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Date of Request: April 23, 2020
NCCN Guidelines Panel: Prostate Cancer Treatment

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request that the NCCN Prostate Cancer Panel review the enclosed request for modifications within the Prostate Cancer guideline, Version 1.2020 – March 16, 2020.

Specific changes:

On PROS-2, Add a 4th bullet under High and Very high Risk Groups

- Germline mutation in *BRCA1* or *BRCA2* gene

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

- "Consider mpMRI and/or prostate biopsy and/or molecular tumor analysis and/or germline testing to confirm candidacy for active surveillance"
- Footnote: See Principles of Genetics (PROS-B)

On PROS-B, add a bullet stating:

- Data suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have a more aggressive phenotype, is associated with significantly reduced survival times, 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 other NCCN guidelines.
Specific suggestions for the second bullet include:

- Personal history of male breast cancer at any age or colorectal cancer ≤50 y
- Ashkenazi Jewish ancestry
- 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
        - Remove Grade Group 1 limitation
    - ≥ 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)

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

Rationale:

The existing published data for germline mutations[1,2] indicate that germline mutations in *BRCA1/2* (and perhaps *ATM*) are associated with disease progression, earlier age at death, and shorter survival time. More recently, data suggests patients with *BRCA1/2* mutations are also more likely to upgrade on repeat biopsy while on active surveillance[3] and have 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 should be reflected in the initial risk stratification and in the management plan.

The current NCCN Prostate Cancer guideline recommends consideration of mpMRI, confirmatory biopsy and/or molecular tumor analysis to confirm candidacy for active surveillance since the standard clinicopathologic features may not truly reflect the aggressiveness of an individual patient's prostate cancer. Given the data regarding higher risk and adverse outcomes noted above, consideration of germline testing, regardless of family history, could provide additional information regarding candidacy for active surveillance.

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. Adding these features relating to prostate cancer would align all of these guidelines. Removing the Gleason Grade Group 1 limitation will help in testing scenarios where detailed information regarding a relative's prostate cancer pathology is unknown.

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. Daly M et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2020
6. Provenzale D et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2019

Sincerely,

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