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

Specific Changes:

1) On GENE-1, replace 2nd bullet with "As many patients have phenotypes that overlap more than one gene/syndrome, clinicians should give strong consideration to multi-gene panel testing when a patient is being assessed for genetic risk. Challenges to testing for only one gene at a time include syndrome overlap, complex or unknown family histories, and inefficiencies in sequential testing."
2) On ADDIT-2, move *RAD51C, RAD51D* and *BRIP1* to the "Intervention Warranted based on gene and/or risk level" section of the table for RRSO.

FDA Clearance: Not applicable.

Rationale: With the cost reductions that have come with next generation sequencing, the need to identify sequential differential diagnoses for genetic testing is reduced. While we currently rely on personal and family history to identify the most appropriate genetic test, this approach has limited utility among patients with a poor understanding of their cancer family history either due to misattributed paternity, poor communication among family members, ignorance of cancer types or small families. Using a broader pan-cancer panel approach can mitigate the limitations in family history collection and provide efficiency in testing for the multiple genes associated with hereditary cancer risk.

Recent papers have shown *RAD51C*, *RAD51D*, and BRIP1 to have ovarian cancer risks similar to the Lynch syndrome genes (6.5%, 7%, 8.3% and 4-24%, respectively). These studies do suggest older ages of onset, making post-menopausal oophorectomy a reasonable consideration for patients with pathogenic variants in these genes.

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.

Syndrome overlap:
Desmond A., et al. Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. *JAMA Oncol.* 2015 Oct 1;1(7):943-51.

Maxwell KN, et al. Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer. *Genet Med.* 2015 Aug;17(8):630-8.

Minion LE, et al. Hereditary predisposition to ovarian cancer, looking beyond BRCA1/BRCA2. *Gynecol Oncol.* 2015 Apr;137(1):86-92.

Tung N, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015 Jan 1;121(1):25-33.

Challenges in family history collection:

Ozanne EM, et al. Bias in the reporting of family history: implications for clinical care. *J Genet Couns.* 2012 Aug;21(4):547-56

Soegaard M, et al. Accuracy of self-reported family history of cancer in a large case-control study of ovarian cancer. *Cancer Causes Control.* 2008 Jun;19(5):469-79.

Wang C, et, al. Impact of family history assessment on communication with family members and health care providers: A report from the Family Healthware™ Impact Trial (FHITr). *Prev Med.* 2015 Aug;77:28-34

Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. *Am J Prev Med.* 2003 Feb;24(2):190-8.

Ovarian cancer risk genes:

Sopik V, Akbari MR, Narod SA. Genetic testing for RAD51C mutations: in the clinic and community. *Clin Genet.* 2015 Oct;88(4):303-12.

Ramus SJ, et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J Natl Cancer Inst.* 2015 Aug 27;107(11).

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 Sep 10;33(26):2901-7.

Rafnar T, et al. Mutations in BRIP1 confer high risk of ovarian cancer. *Nat Genet.* 2011 43:1104-7.

Meindl A, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. *Nat Genet.* 2010 42:410-4.

Loveday C, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. *Nat Genet.* 2012 44:475-6.

Pelttari LM, et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet. 2011 20:3278-88.

Sincerely,

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