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Date of Request: April 13, 2021
NCCN Guidelines Panel: Prostate Cancer Treatment

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request that the NCCN Panel review the enclosed request for modifications within the Prostate Cancer guideline, Version 2.2021 – February 17, 2021.

Specific changes:

On PROS-2, In "Germline Testing" column under Very low-, Low-, and Favorable and Unfavorable Intermediate-Risk Groups

- "*BRCA2* recommended, consider *BRCA1* and *ATM*. Larger panel testing recommended if family history positive See PROS-1"

On PROS-3, PROS-4, and PROS-5 under Active Surveillance, in the algorithm add the following bullet point and add a footnote:

- "*BRCA2* recommended, consider *ATM* germline testing to inform decision-making for Active Surveillance". Please add reference footnote: See Principles of Genetics (PROS-B)

On PROS-B, add a bullet stating:

- Recommend *BRCA2*, consider ATM germline testing to inform decision-making for Active Surveillance. Data suggest that patients with prostate cancer who have *BRCA2*, and possibly ATM, germline mutation(s) have a more aggressive phenotype associated with increased risk of progression on local therapy and decreased overall survival (OS). This information should be discussed with all men if they are considering active surveillance.

On PROS-B, bullet 2, modify elements of the germline testing criteria to align with NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines. Specific suggestions for the second bullet include:

- Personal history of male breast cancer at any age or colorectal cancer ≤50 y
- A positive family history of cancer with any one of the following
    - Brother, father, or multiple family members diagnosed with prostate cancer <60 y or who died from prostate cancer
        - Delete ~~(But not clinically localized Grade Group 1)~~
    - ≥ 1 close blood relative* with ovarian, pancreatic, metastatic prostate cancer, or male breast cancer at any age or female breast, colorectal; or endometrial cancer ≤50 y,
    - ≥ 2 close blood relative* breast, prostate (any age), colorectal, endometrial, or other Lynch syndrome cancers (bile duct, gastric, kidney, small bowel or urothelial)
        - Delete ~~(But not clinically localized Grade Group 1)~~

*close blood relative includes first-, second- and third-degree relatives

Rationale:

The existing published data for germline mutations in men with prostate cancer[1,2] indicate that germline mutations in *BRCA2* (and perhaps *BRCA1* and *ATM*) are associated with disease progression, earlier age at death, and shorter survival time.[3-7] More recently, data suggests patients with *BRCA1/2* mutations are also more likely to have pathologic upgrade on repeat biopsy while on active surveillance[3] and experience worse outcomes when treated with conventional therapy.[4,] These patients are at high risk for adverse outcomes even if their clinicopathologic features suggest otherwise. This important information should be reflected in the initial risk stratification and in the management plan. The addition of the recommendation for *BRCA2* (consideration for *ATM*) germline testing to inform decision making for Active Surveillance would also align these guidelines with the recommendations from the 2019 Philadelphia Prostate Cancer Consensus Meeting[5].

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic[5] and the NCCN Genetic/Familial High-Risk Assessment: Colorectal[6] have detailed the family cancer history features most relevant to identifying individuals appropriate for genetic testing. Removing the Gleason Grade Group 1 exclusion will help where detailed information regarding a relative's prostate cancer pathology is unknown and will also align these guidelines with the NCCN Genetic/Familial High-Risk Assessment: Breast Ovarian and Pancreatic.

Literature Support: the following references support the 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. 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
4. Castro E et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localized prostate cancer. *European Urology*. 2015;68:186-193.
5. Giri V et al. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol.* 2020 38:24, 2798-2811.
6. Darst BF, et al. Germline sequencing DNA repair genes in 5,545 men with aggressive and non-aggressive prostate cancer. *J Nat Can Instit*. 2020;Aug 27:132
7. Matejcic M, et al. Pathogenic Variants in cancer predisposition genes and prostate cancer risk in African Americans. *JCO Prec Onc*. 2020; 4:32-43
8. Daly M et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2020
9. Provenzale D et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2019

Sincerely,

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