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NCCN Guidelines Panel: Prostate Cancer Treatment

Letter 2: Germline Genetic Testing in Active Surveillance

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

Specific changes:

- 1. Modify the statement on PROS-1, 3rd column, bottom listing as follows and add an additional footnote:**
 - Statement: Recommend germline testing.^{c,e,f}
 - Footnote: Data suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have 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.
- 2. On PROS-4, PROS-5, PROS-6, under Active surveillance, in the algorithm (flow chart), add the following bullet point and footnote:**
 - Bullet point: “Recommend germline testing”
 - Footnote: “Data suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have 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.”

Rationale:

The NCCN Prostate Cancer Guidelines Version 2.2019 (April 17, 2019) has included clarification of germline testing. With respect to Specific change #1, since *BRCA1* and *BRCA2* play a central role in DNA repair by homologous recombination¹, which is the mechanism that cells use to repair double-strand breaks induced, for example, by platinum-based chemotherapeutic agents or ionizing radiation, the *BRCA* status may have prognostic implications when considering treatment options for localized prostate cancer.

Recently, Castro et al² addressed this possibility. They evaluated the response of BRCA carriers to conventional treatments for localized prostate cancer by analyzing metastasis-free survival and disease-specific survival following radical prostatectomy or external-beam radiation therapy. In their study, outcomes of 1302 patients with local or locally advanced prostate cancer, including 67 BRCA mutation carriers (18 *BRCA1* and 49 *BRCA2*), was analyzed. Radical prostatectomy was performed on 535 patients (with 35 BRCA carriers), and 767 patients received external-beam radiation (with 32 BRCA carriers). Median survival and 3-, 5-, and 10-yr survival rates were estimated using the Kaplan-Meier method. The 3-, 5-, and 10-yrs disease-specific survival rates were significantly better in the non-carrier than in the BRCA-carriers (99% v 96%, 97% v 76%, 85% v 61%, respectively; $p < 0.001$).

Furthermore, multivariate analysis confirmed BRCA mutations as an independent prognostic factor for metastasis-free survival (hazard ratio [HR]: 2.36; 95% confidence interval [CI], 1.38-4.03; $p = 0.002$) and disease-specific survival (HR: 2.17; 95% CI, 1.16-4.07; $p = 0.016$) (2). Overall, 9% of the carriers had T1 tumors, 48% had T2, and 34% had T3 compared with 26%, 39%, and 28% of non-carriers who had T1, T2, and T3 tumors, respectively ($p < 0.02$).

Differences in tumor grades was also observed between carriers and non-carriers. Specifically, 33% of BRCA carriers presented with Gleason score ≤ 6 , 31% Gleason 7, and 34% Gleason ≥ 8 compared with 50%, 34%, and 15% of non-carriers, respectively ($p < 0.001$). Nodal involvement (N1) was present in 6% of carriers versus 2% of non-carriers ($p = 0.009$). Although preliminary, the data showed that patients with BRCA mutations are high-risk for disease progression.

More recently, Na et al³ assessed whether germline mutations in *BRCA1/2* and *ATM* distinguish lethal from indolent prostate cancer, and whether they confer any effect on age at death. They performed a retrospective case study of 313 patients who died of prostate cancer and 486 patients with low-risk localized prostate cancer of European, African, and Chinese descent. Germline DNA from 799 patients was sequenced for the three genes. The results showed the following: the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal prostate cancer patients (6.07%) than localized prostate cancer (1.44%), $p = 0.0007$.

This rate also differed significantly among lethal prostate cancer patients as a function of age at death and time to death after diagnosis (3). The median survival curve by Kaplan-Meier shows a median survival of 11-yrs for mutation carriers vs. 18-yrs for non-carriers and time to death from initial diagnosis with metastatic disease of 3-yrs in mutation carriers vs. 6-yrs in non-carriers (3).

More importantly, survival analysis in the entire cohort revealed mutation carriers remained an independent predictor of lethal prostate cancer after adjusting for race and age, prostate-specific antigen, and Gleason Score at the time of diagnosis (HR = 2.13, 95% confidence interval: 1.24 – 3.66, $p = 0.004$).

Thus, the conclusion of the study is that mutation status of *BRCA1/2* and *ATM* distinguishes risk for lethal and indolent prostate cancer and is associated with earlier age at death and shorter survival time.

Since *BRCA1/2* mutation status is associated with disease progression, earlier age at death, and shorter survival time, and, more recently, patients are also more likely to upgrade on repeat biopsy while on active surveillance⁴; specific changes #1 and #2 are requested. The addition to the footnote and

algorithm (flow chart) highlights the importance of having a discussion with patients with *BRCA1/2* germline mutations who are considering active surveillance for prostate cancer.

Summary:

Given the existing published data for germline mutations, physicians have begun to incorporate these tests into routine clinical practice. Our request for the above modifications is to highlight the published data that patients with germline mutation, especially *BRCA1/2*, are of high-risk for disease. We believe that these changes will facilitate the improved patient risk stratification, earlier intervention for high risk men, and access to such testing for patients.

Literature Support: The following references support the proposed change.

1. Mateo J, Boysen G, Barbieri CE, et al: DNA repair in prostate cancer: biology and clinical implications. *Eur Urol* 71:417-425, 2017.
2. Castro E, Goh C, Leongamornlert D, et al: Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localized prostate cancer. *Eur Urol* 68:186-193, 2015.
3. Na R, Zheng SL, Han M, 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. *Eur Urol* 71:740-747, 2017.
4. Carter HB, Helfand B, Mamawala M, et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol* 75:743-749, 2018.

Sincerely,



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