INVITED COMMENT | Genetics in Medicine

Germline genetic testing for breast cancer: which patients? What genes?

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The current debate regarding universal genetic testing for breast cancer patients, referred to in the Points to Consider document in *Genetics in Medicine*,[1] revolves around two central questions: (1) what should the threshold of detection of pathogenic variants be to either mandate or offer testing? and (2) what pathogenic variants should we be trying to detect?

With regard to the first question, in health care we are in the midst of two seemingly competing pressures. The first focuses on "value based care," which emphasizes a gold standard of clinical utility wherein a test, procedure, or treatment improves health outcomes. This can be exemplified by such initiatives as the Choosing Wisely campaign from the American Board of Internal Medicine[2] and the US Preventive Services Task Force (USPSTF) recommendation for mammogram starting at 50 for average risk women.[3] In the Choosing Wisely campaign, tests that are commonly used, yet whose clinical utility is not supported by available evidence, have been identified by specialty organizations and their use discouraged. For example, the American Society of Clinical Oncology identified the use of imaging (such as positron emission tomography–computed tomography [PET/CT] or bone scan) in newly identified early stage breast cancer as something to be discouraged. However, it is known that a low but real number of women undergoing mammograms prior to age 50 would be diagnosed with breast cancer, and that some women with early stage breast cancer would be found to have metastatic disease. In this paradigm, we should be aiming to do less.

Simultaneously there is increasing emphasis on doing more, often with the endpoint of diagnostic yield. For example, in women with dense breast tissue on mammographic imaging, supplemental imaging with ultrasound or magnetic resonance imaging (MRI) detects more cancers.[4] Federal legislation has been passed requiring notification of women of the significance of dense breast tissue, and several state laws mandate insurance coverage for supplemental imaging. Yet, there are no data currently available that such supplemental imaging leads to an improvement in breast cancer mortality. Under this framework, we should be doing more.

In the context of these types of debates comes the discussion about the threshold for genetic testing in breast cancer, specifically whether all breast cancer patients should undergo testing.[5] Pal et al.[1] and others[6] have well articulated the associated issues, including the fact that breast cancer patients who do not meet National Comprehensive Cancer Network (NCCN) criteria have a low risk (<1%) of having a pathogenic variant associated with a high penetrance gene and clear clinical utility. The majority of the pathogenic variants that are detected in such patients are either in genes associated with a moderate penetrance of breast cancer risk (such as *CHEK2* and *ATM*) with uncertainty regarding clinical utility or those not associated with breast cancer (i.e., *MUTYH*). Given these and other issues, Pal et al. reasonably "provide a rationale for maintaining support for existing evidence-based, guidelines based on a risk stratification approach while data addressing broader testing strategies emerges."

Guidelines have always changed to reflect new data and should continue to do so. The awareness of the higher prevalence of *BRCA1/2* pathogenic variants in triple negative breast cancer, for example, led to specific NCCN criteria in the population. Therefore it is worth considering what evidence will substantially inform the conversation. Two specific examples would be (1) the demonstration of benefit of adjuvant PARP inhibitors, and (2) improved mortality from the addition of MRI in women with a moderate risk of breast cancer.

The role of adjuvant PARP inhibitors for breast cancer is under study. Two PARP inhibitors, olaparib[7] and talazoparib, are approved by the US Food and Drug Administration (FDA) for treatment of *BRCA1/2* mutation associated metastatic breast cancer. The OlympiA study (NCT02032823) has completed enrollment of >1800 high risk breast cancer patients with germline *BRCA1* or *BRCA2* pathogenic variants. Participants are randomized 1:1 to olaparib versus placebo following the completion of standard

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adjuvant therapy with a primary endpoint of invasive disease free survival. If olaparib is beneficial, this would provide another reason (in addition to risk of second cancers) to find the approximately 0.6% of breast cancer patients who do not meet NCCN criteria yet have *BRCA1/2* pathogenic variants. It is likely that if genetic testing in breast cancer were limited to *BRCA1* and *BRCA2* (and even *PALB2*), there would be less concern about the potential downsides of testing. Indeed, testing all breast cancer patients for *BRCA1/2* and *PALB2* was shown to be cost effective compared with testing of those with a 10% chance of having such a pathogenic variant; however, the threshold of the NCCN criteria are far lower, and testing in this study was modeled based on three genes.[8] Thus, the downstream impact of the detection of pathogenic variants in other genes including enhanced screening and the potential for unnecessary mastectomy in the setting of moderate penetrance genes, was not considered. Genetic testing in the United States is now almost always done with multigene panel testing, which creates many more challenges. What evidence will help us with the question of gene selection?

The inclusion of more genes on genetic testing panels invariably leads to the detection of more pathogenic variants (along with more variants of uncertain significance). Some of these pathogenic variants "matter" more than others. Pathogenic variants in *CHEK2* and *ATM* are found in approximately 2% of unselected breast cancer patients. As discussed by Pal et al.,[1] MRI screening is recommended based on expert opinion with uncertainty regarding clinical utility. Recently, the FaMRIsc trial randomized women with a lifetime risk of breast cancer of >30% to mammogram versus MRI and demonstrated an increased yield for the detection of breast cancer with MRI.[9] Data are not yet available on whether MRI also provided mortality benefit but if it does, this will provide extremely important evidence. If there is no associated mortality benefit, the concern will be that the increased yield reflects overdiagnosis. In addition, due to genetic and other modifiers there is evidence that a significant number of women with *CHEK2* and *ATM* pathogenic variants may not meet criteria for MRI screening based on a threshold of a 20% lifetime risk.[10]

Beyond genes such as *CHEK2* and *ATM*, a particularly important issue is the inclusion of genes with no known association with breast cancer risk. If a large panel is used with the inclusion of such genes, this amounts to population screening. Although arguments have been made for population screening for select genes, the use of large multigene panels extends far beyond such discussions. Several studies have demonstrated that for some genes penetrance estimates derived from testing probands with cancer are not well calibrated for unaffected carriers. Because of these poor risk estimates, it is very difficult to know how to interpret these pathogenic variants when found completely out of context. Examples include *SDHA* and *RET* (specifically p.Val804Met, a common low penetrance pathogenic variant).[11] There is a concern that misinterpretation of these types of results could potentially lead to unnecessary imaging or surgery. There is a strong argument for careful gene selection on multigene panels. More is not necessarily better.

Beyond gene selection, another complicating factor is that patients can now do this without us, their health-care providers. Multiple options are available directly to patients, including for "preventive health," outside of a standard medical and insurance model with costs assessable for many (although clearly not for all). Whether such direct options will worsen the existing racial and socioeconomic disparities for genetic testing is unknown. If patients, even those at very low risk of having a pathogenic variant with clinical utility, desire testing, we should help facilitate including informing the patients that these costs may not be covered by insurance.

We must not lose sight, however, that some patients have a much higher risk of having a pathogenic variant that would significantly alter their medical care than others. We cannot justify "missing" the highest risk patients like we currently do now. Ongoing studies examining how to decrease disparities in testing and improve uptake of testing will provide critical information. As the thresholds for genetic testing become lower and lower, the implementation issues become increasingly more important to solve. Risk stratification has always been an essential part of medicine and will continue to be so as we maximize the utility of genetic information, both in testing and interpretation.

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