



Facing Hereditary Cancer EMPOWERED

February 14, 2024

## **Response to the USPSTF Draft Research Plan for BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing**

<https://www.uspreventiveservicestaskforce.org/uspstf/document/draft-research-plan/brca-related-cancer-risk-assessment-genetic-counseling-testing>

Dear Dr. Barry and esteemed members of the U.S. Preventive Services Task Force,

FORCE (Facing Our Risk of Cancer Empowered) is a national nonprofit organization dedicated to empowering the millions of individuals and families facing hereditary cancers. Its community includes people with BRCA, ATM, PALB2, CHEK2, PTEN, or other inherited gene mutations and those diagnosed with Lynch syndrome. We accomplish this through education, support, advocacy and research efforts.

Following are FORCE's recommendations and responses to the questions posed by the USPSTF for its research approach to this guideline update. Many of our comments fall into these critical areas:

### **1) Scope of research plan and corresponding recommendations**

These questions and future recommendations should not focus solely on BRCA1/2. Testing for only BRCA1/2 mutations is insufficient and is no longer aligned with current standard-of-care practices. Pathogenic and likely pathogenic variants in several other genes fall under the umbrella of Hereditary Breast and Ovarian Cancer (HBOC) Syndrome and have similar phenotypes as BRCA1 and BRCA2. Additionally, mutations in genes associated with HBOC Syndrome convey an increased risk of cancers beyond breast and ovarian, including prostate, pancreatic, gastric and melanoma. Another concern is the overlap in ovarian cancer and prostate cancer risk with Inherited Colorectal Cancer Syndrome (e.g., Lynch Syndrome) genes. The current standard of care is multigene panel testing. We urge the Task Force to acknowledge and incorporate current science and medical practice to stay relevant and ensure appropriate care is provided to the American population.

### **2) Population under consideration**

The title of these guidelines is "BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing." The population should include all individuals at risk of an inherited mutation linked to increased risk for these cancers. Men carry BRCA and other heritable cancer-related mutations at equal rates as women. Like women, men with mutations benefit from evidence-based interventions such as increased screening.

### 3) Downstream Interventions and care

The research plan will explore interventions such as intensive screening, risk-reducing medications, and risk-reducing surgery that may be performed for preventive purposes in patients identified with pathogenic BRCA1/2 mutations. The research and related recommendations should also include interventions that are pertinent to early detection of all cancers related to the mutations in question, including prostate. In addition, because the interventions are “preventive” they should be included in the Task Force recommendations. This will facilitate access to appropriate screenings and risk management.

## Proposed Analytical Framework, Key Questions, Contextual Questions, Assessing Health Equity and Research Approach Comments

### Proposed Analytical Framework

No comments

### Proposed Key Questions

1. *In women with unknown carrier status for pathogenic BRCA1/2 mutations, does risk assessment, genetic counseling, and genetic testing reduce the incidence of BRCA-related cancer and cause-specific and all-cause mortality?*

As noted in our initial comments, to adequately address cancer risk and mortality, we must consider genetic mutations in men and mutations beyond BRCA1/2.

2.a. *What is the accuracy of familial cancer risk assessment methods to identify women with pathogenic BRCA1/2 mutations when performed by a nonspecialist in genetics in a clinical setting? What are the optimal ages and intervals for risk assessment?*

For individuals with a BRCA mutation, NCCN guidelines recommend the commencement of screening with breast MRIs at age 25 or individualized based on family history if a breast cancer diagnosis before age 30 is present. However, breast awareness is recommended beginning at age 18. As such, risk assessment beginning at age 18 is reasonable and assessment by age 25 is ideal.

The engagement of nonspecialists such as primary care physicians and gynecologists in risk assessment is crucial to the identification of individuals who may carry a pathogenic mutation associated with hereditary cancer. However, these professionals often lack the time and expertise to accurately collect family health history and assess an individual’s risk as well as counsel patients on all the information they should know before genetic testing.

2.b. *What are the benefits of genetic counseling in determining eligibility for genetic testing for pathogenic BRCA1/2 mutations?*

Pre-test genetic counseling is instrumental in the proper collection of family/personal health history and risk assessment; it also ensures that the appropriate test is ordered, as genetic testing has become increasingly complex. Counseling before testing also helps individuals understand

hereditary cancer, the risks and benefits of genetic testing, possible test results and what they may mean for the individual and their family, as well as risk/disease management options. Genetic specialists also communicate details about and help obtain insurance coverage for appropriate genetic testing.

Importantly, the Genetic Information Nondiscrimination Act (GINA) protects against the use of genetic information in healthcare or employment. However, genetic test results can be used to deny life, long-term care and disability insurance policies, or increase premiums. This is crucial information that individuals should receive before genetic testing. Many physicians without genetics expertise lack knowledge of GINA, its protections and gaps.

*2.c. What are the benefits of posttest counseling to interpret results and determine eligibility for interventions to reduce risk of BRCA1/2-related cancer?*

Post-test genetic counseling is critical in the appropriate interpretation and communication of test results. It informs the individual about guideline-recommended risk management and treatment options, helps them deal with emotional concerns, provides referrals to other healthcare professionals, and identifies other family members who may benefit from genetic counseling and testing.

