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

Specific Changes: On page GENE-1, delete bullet point 7 (regarding moderate penetrance genes) and modify bullet point 2 as follows:

- The majority of patients meeting assessment and testing criteria for inherited breast and/or ovarian cancer risk have personal and/or family histories that can be explained by multiple genes or syndromes, and are therefore most appropriately tested with a multi-gene panel. A small subset of patients with a personal or family history narrowly suggestive of a single syndrome with highly distinctive features (e.g., Peutz-Jeghers Syndrome or Neurofibromatosis I) may be most appropriately managed by genetic testing for that specific syndrome.

FDA Clearance: Not applicable.

Rationale: In the past few years, multiple studies in varied populations of women at risk for hereditary breast, ovarian and other cancers have demonstrated that multi-gene/syndrome panels result in a significant increase in the identification of individuals who can benefit from substantive medical management interventions compared to testing for single genes/syndromes or family history analysis. Among women meeting current NCCN criteria for *BRCA1/2* testing, there are no criteria by which it is possible to reliably determine who is more or less likely to benefit from testing with a panel including most of the genes listed in the table on pages GENE-2 to GENE-4, and there is evidence that panel test findings, including those in moderate penetrance genes, frequently result in medical management recommendations that would not have been identified by family history analysis alone.

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.

Castéra L, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. Eur J Hum Genet. 2014 22:1305-13 PMID: 24549055.

Couch FJ, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015 33:304-11. PMID: 25452441.

Cybulski C, et al. Mutations predisposing to breast cancer in 12 candidate genes in breast cancer patients from Poland. Clin Genet. 2015 88:366-70. PMID: 25330149.

Desmond A, et al. Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. JAMA Oncol. 2015 1:943-51. PMID: 26270727.

Hermel DJ, et al. Multi-gene panel testing for hereditary cancer susceptibility in a rural Familial Cancer Program. Fam Cancer. 2017 16:159-166. PMID: 27401692.

Kapoor NS, et al. Multigene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer. Ann Surg Oncol. 2015 22:3282-8. PMID: 26219241.

Kuusisto KM, et al. Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. Breast Cancer Res. 2011 13:R20. PMID: 21356067.

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 17:630-8. PMID: 25503501.

Minion LE, et al. Hereditary predisposition to ovarian cancer, looking beyond BRCA1/BRCA2. Gynecol Oncol. 2015 137:86-92. PMID: 25622547.

Rosenthal ET, et al. Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing. J Am Coll Radiol. 2016 S1546-1440 [Epub ahead of print] PMID: 28011157.

Tung N, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. J Clin Oncol. 2016 34:1460-8. PMID: 26976419.

Yadav S, et al. Outcomes of retesting BRCA negative patients using multigene panels. Fam Cancer. 2016 Nov 22. [Epub ahead of print] PubMed PMID: 27878467.

Yorczyk A, et al. Use of panel tests in place of single gene tests in the cancer genetics clinic. Clin Genet. 2015 88:278-82. PMID: 25318351.

Yurgelun MB, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017 35:1086-1095. PMID: 28135145.

Sincerely,

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