On behalf of Ambry Genetics, I respectfully request the NCCN (Genetic/Familial High Risk Assessment: Breast and Ovarian Guideline Panel) to review the enclosed data on *BARD1* and *RAD51D*-associated breast cancer risk.

**Specific Changes:**

**GENE-2 (now GENE-A 1 of 5)**
- Update text in the *BARD1* Breast Cancer Risk and Management cell from: Potential increase in breast cancer risk, with insufficient evidence for management recommendations. To: Increased risk of breast cancer; Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40y; RRM: Evidence insufficient, manage based on family history.

**GENE-4 (Addressed during 2020 update)**
- Update text in the *RAD51D* Breast Cancer Risk and Management cell from: Unknown or insufficient evidence for breast cancer risk. To: Potential increase in breast cancer risk, with insufficient evidence for management recommendations.

**FDA Clearance:** N/A

**Rationale:** Recent publications have shown breast cancer odds ratios of approximately 2-fold or greater, including two studies that have been published since the release date of the last guidelines update.

Previously, we reported a 2.16-fold (95%CI 1.31-3.63) increase in breast cancer risk in *BARD1* carriers based on a comparison of a cohort of 28536 breast cancer patients who received multigene panel testing and ExAc public reference controls¹. In an update to these data consisting of a larger sample of cases (89225 breast cancer patients) and improved quality amongst control alleles (gnomAD), we again observed a 2-fold increase in breast cancer risk with tighter confidence intervals (2.09; 95%CI 1.49-2.96). A similar risk was observed for *RAD51D* carriers, in which an OR of 3.07 (95% CI 1.21-7.88) was reported in 2017 and an OR of 2.09 (95% CI 1.20-3.72) was reported in 2019. These trends demonstrate the importance of study size in clarifying the true nature of risk for these exceedingly rare alterations.

In addition, a study focusing on triple negative breast cancer (TNBC) cases found dramatically increased risk associated with *BARD1* and *RAD51D*². Odds ratios ranged from 6.97 to 11.62
for TNBC in RAD51D carriers and 4.35 to 5.92 in BARD1 carriers, depending on the sample group (Ambry Genetics clinical testing cohort or consortium of TNBC cases from hospital-based studies). When the OR was applied to age-adjusted breast cancer incidence from SEER statistics, lifetime risks were calculated to be 5% for TNBC and 26% for overall breast cancer in RAD51D carriers, and 7% for TNBC and 21% for overall cancer in BARD1 carriers (compared to 1.8% lifetime TNBC risk in the general population). A 20% lifetime risk threshold has been used to categorize women at high risk for breast cancer and eligible for enhanced screening. Thus, increased surveillance would be warranted for BARD1 and RAD51D carriers, especially when considering the high contribution of TNBC to their overall breast cancer risk and the utility of breast MRI in screening for TNBC4.

Another recent study provides additional evidence for BARD1 as a breast cancer susceptibility gene. A retrospective cohort study of 4469 familial breast cancer cases from the German Consortium for HBOC and 37265 controls found an OR of 5.4 (95% CI 3.2-9.0) for breast cancer5. The impact was even higher in individuals with breast cancer diagnosed under age 50y (OR 7.4; 95% CI 4.3-13.0) and under 40y (OR 12.0; 95% CI 5.8-25.1). Authors note that their study sample, which was selected for positive family history and stratified by age of diagnosis, may better represent individuals in high risk clinical setting than samples that are unselected or population-based.

In conclusion, studies have shown that the magnitude of increased risk among BARD1 and RAD51D carriers is similar to that in other groups eligible for heightened surveillance, such as ATM/CHEK2 carriers and individuals with elevated risk based on personal and family history. Data has likely been difficult to accumulate to this point due to the rarity of these mutations rather than the degree of impact on cancer risk. Based on the evidence presented here, please consider adjusting the breast cancer risk category for BARD1 and RAD51D accordingly.

Citations:


