated and/or unexpected results. Most laboratories offer multiple cancer-specific panels of different numbers and types of genes based on disease type, penetrance, and/or actionability. Ordering such panels assumes the clinician is familiar with all the genes on the given panel. If one is not comfortable making medical management recommendations for all of the genes included, it might be worth considering a smaller panel that is specific to breast cancer and includes only genes with established medical management guidelines or seeking help from someone with more experience in genetics.

While there are various results that can come from ordering a multigene cancer panel, the following example demonstrates what to do when a pathogenic variant is identified but was unexpected based on the patient's reported personal and family history: A 36-year-old unaffected woman presents for consultation because of a family history of breast cancer. Her mother, diagnosed at 47, two maternal aunts, and her maternal grandmother are all reported to have a history of breast cancer. Multigene cancer panel testing, which included *BRCA1/2* and *PALB2,* only revealed a pathogenic variant in *PMS2*.

PMS2 is associated with Lynch syndrome and is described as a lower-penetrant mismatch repair gene. The most commonly reported cancers associated with germ-line pathogenic variants in *PMS2* include, but are not limited to, colon (20 %) and endometrial (11–15 %) cancer.[11,12] Whether breast cancer should be included in the Lynch syndrome spectrum is still debated, with no consensus in the literature. A recent publication did, however, report a higher incidence of breast cancer in their *PMS2* female cohort, with a standard incidence ratio of 3.8 (95 % confidence interval 1.9–6.8).[13]

NCCN offers medical management guidelines for Lynch syndrome, which includes *PMS2;* however, not surprisingly, there are no breast cancer screening recommendations. In these situations, medical management recommendations should be made on the basis of the individual patient's reported family history of breast

cancer. As a result, a woman should have her first mammogram 10 years before her mother's diagnosis (age 37), and appropriate risk models should be run (e.g., Tyrer-Cuzick, Claus) to see if she meets the criteria (lifetime risk >20 %) for increased screening with breast MRI. Of critical importance is referring her to a gastroenterologist for frequent colonoscopies and a gynecologist to discuss endometrial and ovarian screening and/or prophylactic surgery. In ordering a genetic test, the clinician is responsible for arranging management of any organ at risk.

COUNSELING PATIENTS WITH A VUS

The most common genetic alteration identified in genetic testing is a VUS. These present unique challenges for ordering clinicians, as many of these do not affect disease risk. A minority of alterations, or pathogenic variants, can affect the biological function of a gene to the extent that the risk of disease is significantly elevated. VUS are defined as genetic alterations for which the impact on disease risk cannot be established with current data. There are various reasons for the uncertainty, which include a lack of understanding regarding the functionality of the gene in a cancer pathway, unknown gene function, and unclear genotype/phenotype association.[13] Currently, most laboratories that offer multigene panel testing cite 15 to 40 % VUS detection rates.[14,15] Comparatively, *BRCA1/2* VUS rates at the most experienced labs today are <3 %.[16]

The principal concern surrounding VUS is the lack of a database or uniformity for VUS classification across laboratories. Each laboratory has its own process, which creates concern regarding potential differences in VUS classification across institutions. A study found that 53 % of VUS were classified differently between two major U.S. laboratories.[17] Some laboratories do not report VUS findings at all. Additionally, the lack of ethnic diversity in variant databases decreases the understanding of the biological impact in nonwhite patients.

Variants are classified along a spectrum: variant likely benign (VLB) are variants that are less likely to cause disease, while variant likely pathogenic (VLP) are variants more likely to lead to disease. Uniform recommendations for interpretation of these variants have not been established. VLPs are typically managed as a mutation associated with an increased cancer risk; appropriate management recommendations are made in conjunction with relevant clinical and family history. A true VUS (not VLP or VLB) should not alter a patient's medical management. Additionally, family member testing for a VUS is not routinely recommended for the same reason. However, sometimes familial testing can help laboratories sort out the meaning of a VUS. For example, if there is a strong maternal history of the cancer but a VUS is from the paternal side, where no cancers are found, this may add to information that helps reclassify that VUS.

Given the complexity of variant classification and the diversity between laboratories, it is important for healthcare providers to do their own research; this may include contacting other laboratories to determine their viewpoint on a given variant or investigating established databases like ClinVar. Reclassification notices are regularly sent to the ordering healthcare provider as additional information regarding the variant is obtained. It is the responsibility of healthcare providers to notify patients of these updates.

