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

Specific Changes: Provide specific testing criteria, as well as management recommendations, for *PALB2* analogous to the testing criteria and recommendations provided for *BRCA1/2*, PHTS, LFS, and the other genes/syndromes addressed in the guidelines.

FDA Clearance: Not applicable.

Rationale: Multiple studies have demonstrated that the female breast cancer risk associated with pathogenic variants in *PALB2* is similar to that for *BRCA2*, and this level of risk is high enough to justify consideration of breast cancer risk reduction measures similar to the recommendations for women with pathogenic variants detected in *BRCA1/2*. Depending on the study population and mutation detection strategy utilized, 0.4% to 4.5% of women ascertained for *BRCA1/2* testing have been found to carry pathogenic variants in *PALB2*, demonstrating that this gene is a significant contributor to hereditary female breast cancer risk, as well as pancreatic cancer, and possibly male breast cancer and ovarian cancer.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Antoniou AC et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med 2014 371(6):497–506. PMID: 25099575

Casadei S, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011 71:2222-9. PMID: 21285249.

Damiola F, et al. Mutation analysis of PALB2 gene in French breast cancer families. Breast Cancer Res Treat. 2015 154:463-71. PubMed PMID: 26564480. (See table S4 in Supplementary Materials for review of studies.)

Haanpää M, et al. Evaluation of the need for routine clinical testing of PALB2 c.1592delT mutation in BRCA negative Northern Finnish breast cancer families. BMC Med Genet. 2013 14:82. PMID: 23941127.

Lerner-Ellis J, et al. A high frequency of PALB2 mutations in Jamaican patients with breast cancer. Breast Cancer Res Treat. 2017 162:591-596. PMID: 28194609.

Rahman N, et al. Breast Cancer Susceptibility Collaboration (UK). PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. 2007 39:165-7. PMID: 17200668.

Southey MC, et al. A PALB2 mutation associated with high risk of breast cancer. Breast Cancer Res. 2010 12:R109 PMID: 21182766.

Sincerely,

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