Letter 1: Germline Genetic Testing and Risk Stratification:

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request that the NCCN Prostate Cancer Panel review the enclosed modification request for germline based testing presented within the Prostate Cancer guideline, Version 2.2019 – April 17, 2019.

Specific changes:

1. **Modify elements of the prostate cancer genetic testing criteria on page PROS-1 to align with recommendations in the NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian and the NCCN Genetic/Familial High Risk Assessment: Colorectal.** Specific suggestions are to modify footnote d as follows:
   - Personal or family cancer history criteria for genetic testing:
     1. Personal history of male breast cancer or colorectal cancer ≤50 y
     2. Personal history prostate cancer and close blood relative* with any one of the following
        - Brother or father diagnosed with prostate cancer <60 y or who died from prostate cancer
        - ≥ 1 Ovarian cancer, pancreatic cancer, metastatic prostate cancer, male breast cancer, female breast cancer ≤50 y, colorectal cancer ≤50 y; or endometrial cancer ≤50 y,
        - ≥2 breast, prostate (any age), colorectal, endometrial, or other Lynch syndrome cancers (bile duct, gastric, kidney, small bowel or urothelial)
        - Ashkenazi Jewish ancestry
   *close blood relative includes first, second and third degree relatives

2. **For greater clarity, modify the following criteria to PROS-1, 2nd column, top listing, last feature**
   - Metastatic, Regional, Very High or High NCCN Risk Group or presence of intraductal carcinoma on biopsy
   (Subsequent to this change, the statement on PROS-1, 3rd column, bottom listing may be deleted as clinical features are captured in 2nd column)
3. **Add a 4th bullet to PROS-2 under High and Very High Risk Groups**
   - Germline *BRCA1/2* mutation

**Rationale:**

The NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian\(^1\) and the NCCN Genetic/Familial High Risk Assessment: Colorectal Guidelines\(^2\) 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 these guidelines with the NCCN Guidelines: Prostate Cancer.

The existing published data for germline mutations\(^3,4\) 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.\(^5\) This would indicate that these patients are at high risk for adverse outcomes which should be reflected in the initial risk stratification.

**Literature Support: the following references support the proposed change:**

1. Daly M et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 3.2019
2. Provenzale D et al. NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2018

Sincerely,

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