Potential negative impacts to the patient upon receiving VUS results include anxiety regarding the unknown and decisions made on the basis of incomplete information. The importance of pretest counseling to address these possibilities has been highlighted in recent literature.[18–22]

A national call for centralizing variant research has helped to initiate PROMPT (Prospective Registry of MultiPlex Testing) and ClinGen, a National Institutes of Health project combining researchers and clinicians from several U.S. institutions in data sharing efforts. The U.S. Food and Drug Administration also plans to become more active in the regulation of clinical genetic testing, which may encompass variant classification practices.

MANAGEMENT OF PATIENTS WITH BREAST CANCER AND A PATHOGENIC VARIANT

Identifying a pathogenic variant can change screening and treatment practices. The most comprehensive data for enhanced screening, prophylactic surgery, and surgery to treat an index cancer are found in the cohort of patients with germ-line mutations in the *BRCA1/2* genes and forms the basis for the following discussion. *BRCA1* and *BRCA2* predispose patients to a much higher risk of breast cancer compared to the baseline population.[23] Surgical options for mutation carriers with breast cancer are dependent on the relative risks of in-breast tumor recurrence (IBTR) and CBC. Quantification of ipsilateral and CBC risk can help inform surgical decisions.

In the sporadic cancer population, studies have demonstrated IBTR rates of 1–8 % at 10 years and CBC risk of 5–8 % at 10 years.[24,25] Pierce et al. evaluated 160 *BRCA1* and *BRCA2* carriers with breast cancer who were treated with breast-conserving surgery and found IBTR rates of 12 and 24 % at 10 and 15 years, respectively.[26] Although an increased CBC risk was noted, there was no difference in overall survival. The increased risk of CBC in *BRCA* carriers has been shown in other studies to be 13–40 % at 10 years.[27,28] This risk seems to be influenced by several factors including age at diagnosis, family history of breast

cancer, and oophorectomy. Metcalfe et al. found that patients diagnosed before age 40 had a 42 % risk of CBC and those diagnosed after age 50 had a risk of 19 %. Every first-degree relative with cancer increased the CBC risk by 40 %. Oophorectomy was the strongest predictor of reduced risk, offering a 60 % decrease in CBC risk in those diagnosed and undergoing oophorectomy before age 50. These effects seem to be cumulative. For a *BRCA* carrier with intact ovaries and breast cancer diagnosed before age 50, the CBC risk was 58 %. If the same patient had two or more first-degree relatives with breast cancer, the CBC risk was 68 %.[29]

Given the increased risk of CBC in patients carrying a *BRCA1* and *BRCA2* mutation, many patients opt for prophylactic contralateral mastectomy (CPM). One study showed that 50 % of patients chose this approach. Furthermore, comparison studies indicate that patient satisfaction with this approach is high.[30] Whether CPM offers any survival benefit has been subject to debate. Metcalfe et al. evaluated a population for which the mean follow-up was 13 years.[31] In this study, the 20-year breast-specific mortality for patients who underwent unilateral mastectomy was 31 %, and for those undergoing CPM, it was associated with a 48 % reduction in mortality. Of the patients who underwent CPM, 12 % were initially treated with unilateral mastectomy, but 40 % of this group opted for CPM at some point thereafter, likely because they became aware of their *BRCA1/2* status. Two additional studies also demonstrated a survival advantage to CPM in *BRCA1/2* pathogenic variant carriers.[32,33]

Available data would suggest that pathogenic variant carriers at significant increased risk of either IBTR or CBC should consider bilateral mastectomy. This includes patients diagnosed before age 40, those with intact ovaries, and/or those with first-degree relatives with breast cancer. Conversely, a relatively low-risk subset of patients exists that could be offered breast-conserving surgery, with risks that are comparable to non–mutation carriers. This would include patients diagnosed after age 50 and with no family history. This also emphasizes the importance of having the results of genetic testing available when making treatment decisions.

In conclusion, risk assessment is critical in making management decisions for women at increased risk of breast cancer. Contemporary genetic assessment, when deemed appropriate, is focused on multigene cancer panel testing. While this provides large amounts of individualized data, it can also lead clinicians and patients to complicated and/or unexpected results. Clinicians must understand the complexities and limitations of these panels, be capable of taking a three-generation pedigree, and be familiar with professional working groups that specialize in hereditary cancer syndromes. Changes in the way that VUS are characterized, cataloged, and evaluated will continue to affect all health care providers who engage in genetic testing. Further assistance from genetic counselors is available and can be found at the National Society of Genetic Counselors Web site (http://www.nsgc.org/). Patients with a pathogenic variant and a diagnosis of breast cancer should undergo an assessment to determine their risks of ipsilateral recurrence and CBC. Awareness of one's pathogenic variant status before surgery is critical in properly counseling these patients about their options.

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