Submitted by:	Senior VP Medical Affairs, Oncology
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Date of request:	March 16, 2021
NCCN Guidelines Panel:	Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic

Dear NCCN panel members,

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request your review of the following proposed modifications of the High-Risk Assessment: Breast, Ovarian and Prostate guideline, version 2.2021.

Specific changes (noted with strikethroughs and capitalization):

On EVAL-A 3 of 6, please change the last bullet regarding PRS to "There are ~~significant~~ limitations (I.E., VALIDATED ONLY IN SELECT ANCESTRIES, LACK OF RANDOMIZED CONTROL DATA) in the interpretation of polygenic risk scores (PRSs). ~~PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial.~~ LIMIT PRS USE TO PATIENT APPROPRIATE VALIDATED MODELS THAT INCORPORATE OTHER CLINCAL FACTORS AND FAMILY HISTORY. See Discussion."

On MS-31, at the end of the "Probability Models section" please add: Validated clinical and family history-based models that incorporate polygenic risk scores (PRS) are emerging [Hughes et al., 2020; Mavaddat et al., 2019; Rosner et al., 2020]. Scores at or above a remaining lifetime risk of 20% should similarly be considered for tailored management.

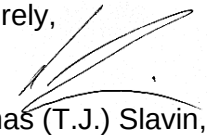
FDA Clearance: Not applicable.

Rationale: Recently, multiple PRS models that incorporate clinical and family history variables have been developed and validated (Nurse's Health Study and Mayo Mammography Health Study, Rosner et al., 2020; UK Biobank, Mavaddat et al., 2019; Myriad's testing population and a prospectively acquired imaging population, Hughes et al., 2021). Collectively these publications demonstrate the value of PRS as a component in breast cancer risk stratification for women [Hughes et al., 2021; Mavaddat et al., 2019; Rosner et al., 2020]. Furthermore, Hughes, et al., 2021 identified that 18.5% of individuals (almost 1 in 5) had discordant remaining lifetime risk with Tyrer-Cuzick alone compared to Tyrer-Cuzick plus PRS. When PRS was incorporated into the model, 8% and 10.5% of individuals in the clinical performance cohort had their remaining lifetime risk increased or decreased surrounding a 20% threshold, respectively [Hughes et al., 2021]. Models that include PRS are increasingly being incorporated into medical decision-making to further tailor the shared decision-making process between a woman and her clinician.

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

- Rosner BA, Tamimi RM, Kraft P, Gao C, Mu Y, Scott CG, Winham SJ, Vachon CM, Colditz GA.. Simplified breast risk tool integrating questionnaire risk factors, mammographic density, and polygenic risk score: development and validation. Cancer Epidemiol Biomarkers Prev. 2020 Dec 4. PMID: 33277321
- Mavaddat N, Michailidou K, Dennis J., 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 PMCID: PMC6323553
- Hughes E, Tshiaba P, Wagner S., et al., Integrating Clinical and Polygenic Factors to Predict Breast Cancer Risk in Women Undergoing Genetic Testing. JCO PO Jan 2021. E pub ahead of print https://ascopubs.org/doi/full/10.1200/PO.20.00246. DOI: 10.1200/PO.20.00246

Sincerely,



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