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

Specific Changes:

Modify elements of the prostate cancer testing criteria included on page BRCA-1 to align with recommendations in the NCCN Prostate Cancer Treatment guidelines. Specific suggestions are:

Modify the 3rd bullet point on the 2nd column as follows and add an additional footnote to:

- Personal history of metastatic prostate cancer^g or NCCN risk group High or Very High prostate cancer*.
- Footnote: *See the relevant NCCN treatment guidelines (NCCN Guidelines for Prostate Cancer) for further details.

Modify the 4th bullet on the 2nd column as follows and add an additional footnote to:

- Personal history of prostate cancer at any age with* (Note: Sub-bullets remain the same)
- Footnote: *For men considering active surveillance or watchful waiting, consider germline testing regardless of family history as germline mutations status may impact management decisions (see NCCN Guidelines for Prostate Cancer treatment).

Modify footnote g to include prostate cancer specific mortality as a criteria for metastatic prostate cancer.

- Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis, regional bed or nodes or prostate cancer-specific mortality. It is not a biochemical recurrence.
- Note: Patients may not be aware of the specific cancer-related details of their male relatives who had prostate cancer, especially documentation of metastasis. Prostate cancer specific mortality should be a surrogate for metastatic disease for family history purposes.

FDA Clearance: Not applicable

Rationale:

Multiple studies and the NCCN Guidelines for Prostate Cancer Version 1 2019 note that men with DNA-repair gene germline mutations are more likely to present with metastatic prostate cancer and high grade prostate cancer.¹⁻⁴ Family history alone may not be an adequate

predictor of germline status using current NCCN guidelines.^{3,6} 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.⁵ 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).^{5,7,8}

In addition, men with germline mutations in certain genes (e.g., *BRCA1*, *BRCA2* and *ATM*) are more likely to progress to metastatic disease and/or death at a faster rate, even when the prostate cancer is localized at diagnosis.^{1,2} 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.”⁵

The following references support this proposed change:

1. 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.
2. 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.
3. 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.
4. 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.
5. Mohler J et al. NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines Version 1.2019 Prostate Cancer.
6. Nicolosi P et al. Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. *JAMA Oncology*. 2019; Feb 7:10.1001/jamaoncol.2018.6760.
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*. 2018;Oct 8. 10.1016/j.eururo.2018.09.021

Sincerely,



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