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

Specific Changes:

On page CRIT-1, please modify elements of the prostate cancer testing criteria included on criteria 3 "Personal history of cancer" as follows:

- Bullet 1, sub-bullet 2 "Diagnosed at age 46-50 y with:"
  - Remove "high-grade (Gleason Score ≥7) or intraductal" requirement from prostate cancer
- Bullet 4: Modify "Metastatic or intraductal prostate cancer at any age" to:
  - Metastatic, NCCN risk group High or Very High prostate cancer, or intraductal/cribriform prostate cancer at any age.*
  - Add footnote: *See the relevant NCCN treatment guidelines (NCCN Guidelines for Prostate Cancer) for further details.
- Bullet 5: Modify criteria "High-grade (Gleason Score ≥7) prostate cancer with:" to "Prostate cancer at any age with:" (Note: Sub-bullets remain the same)

On page CRIT-2, modify as follows:

- Under "Testing may be considered in the following scenarios" add another scenario:
  - For men with prostate cancer considering active surveillance or watchful waiting, testing regardless of family history may be considered as germline mutations status may impact management decisions (see NCCN Guidelines for Prostate Cancer treatment).
- Under "There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios" modify scenario 2 as follows:
  - "Men diagnosed with non-intraductal/cribriform histology in the NCCN risk groups of very-low, low, and intermediate prostate cancer and no close relative with breast, ovarian, pancreatic or prostate cancer."

Throughout the guideline

- Please add cribriform after intraductal throughout the criteria.

FDA Clearance: Not applicable

Rationale:

The NCCN Prostate Cancer Guidelines state that multiple clinicopathologic features should be utilized for risk stratification and management in newly diagnosed localized prostate cancer.[1] In the guidelines, there are now six risk groups that include Gleason Grade Group (which separates Gleason Score 7 into two different risk categories), PSA, clinical T-stage and percent positive cores (see PROS-2). More recently, molecular/biomarker analysis of the tumor as well as imaging studies are used to improve risk stratification (see PROS-2).[1] Specifically, studies have shown that molecular assays performed on prostate biopsy provide prognostic information independent of NCCN or CAPRA risk groups (see PROS-

7A).[1] There is also now an increasing role for germline genetic testing in the risk stratification, staging and management of men with prostate cancer and the NCCN Prostate Cancer guideline recommends testing based on family history, histology and risk groups (see PROS-2, MS-5).[1]

Multiple studies and the NCCN Guidelines for Prostate Cancer Version 1 2020 note that men with DNA-repair gene germline mutations are more likely to present with metastatic prostate cancer and high grade prostate cancer.[1-3] Family history alone may not be an adequate predictor of germline status using current NCCN guidelines.[4,6] Germline testing for men with metastatic, regional, high risk or very high risk prostate cancer, regardless of family history, is consistent with the current NCCN Prostate Cancer Guidelines (see PROS-2, PROS-8).[1] In addition, the presence of cribriform histology as well as intraductal histology has been added as criteria for germline testing (see PROS-1). Removing the personal history of "High-grade (Gleason Score $\geq$7) prostate cancer" requirement will harmonize both the NCCN Prostate Cancer and the NCCN Genetic/High risk assessment: Breast, Ovarian and Pancreatic guidelines. Removing "high-grade (Gleason Score $\geq$7) or intraductal" from the family history requirement will help in testing scenarios where detailed information regarding a relative's prostate cancer pathology is unknown. Finally, once identified as mutation carriers, men with prostate cancer may be eligible for targeted therapies (e.g., PARP inhibitor trials, earlier use of platinum-based chemotherapies).[1,7.8]

In addition, men with germline mutations in certain genes (e.g., *BRCA1* or *BRCA2*) are more likely to progress to metastatic disease and/or death at a faster rate, even when the prostate cancer is localized at diagnosis.[2,3] While on active surveillance, they are also more likely to upgrade on repeat biopsy.[9] Knowledge of the germline status of men with prostate cancer may alter the management discussion in newly diagnosed patients, including the option of active surveillance in men with localized prostate cancer. As noted in the NCCN Prostate Cancer Guidelines, "this information should be discussed with such men if they are considering active surveillance."(see MS-3)[1]

The following references support this proposed change:

1. Mohler J et al. NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines Version 1.2020 Prostate Cancer.
2. Castro E et al. Germline BRCA Mutations Are Associated With Higher Risk of Nodal Involvement, Distant Metastasis, and Poor Survival Outcomes in Prostate Cancer. *Journal of Clinical Oncology*. 2013;31(14):1748-1757.
3. Na R et al. Germline Mutations in ATM and BRCA1/2 Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. *European Urology*. 2017;71(5):740-747.
4. Pritchard C et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *New England Journal of Medicine*. 2016;375(5):443-453.
5. Giri V et al. Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. *Journal of Clinical Oncology*. 2018;36(4):414-424.
6. Nicolosi P et al. Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. *JAMA Oncology*. 2019;5(4):523-528.
7. Pomerantz M et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. *Cancer*. 2017;123(18):3532-3539.
8. Mateo J et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *New England Journal of Medicine*. 2015;373(18):1697-1708.
9. Carter HB et al. Germline Mutations in ATM and BRCA1/2 Are Associated with Grade Reclassification in Men on Active Surveillance for Prostate Cancer. *European Urology*. 2019;75(5):743-749.

Sincerely,

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