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EDITORIAL

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Genetic testing for hereditary breast and ovarian cancer and the USPSTF recommendations

In 2005, the US Preventive Services Task Force (USPSTF)[1] recommended that women with a family history associated with increased risk for a deleterious mutation in *BRCA1* or *BRCA2* should be referred for genetic counseling and consideration of genetic testing. In 2014 these recommendations were updated, suggesting that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools and refer women with positive screening for genetic counseling and testing.[2] The USPSTF has just completed another review of this topic and published their review for public comment. The newest review confirms their 2014 recommendations regarding BRCA testing for women with a concerning family history. They state that the recommendations should apply to asymptomatic women as well as women with a prior breast, ovarian, or peritoneal cancer diagnosis. Their recommendations endorse the use of one of several family history tools to identify candidates for genetic counseling and testing. These tools include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, FHS-7, and brief versions of BRCAPRO.

These latest USPSTF recommendations have not considered the following factors:

(a) Recent changes in how genetic testing is performed and offered to patients; (b) Current knowledge regarding the phenotype of BRCA1 and BRCA2; (c) Indications that differ for genetic testing for individuals with and without cancer; and (d) Recent data demonstrating that individuals with previously unrecognized links to the BRCA1 and BRCA2 genes, including individuals with pancreatic cancer or prostate cancer, are candidates for BRCA testing.

The field of cancer genetics has changed significantly over the past 5 years. The development of next-generation sequencing (NGS) has increased the ability to test for many genes concurrently and significantly reduced the cost of genetic testing. Our understanding of hereditary cancer has advanced, with identification of additional genes found to confer significant risk for either breast or ovarian cancer. Several studies evaluating women who test negative for *BRCA1* and *BRCA2* show that between 4% and 16% will be found to have pathogenic variants in other high or moderately penetrant genes.[3-5] The identification of potentially actionable mutation in genes other than *BRCA1* and *BRCA2* has led to the suggestion that panel testing should replace *BRCA* testing alone for most women at increased risk for breast cancer,[6,7] ovarian cancer,[8] or both.[9] Studies have shown the ability of expanded panel testing to not only improve identification of hereditary breast and ovarian cancer predisposition but also to impact the care of both patients with and without cancer.[10,11] Furthermore, panel testing is more cost effective compared to BRCA-only testing.[12,13] Panel testing has now become the norm in cancer genetics programs,[14-16] although there are no specific guidelines regarding the optimal number of genes that should comprise a panel.[6,7]

Current indications for cancer genetic testing of affected individuals differ significantly from indications for testing of unaffected individuals. While family history is an important consideration in both instances, among affected women, having a specific tumor biology or histology (such as triple negative breast cancer and high-grade serous ovarian cancer) has become a specific indication for genetic testing, independent of family cancer history.[17] The development of specific therapies that demonstrate superior or exclusive efficacy in individuals with cancer who carry a BRCA mutation has led to NCCN guideline recommendations to test all individuals with ovarian, pancreatic, and metastatic breast and prostate cancers.[18,19] The latest USPSTF recommendations should clarify that family history tools should be used for risk assessment in unaffected, not affected, individuals and that additional considerations beyond family history must be utilized to make appropriate decisions for genetic testing in affected individuals.

We agree with the USPSTF that primary care providers should screen women for family cancer history and refer those with a strong family history for genetic counseling. The USPSTF has limited their investigation of family history tools to those designed to identify candidates for BRCA testing (the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, FHS-7 and brief versions of BRCAPRO). However, the evaluated family history tools have not been updated to consider inclusion of other key BRCA- related cancers such as pancreatic cancer or high-grade prostate cancer. Additionally the accuracy of family history has been shown to be limited, especially for cancer diagnoses in the abdomen/pelvis.[20-22] A focus exclusively on the BRCA1,2 genes seems limited given that there are a number of highly penetrant genes associated with either breast cancer (PTEN, LFS, HDGC, PALB2) or ovarian cancer (Lynch genes, RAD51C, RAD51D, etc). It may be more appropriate to focus on key elements of family history for referral.[17]

There are also important implications of the expanded spectrum of BRCA-associated cancers, which have been recognized over time. While the most common cancers continue to be breast and ovarian cancers, additional cancers have been found to be significantly

associated with BRCA gene mutations, specifically prostate and pancreatic cancer, each associated with mutations in several genes, with BRCA2 mutations being the most prevalent.[23-26] Given this new information, we believe that recommendations for "BRCA-related Cancer, Genetic Counseling, and Genetic Testing" should consider individuals affected with breast, ovarian, pancreatic, and prostate cancer. It should be noted that one of the most effective approaches to identifying unaffected individuals is the testing of individuals who have a close relative with cancer and a mutation, so-called Cascade testing.[27]

In summary, a recommendation focused on BRCA-only testing (and not panel testing) for identification of hereditary breast and ovarian cancer has significant adverse consequences. These include the potential to miss important genes associated with hereditary breast and ovarian cancer, the potential to miss actionable mutations that were not suggested by family history, and for affected individuals, the potential to miss actionable mutations that may affect treatment opportunities. For instance, individuals with mutations in BRCA or other DNA repair genes may respond to PARP inhibitors and individuals with mutations in mismatch repair genes may respond to immunotherapy. Finally, the approach of testing for BRCA-only genes has the potential to create significant out of pocket costs for patients, since the insurance companies will often only cover one genetic test, thus limiting the possibility of future expanded panel testing among individuals meeting criteria who do not carry a mutation in one of the BRCA genes.

Marie E. Wood MD[1]
Judy E. Garber MD, MPH[2]
Claudine Isaacs MD[3]
Shahla Masood MD[4]
Isabelle Bedrosian MD[5]
Nadine Tung MD[6]
Jennifer Chun MPH[7]
Freya R. Schnabel MD[7]
Banu K. Arun MD[8]
The International Society of Cancer Risk Assessment and Management[9]

[1]*Department of Medicine, University of Vermont, Burlington, Vermont*
[2]*Department of Medicine, Harvard Medical School, Dana Farber Cancer Institute, Boston, Massachusetts*
[3]*Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia*
[4]*Department of Pathology and Lab Medicine, University of Florida College of Medicine, Jacksonville, Florida*
[5]*Department of Surgical Oncology, M. D. Anderson Cancer Center, University of Texas, Houston, Texas*
[6]*Department of Hematology-Oncology Boston, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts*
[7]*Department of Surgery, New York University Langone Health, New York, New york*
[8]*Department of Medical Oncology, M. D. Anderson Cancer Center, University of Texas, Houston, Texas*
[9]*www.isc-ram.com*

Correspondence
Marie E. Wood, MD, Department of Medicine, University of Vermont, Burlington, VT.
Email: Marie.Wood@uvmhealth.org

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