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

Specific Changes:

1) On CRIT-1, please include a single bullet point that states: "Personal history of breast cancer diagnosed ≤ 65 y regardless of family history." Please then delete the other non-pertinent age-related bullet points throughout the testing criterion.

FDA Clearance: Not applicable.

Rationale:

Yadav et al (2020)[1] and Kurian et al (2020)[2] recently added studies supporting expansion of germline cancer predisposition testing to all women with breast cancer diagnosed ≤ 65 years regardless of other qualifiers[1, 2]. Yadav et al., identified that a substantial proportion of women with breast cancer at any age who do not qualify for testing by current NCCN criteria still have a substantial proportion of breast predisposition PVs in *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, and *TP53* (3.5%).[1] Their data particularly supports the expansion of NCCN criteria to include all women diagnosed ≤ 65 years of age which improves the sensitivity (>90% sensitivity for 9 predisposition genes and >98% sensitivity for *BRCA1* and *BRCA2)* of the selection criteria without adopting testing of all women with breast cancer. Similarly, evaluating post-menopausal women through the Women's Health Initiative cohort, Kurian et al., identified a 3.55% prevalence of PVs in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *STK11*, and *TP53*[2]. A 2.21% prevalence of *BRCA1* and *BRCA2* PVs was identified in women diagnosed with breast cancer <65. There was no age-related trend in PV prevalence in *BRCA1* or *BRCA2* (p=0.34) or with PVs in other breast cancer associated genes (p=0.54).

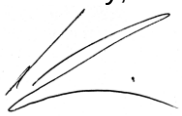
Studies have uniformly demonstrated that the traditional clinical and family history features used to select patients for hereditary cancer testing miss a substantial proportion of germline mutation carriers who could benefit from germline testing.[2-8] Knowing germline status can be used to guide both targeted therapies for breast cancer and risk reduction measures to prevent additional cancers in patients and their family members. Expanding the age of germline predisposition testing to all women diagnosed with breast cancer ≤ age 65 will clarify testing guidance and lead to enhanced detection of PV carriers.

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

1. Yadav et al. Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer. Journal of Clinical Oncology. DOI: 10.1200/JCO.19.02190 Published online March 03, 2020. PMID: 32125938.
2. Kurian AW, Bernhisel R, Larson K, Caswell-Jin JL, Shadyab AH, Ochs-Balcom H, Stefanick ML. Prevalence of Pathogenic Variants in Cancer Susceptibility Genes Among Women With Postmenopausal Breast Cancer. JAMA. 2020 Mar 10;323(10):995-997. doi: 10.1001/jama.2020.0229. PubMed PMID: 32154851.

3. Manahan ER et al. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol 26:3025-3031, 2019. PMID: 31342359.
4. Li J et al. Prevalence of *BRCA1* and *BRCA2* pathogenic variants in a large, unselected breast cancer cohort. Int J Cancer. 2019 Mar 1;144(5):1195-1204. Epub 2018 Nov 9. PMID: 30175445.
5. Knerr et al. Trends in BRCA Test Utilization in an Integrated Health System, 2005-2015 J Natl Cancer Inst. 2019 Feb 8. PMID: 30753636.
6. Beitsch PD, et al. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? J Clin Oncol. 2019;37(6):453-460. PMID: 30526229.
7. Buchanan et al. Early cancer diagnoses through BRCA1/2 screening of unselected adult biobank participants. Genet Med. 2018 Apr;20(5):554-558. PMID: 29261187.
8. Yang et al. Underdiagnosis of Hereditary Breast and Ovarian Cancer in Medicare Patients: Genetic Testing Criteria Miss the Mark. Ann Surg Oncol. 2018 Oct;25(10):2925-2931. PMID: 29998407.

Sincerely,



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