*3. What are the adverse effects of: 3a) risk assessment, 3b) genetic counseling, 3c) genetic testing, and 3d) posttest genetic counseling for BRCA1/2-related cancer?*

The primary adverse effects are potential anxiety and emotional distress. Pre- and post-test genetic counseling can help alleviate this. Studies have shown that this anxiety and stress is transient in most people.

*4. In women with pathogenic BRCA1/2 mutations, do interventions reduce the incidence of BRCA-related cancer and mortality?*

More intensive, more frequent cancer screenings at younger ages than the general population identify cancer at earlier stages when it is easier to treat. Risk-reducing bilateral salpingo-oophorectomy, hysterectomy, and/or mastectomy significantly mitigate the probability of being diagnosed with cancer. Further, risk-reducing salpingo-oophorectomy has been shown to lower the risk of mortality in women at high risk for ovarian cancer.

*5. What are the potential adverse effects of interventions to reduce risk for BRCA1/2-related cancer in women with pathogenic BRCA1/2 mutations?*

Adverse effects may include anxiety due to frequent cancer screenings and an increased number of biopsies. Some women experience body image issues as a result of risk-reducing surgery. Surgical menopause due to risk-reducing bilateral salpingo-oophorectomy can have health repercussions.

## Proposed Contextual Questions

1. *How does risk assessment for pathogenic BRCA1/2 mutations for women without BRCA1/2-related cancer in primary care practice settings vary across socioeconomic, racial, and ancestry groups? Are there differences in access to risk assessment in primary care settings among groups with lower educational levels, socioeconomic status, or access to care?*

There are disparities in access to genetic testing based on factors such as race, education, socioeconomic and insurance status. This must be examined to identify barriers and develop solutions to reduce disparities in access and health outcomes. These same barriers exist with regards to access to risk-appropriate screening and risk-reducing interventions. The Task Force could assist in reducing these barriers by including evidence-based screening and risk-reduction interventions in its review and assigning letter grades to these interventions, including breast MRI, mammograms at an earlier age and risk-reducing salpingo-oophorectomy.

2. *Among women with increased risk for BRCA1/2-related cancer, what are the benefits and harms of testing family members to determine the presence of BRCA1/2 mutations? This may include testing other family members at higher risk before testing the index patient, including men, in addition to the potential benefits and harms of testing for family members of the index case.*

Testing within a family is more cost-effective and most likely to yield a conclusive result if it begins with someone who has had a cancer diagnosis consistent with a hereditary cancer syndrome. Testing older family members, including men, and/or those who have/had a cancer diagnosis is ideal because it establishes the appropriateness of cascade testing for other relatives. The benefits and harms of this approach align with those of testing a single individual, explored in the *Key Questions*. Ultimately, it allows family members to make informed medical decisions.

It is important to acknowledge that some family members are not available or do not want to undergo genetic testing. This should not be a barrier to other family members who are interested in genetic testing to learn about and manage their cancer risk.

3. *What is the diagnostic accuracy of single vs. multigene panel testing for detecting pathogenic BRCA1/2 mutations?*

With tremendous technological advances due to next-generation sequencing technologies, there has been a nearly universal shift to simultaneously testing many genes at once. Importantly, panel gene testing has been shown to identify pathogenic cancer-predisposing mutations that a pedigree would not suggest on a gene-by-gene basis. In addition, there are other well-documented benefits of using multigene panels versus single gene testing that include cost, speed and that panel testing is very efficient for differential diagnoses.

Cragun D, Kinney AY, Pal T. [Care delivery considerations for widespread and equitable implementation of inherited cancer predisposition testing](#). *Expert Rev Mol Diagn*. 2017 Jan;17(1):57-70. doi: 10.1080/14737159.2017.1267567. Epub 2016 Dec 13. PMID: 27910721; PMCID: PMC5642111.

Multigene panel testing has been available since the mid 2010's. Since then, there have been numerous publications on the accuracy of multigene panel testing for detecting pathogenic BRCA1/2 and other high-penetrance gene mutations linked to these cancers. We include some (out of over one hundred) of the most notable publications.

**The following study demonstrated that multiple-gene sequencing rapidly replaced BRCA1/2-only testing for patients with breast cancer and enabled 2-fold higher detection of clinically relevant pathogenic variants.**

Kurian AW, Ward KC, Hamilton AS, Deapen DM, Abrahamse P, Bondarenko I, Li Y, Hawley ST, Morrow M, Jagsi R, Katz SJ. [Uptake, Results, and Outcomes of Germline Multiple-Gene Sequencing After Diagnosis of Breast Cancer](#). JAMA Oncol. 2018 Aug 1;4(8):1066-1072. doi: 10.1001/jamaoncol.2018.0644. PMID: 29801090; PMCID: PMC6143044.

