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

Specific Changes:

1) In the GENE-A table, please provide high risk breast cancer management guidelines for women with either the *ATM* c.7271T>G variant or biallelic *CHEK2* pathogenic variants (PVs).

2) On CRIT-1 & 2, please update the list of high penetrance genes at the top of the page ("This often includes *BRCA1, BRCA2, BRIP1, CDH1, PALB2, PTEN, RAD51C, RAD51D*, *TP53,* Lynch syndrome associated genes, and certain findings in *ATM* and *CHEK2*, among others").

FDA Clearance: Not applicable.

Rationale:

Regarding # 1) As already noted in the guidelines (GENE-A page 1), the *ATM* variant c.7271T>G has been shown to confer high breast cancer risk, close to that associated with pathogenic variants (PVs) in *BRCA2* and *PALB2*. A recent study presented at the San Antonio Breast Cancer Symposium, based on over 200 women with this variant, calculated an odds ratio (OR) for invasive breast cancer of 3.8 (95% CI, 2.8 – 5.1)[1]. Individuals with c.7271T>G compared to those with other *ATM* PVs also had a slightly earlier age of breast cancer onset[1]. This *ATM* variant constituted 5% of all *ATM* PVs detected in the cohort, making it more, or only slightly less prevalent than PVs in *PTEN, CDH1* and *TP53*. This epidemiology work complements previously published estimates of cancer risk for the c.7271T>G variant[3,9], as well as functional data regarding its unique dominant negative nature[2,3].

In terms of biallelic *CHEK2* PVs, a recently published study that included a sample of 42 women with biallelic *CHEK2* PVs calculated an invasive breast cancer OR of 8.7 (95% CI, 3.7 – 20.5), confirming previous findings of high breast cancer risk suggested by smaller studies[4]. Women with *CHEK2* biallelic PVs were almost 3 times more likely to have been diagnosed ≤50 than those with monoallelic findings[4]. A trend towards younger ages of diagnosis was also found in previous studies[5, 6]. Biallelic findings in *CHEK2* are much less common than monoallelic findings, but not much less common that PVs in *PTEN* (0.026% in high risk cohorts)[7,8].

As above, certain scenarios in both genes convey a high risk for breast cancer at or above *BRCA2* or *PALB2* PV lifetime breast cancer risks. Therefore, the above scenarios could include management guidelines at least similar to *PALB2*, including screening by annual mammogram with consideration of tomosynthesis and breast MRI with contrast starting at age 30-35 or consideration of risk-reducing mastectomy.

Regarding #2) Since biallelic *CHEK2* PVs and the *ATM* c.7271T>G variant are associated with breast cancer risks close to, or above those for *PALB2* or *BRCA2* (other genes considered high penetrance), it is clinically important to prominently highlight these scenarios to promote appropriate uptake by the genetics community/ health systems beyond what is realized by their mention in table GENE-A alone[1,4-6,9]. The same rationale would apply to other genes with NCCN surgical risk reduction consideration guidelines: such as the surgical gynecologic management implications with PVs in *BRIP1*, *RAD51C*, *RAD51D*, and the Lynch syndrome associated genes.

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

1. Hall et al. Cancer risks associated with pathogenic variants in the ataxia telangeictasia mutated (*ATM*) gene. San Antonio Breast Cancer Symposium 2019. (Manuscript in preparation).
2. Waddell N, et al. Characterization of the breast cancer associated *ATM* 7271T>G (V2424G) mutation by gene expression profiling. Genes Chromosomes Cancer. 2006 Dec;45(12):1169-81. PMID: 17001622.
3. Chenevix-Trench G, et al. Dominant negative *ATM* mutations in breast cancer families. J Natl Cancer Inst. 2002 Feb 6;94(3):205-15. PMID: 11830610.
4. Rainville I, et al. High risk of breast cancer in women with biallelic pathogenic variants in *CHEK2*. Breast Cancer Res Treat. 2020 Jan 28. [Epub ahead of print] PMID: 31993860.
5. Adank MA, et al. *CHEK2**1100delC homozygosity is associated with a high breast cancer risk in women. J Med Genet. 2011 Dec;48(12):860-3. Epub 2011 Nov 5. PMID: 22058428.
6. Huijts PE, et al. *CHEK2**1100delC homozygosity in the Netherlands--prevalence and risk of breast and lung cancer. Eur J Hum Genet. 2014 Jan;22(1):46-51. 5. Epub 2013 May 8. PMID: 23652375.
7. Rosenthal ET, et al. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. Cancer Genet. 2017 Dec;218-219:58-68. Epub 2017 Sep 25. PMID:29153097.
8. Kurian AW, et al, Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precision Oncology 2017 :1, 1-12.
9. Goldgar DE, et al. Rare variants in the *ATM* gene and risk of breast cancer. Breast Cancer Res. 2011 Jul 25;13(4): R73. PMID: 21787400.

Sincerely,

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