Submitted by: Chief Medical Officer
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NCCN Guidelines Panel: Genetic/Familial High Risk Assessment: Breast and Ovarian

Specific Changes:
On page BRCA-1:

1-Add text to bullet at bottom of first column "**Personal history of ovarian carcinoma**" so it reads, "**Personal history of ovarian carcinoma (this criteria warrants *BRIP1, RAD51C, RAD51D* testing)**"

2-Add additional text to footnote k that says **"If the patient has a family history of ovarian cancer, add *BRIP1, RAD51C, RAD51D* to the testing."**

FDA Clearance: Not applicable

Rationale:
With the advent of panel testing, other genes with risk for breast and ovarian cancer are regularly included along with testing of *BRCA1/2* and many of these genes are noted on page GENE-2 to GENE-4 but there should be higher visibility in the testing criteria for the subset of those genes with risk reducing implications. Since current NCCN guidelines (Genetic/Familial High Risk Assessment: Breast and Ovarian, GENE-2 and GENE-4) support offering patients risk reducing oophorectomy for patients with *RAD51C, RAD51D* and *BRIP1* pathogenic variants, all patient with personal or family history of ovarian cancer should be offered testing for these genes in addition to *BRCA1/2*.

The following references are submitted in support of this proposed change:

Ramus SJ, et al. Germline Mutations in the *BRIP1*, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J Natl Cancer Inst. 2015 107.

Song H, et al. Contribution of Germline Mutations in the RAD51B, *RAD51C*, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015 10:2901-7.

Norquist BM et al. Inherited Mutations in Women with Ovarian Carcinoma. JAMA Oncol. 2016 2(4): 482–490.

Lilyquist J et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. 2017 Nov

Weber-Lassalle N et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. 2018 Jan 24.

Sincerely,

Johnathan Lancaster, MD, PhD
Chief Medical Officer
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