**The results of the following study showed that multigene panel testing detects pathogenic BRCA1/2 variants at equivalent rates as single gene testing and increases the diagnostic yield.**

Kapoor NS, Curcio LD, Blakemore CA, Bremner AK, McFarland RE, West JG, Banks KC. [Multigene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer](#). Ann Surg Oncol. 2015 Oct;22(10):3282-8. doi: 10.1245/s10434-015-4754-2. Epub 2015 Jul 29. PMID: 26219241.

**This study established the relevance of panel testing that included high- and moderate-risk breast cancer genes and provided estimates of breast cancer risk.**

Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, Hallberg E, Moore R, Thomas A, Lilyquist J, Feng B, McFarland R, Pesaran T, Huether R, LaDuca H, Chao EC, Goldgar DE, Dolinsky JS. [Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer](#). JAMA Oncol. 2017 Sep 1;3(9):1190-1196. doi: 10.1001/jamaoncol.2017.0424. PMID: 28418444; PMCID: PMC5599323.

**Results of the following study demonstrate that panel testing increased the number of women identified as carrying a pathogenic variant compared with BRCA testing alone.**

Buyss SS, Sandbach JF, Gammon A, Patel G, Kidd J, Brown KL, Sharma L, Saam J, Lancaster J, Daly MB. [A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes](#). Cancer. 2017 May 15;123(10):1721-1730. doi: 10.1002/cncr.30498. Epub 2017 Jan 13. PMID: 28085182.

**This study highlights the importance of a panel testing approach to comprehensively identifying germline variants contributing to cancer predisposition broadly.**

Cheng DT, Prasad M, Chekaluk Y, Benayed R, Sadowska J, Zehir A, Syed A, Wang YE, Somar J, Li Y, Yelskaya Z, Wong D, Robson ME, Offit K, Berger MF, Nafa K, Ladanyi M, Zhang L. [Comprehensive detection of germline variants by MSK-IMPACT, a clinical diagnostic platform for solid tumor molecular oncology and concurrent cancer predisposition testing](#). BMC Med Genomics. 2017 May 19;10(1):33. doi: 10.1186/s12920-017-0271-4. PMID: 28526081; PMCID: PMC5437632.

#### 4. *What is the prevalence of pathogenic BRCA1/2 mutations in common ancestry groups in the United States?*

Certain ancestry groups have a higher prevalence of BRCA and other mutations, i.e., 1:40 in the Ashkenazi Jewish, Eastern European population. Founder mutations have also been identified in other populations, such as Norwegian, Dutch, and Icelandic people. We need to know more about the prevalence of mutations in people with Latin and African American ancestry. Research shows that healthcare professionals may be less likely to discuss genetic counseling and testing with black and Spanish-speaking Hispanic individuals at risk for carrying a mutation. This must be addressed to gain a better understanding of the prevalence of pathogenic mutations in various populations and to develop appropriate education, outreach and risk-intervention models.

### **Proposed Research Approach**

#### **Populations**

*KQs 1–5: Women with unknown BRCA1/2 mutation status*

The populations should include men and other mutations that increase the risk of hereditary cancers.

#### **Interventions**

*KQ 1: Risk assessment initiated by a nonspecialist in genetics, pretest genetic counseling, genetic testing, and posttest counseling*

Define “nonspecialist in genetics.”

*KQs 4, 5: Intensive screening (earlier and more frequent screening or use of additional screening methods), use of risk-reducing medications (aromatase inhibitors and tamoxifen), and risk-reducing surgery (mastectomy, salpingo-oophorectomy, and other procedures) performed for preventive purposes in patients identified with pathogenic BRCA1/2 mutations*

Risk management for men should be included. Given that the ACA looks to the USPSTF for guidance on coverage of preventive health services with no cost-sharing, the interventions should be included in the recommendations. Knowledge of a mutation is pointless if an individual doesn't have access to the appropriate downstream care.

#### **Comparisons**

*KQs 2a, 3a: Risk assessment by a nonspecialist in genetics vs. usual care or alternative approaches.*

- Define “nonspecialist in genetics.”
- Include risk assessment by a trained genetics specialist vs. usual care or alternative approaches.

*KQs 4, 5: Intensive screening, risk-reducing medications, or risk-reducing surgery vs. no intervention or alternative approaches*

As noted under Interventions, risk management for men should be included. Given that the ACA looks to the USPSTF for guidance on coverage of preventive health services with no cost-sharing, the interventions should be included in the recommendations. Knowledge of a mutation is pointless if an individual doesn't have access to the appropriate downstream care.


## **Outcomes**

*KQs 1, 4: Incidence of BRCA1/2-related cancer; disease-specific and all-cause mortality*

Hereditary cancers occur in men as well as women. The outcomes studied should be expanded to include the incidence of hereditary cancer in all individuals. We also encourage consideration of actionable moderate- and high-penetrance mutations associated with such cancers including ATM, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11 and TP53.

In closing, USPSTF guidelines play a critical role in guiding clinical decisions and access to care. The Task Force must expand its recommendations to encompass current science and medical practice to meet the needs of clinicians and patients. We welcome the opportunity to discuss the feedback and suggestions outlined herein.

Sincerely,



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