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NCCN Guidelines Panel: Breast Cancer Risk Reduction

Specific Changes:
1) On Page BRISK-3 and BRISK-3A, remove footnote "o" which states "There are no validated studies to support the use of polygenic risk scores in clinical settings".
2) Add information for riskScore™ (a prospectively validated risk assessment tool that includes PRS, family history, and clinical factors) to BRISK-C as below:

| | **Description** | **Factors Included** | **Benefits** | **Limitations** |
|---|---|---|---|---|
| **riskScore** | • Prospectively validated model available through Myriad Genetics that estimates breast cancer risk in women, personally unaffected by breast cancer, combining a polygenic risk score (PRS) with clinical and family history information<br>• Provides 5-year and remaining lifetime risk estimates | •86 SNP PRS<br>•Hereditary genetic test results (i.e., *BRCA1* status)<br>•All factors included in Tyrer-Cuzick (IBIS) version 7.02 | •Can be used in women <age 85<br>•Provides a precision risk estimate by combining PRS with personal, clinical, and family history information | •Currently available for women of solely European ancestry<br>•Not available for women with a personal history of breast cancer, hyperplasia, or LCIS<br>• Currently unavailable for women who test positive for a breast cancer associated gene mutation (I.e., *CHEK2*) |

FDA Clearance: Not applicable

Rationale:

In addition to Mendelian breast cancer susceptibility gene risk (i.e., due to *BRCA1*, *BRCA2*, etc.), polygenic risk scores (PRS) has been reported to account for an additional 20% of familial breast cancer[1-8]. PRS now serves as an important factor to include when considering clinical breast cancer risk estimation in addition to standard breast cancer susceptibility genetic testing and family history-based algorithm modules (i.e., BRCAPRO, Claus, Tyrer-Cuzick)[4,8].

Myriad Genetics, Inc. has validated riskScore, a risk assessment tool that includes PRS, family history, and clinical factors[9,10]. Hughes, et al, (2020) utilized data from over 178,000 prospectively identified individuals in the development and validation of the PRS component of the tool[4]. Subsequently, it was shown that the accuracy of risk estimates is further improved when the PRS is combined with the established Tyrer-Cuzick model (V7.02) carefully incorporating adjustments for overlap between risk captured by the PRS and individual Tyrer-Cuzick

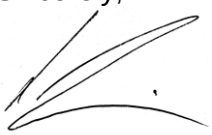
variables (riskScore) [9,10]. Post-validation application of riskScore in a large prospectively collected clinical cohort of 30,891 individuals identified riskScore to be more precise in risk estimation than Tyrer-Cuzick alone[10]. In fact, 8.4% (n=2616) of patients who were low risk by Tyrer-Cuzick were high risk according to riskScore, and 8.4% (2,589) of patients who were high risk by Tyrer-Cuzick were low risk according to riskScore (*manuscript under review*)[10]. This has important implications for clinical care.

Citations:

The following articles are submitted in support of these requested changes. We would like to acknowledge the contributions of NCCN panel member(s) who are also co-authors or co-contributors of some of these publications.


1. Mavaddat N et al., Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst.* 2015;107(5). PMID: 25855707.
2. Mavaddat N et al., Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet.* 2019 Jan 3;104(1):21-34. PMID: 30554720.
3. Michailidou K et al., Association analysis identifies 65 new breast cancer risk loci. *Nature*. 2017 Nov 2;551(7678):92-94. PMID: 29059683.
4. Hughes E, et al., Development and validation of a clinical polygenic risk score to predict breast cancer risk. *JCO Precision Oncology*. 2020:4, 585-592.
5. Khera AV et al., Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet.* 2018 Sep;50(9):1219-1224. PMID: 30104762.
6. Lambert SA et al., Towards clinical utility of polygenic risk scores. *Hum Mol Gene*t. 2019 Nov 21;28(R2):R133-R142. PMID: 31363735.
7. Yanes T et al., Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field. *Breast Cancer Res*. 2020 Feb 17;22(1):21. PMID: 32066492.
8. Saslow D et al., American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. American Cancer Society Breast Cancer Advisory Group. CA Cancer J Clin. 2007 Mar-Apr;57(2):75-89. PMID: 17392385.
9. Hughes E, et al., Development and validation of a combined residual risk score to predict breast cancer risk in unaffected women negative for mutations on a multi-gene hereditary cancer panel. San Antonio will Breast Cancer Symposium annual meeting, 2017.
10. Baron P, et al., A polygenic risk score can refine breast cancer risk in unaffected women referred for hereditary cancer testing, American Society of Breast Surgeons annual meeting, poster 2018.


Sincerely,

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