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NCCN Guidelines Panel*:* Genetic/Familial High Risk Assessment: Breast and Ovarian

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 controls[1]. 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*[3]. 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 TNBC[4].

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 cancer[5]. 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:

1) Couch FJ, Shimelis H, Hu C, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol*. 2017;3(9):1190-1196.

2) LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: Evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2019 Aug 13. doi: 10.1038/s41436-019-0633-8. [Epub ahead of print]

3) Shimelis H, LaDuca H, Hu C et al. Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. *J Natl Cancer Inst.* 2018 Aug 1;110(8):855-862. doi: 10.1093/jnci/djy106.

4) Podo F, Santoro F, Di Leo G, et al. Triple-negative versus non-triple-negative breast cancers in high-risk women: Phenotype features and survival from the HIBCRIT-1 MRI-Including Screening Study. *Clin Cancer Res.* 2016;22(4):895–904.

5) Weber-Lassalle N, Borde J, Weber-Lassalle K et al. Germline loss-of-function variants in the *BARD1* gene are associated with early-onset familial breast cancer but not ovarian cancer. *Breast Cancer Res*. 2019 Apr 29;21(1):55. doi: 10.1186/s13058-019-1137-9.