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TOPICS IN BREAST CANCER (K HUNT, SECTION EDITOR)

Hot Topic: Should all Women with Breast Cancer Undergo Genetic Testing?

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Abstract

Purpose of Review Panel testing for germline mutations in cancer patients has advanced rapidly in recent years. In breast cancer, these advances have raised questions about the indications for testing, with some groups advocating testing of all patients with breast cancer.
Recent Findings Studies uniformly demonstrate that expanded scope of genetic testing will result in identification of more women with germline mutations. However, many challenges remain in interpretation of such broad panel testing, including limited information about the risks of second cancers conferred by most of these germline mutations and the high rates of VUS that risk causing anxiety and driving decisions towards unwarranted CPM. These challenges limit the utility of panel testing and are further compounded by lack of sufficient genetic counseling support to facilitate discussion with patients around these complex issues.
Summary For most women, the benefits of broad panel testing are limited. A tailored approach to genetic testing, based on detailed family history and tumor phenotype, remains the preferred approach.

Keywords Breast cancer · Genetics · Genetic testing · Testing guidelines

Introduction

Genetic testing has evolved over the last 2 decades, and therefore, our understanding of the incidence of hereditary breast cancer (HBC) has improved. Older studies suggest that approximately 5–10% of all breast cancer is hereditary [1, 2]. More recent studies using larger panels of genes suggest that this number may be higher [3–6]. Studies of patients undergoing genomic or tumor-based testing confirm that the incidence of HBC may be more in the range of 15–20% [7•, 8, 9].

To address the growing availability of genetic testing, several societies have developed guidelines for referral of women for consideration of genetic testing [10••, 11, 12, 13]. These referral guidelines are largely based on personal and family history of cancer. For example, ASCO [11] and NCCN [13] guidelines include consideration of genetic testing for women with triple-negative breast cancer. NCCN recommendations also include consideration of genetic testing for women diagnosed at a young age. However, only a small percentage of patients are referred for genetic testing [14•, 15] based on these guidelines.

Recently, Beitsch and colleagues examined how well such guideline-based referrals identified women with HBC [16•]. In a series of 1000 women with breast cancer, all of whom underwent genetic testing using an 80 gene panel, there was not a significant difference in pathogenic/likely pathogenic mutation rates between women who did or did not meet the guidelines for genetic testing. Other studies examining the use of panel testing among women with breast cancer have found a significant incidence of unexpected findings, that is, germline mutations not expected due to personal or family history. Oleary and colleagues examined test results for women with breast cancer who underwent genetic testing through a single clinical laboratory. They found that 13.7% of test results were unexpected findings [17]. Couch and colleagues examined women with triple-negative breast cancer who were negative for BRCA1 or BRCA2, finding that 8% of women had mutations not suspected due to personal or family history.

These studies have prompted consideration of genetic testing for all women diagnosed with breast cancer. This is not a new concept, and other groups [18] and even societies and

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guidelines have advocated for broader genetic testing approaches [10••, 12, 13].

Given the above information, should we be testing all women with breast cancer? To answer this question, we must look more closely at the studies by Oleary, Couch, and Beitsch. It should be noted that in all 3 of these studies, the unanticipated results or mutations identified in women not fitting the current guidelines for genetic testing were in genes for which cancer risk is less well established. In the Beitsch study, the top 3 genes identified in women not meeting the guidelines were MUTYH, CHEK2, and ATM compared to BRCA2, PALB2, and CHEK2 for those meeting the guidelines. In the Oleary study, the most common genes identified were CHEK2, MUTYH, and ATM. While guidelines do exist for ATM and CHEK2 mutation carriers, the risks associated with cancer for these genes are variable and, especially for CHEK2, depend on family history [19–22]. The cancer risk associated with a heterozygous MUTYH mutation may be no different than risk based on family history alone [23, 24]. Therefore, for some patients found to have unanticipated genetic testing results, their exact cancer risk and the most appropriate management plan will not be known, thus limiting the benefits of testing.

It is important to also note that these limits to our current understanding of the risks conferred by many of the mutations now available on genetic panels have impact on patients' anxiety, quality of life, and decision-making. Studies have shown rates of contralateral prophylactic mastectomy (CPM) approaching that for BRCA mutation carriers, in women who have non-BRCA mutations detected through panel testing [25] and even among women noted to carry a variant of uncertain significance (VUS), high rates of CPM have been reported [26]. Given the findings by Beitsch and colleagues of a VUS rate of 54%, there is reason for concern that routine, expanded panel testing may fuel further increases in rates of bilateral mastectomy. Further, given the rapid expansion of genetic testing and the scarcity of counseling resources, many women are making life-altering decision around bilateral mastectomy without the benefit of discussion with a genetic counselor [26]. Recognizing the full downstream impact of expanded testing is important for decisions regarding how to best integrate genetics into clinical practice.

Lastly, it should be remembered that the original guidelines for genetic testing were developed for identification of women with BRCA1 or BRCA2 mutations. Since that time, as discussed above, additional genes associated with HBC have been identified and importantly the phenotype and cancers associated with BRCA1 and BRCA2 have evolved. For example, individuals with BRCA2 mutations are also at increased risk for melanoma and pancreatic and prostate cancer [27–30]. It should therefore not be surprising that guidelines fail to identify all individuals with HBC and as guidelines do at times lag the rapid advances in knowledge. Underscoring this point, in the study by Beitsch et al., only 0.63% of the women who did not meet the guideline for genetic testing were found to have germline mutations in BRCA1 or BRCA2. In contrast, the proportion of women who tested positive for any pathogenic mutation across the 80 genes on the panel was similar between the in and out of guideline groups. Therefore, delays in aligning guidelines with the rapidly expanding field of genetics should not be misconstrued as an opportunity for routine testing of all patients with breast cancer, arguing instead for more timely updates to the guidelines that allows for rapid dissemination of important new information without risk of the uncertainties created through a "test all" approach.

Conclusion

Based on the current uncertainties in cancer risk associated with many of the genes now available for testing, the limited impact these findings have in tailoring cancer care, and the potential to unnecessarily increase the rates of bilateral mastectomy, we conclude that routine, expanded genetic testing for all women with newly diagnosed breast cancer is not warranted. Given the limited availability of genetic counseling resources and considering that most women will test negative or have a VUS, a more rational approach is warranted. We believe careful attention should be given by oncology providers to obtaining a detailed family history. Women with a phenotype associated with HBC (diagnosis under age 50, triple-negative breast cancer, bilateral breast cancer, or multiple primaries), women with a family history of cancer (in a 1st and/or 2nd degree relative), or women for whom a positive genetic test would change management should be offered genetic testing. Clinicians in community or more rural practices should be aware of tele-counseling services as this may help alleviate the stress of incorporating genetic counseling into their practices and/or assist in making sure that the right test is performed.

Compliance with Ethics Guidelines

Conflict of Interest Marie Wood and Isabelle Bedrosian declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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