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NCCN Guidelines Panel: Prostate Cancer Treatment

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request the NCCN Prostate Cancer Panel to review the enclosed data in support of adding Prolaris Post-RP to the guidelines.

Specific changes:

1. On page PROS-10, we ask that the Prolaris Post-RP test be included under "Monitoring" following "Initial definitive therapy".

   Under Monitoring:

   - PSA every 6-12 mos for 5 y, then every year
   - DRE every year, but may be omitted if PSA undetectable
   - (insert) ***Prolaris Post-RP test for risk of biochemical recurrence***

Rationale: The request to include the Prolaris Post-RP test in the algorithm is based on multiple studies demonstrating that the Prolaris cell-cycle progression score adds significantly to the prediction of biochemical recurrence in multivariate analysis across all ranges of clinical risk. Since the first mention of tumor-based molecular assays in the 2015 NCCN Prostate Cancer guidelines, additional data has been published in support of the Prolaris® test, a 46-gene RNA-expression assay that directly measures tumor cell growth characteristics to generate a cell-cycle progression (CCP) score. In multiple published studies, the CCP score proved to be an independent and powerful variable in predicting the risk of lethal prostate cancer, as determined by the clinically meaningful oncologic endpoints of prostate cancer-specific mortality, metastasis, and biochemical recurrence after radical prostatectomy. [1-10]

Cooperberg et al.[3] demonstrated that the Prolaris Post-RP test added significantly to the prediction of biochemical recurrence (BCR) in multivariate analysis. In the study, the CCP score was assessed for independent prognostic utility beyond a standard postoperative risk assessment (Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score). The authors demonstrated that Prolaris Post-RP test consistently predicted outcomes (BCR) across the ranges of clinical risk, and that the CCP score was validated to have significant prognostic accuracy after controlling for all available clinical and pathologic data, i.e., independent prognostic information after RP and stratifies beyond PSA, pathologic Gleason score, and pathological stage (surgical margin status, extracapsular extension, seminal vesicle invasion, and lymph node invasion). The hazard ratio for each unit increase in CCP score was 2.1. The authors also concluded that on the basis of its performance among men with intermediate to high-risk clinical

characteristics (CAPRA-S 3-10), the CCP score may also be helpful in selecting men for adjuvant therapy after RP and may be valuable in stratifying men for future adjuvant studies.

Other studies have demonstrated that CCP, even from an initial diagnostic biopsy, can predict BCR and metastasis following radical prostatectomy. For example,

- Bishoff et al.[5] demonstrated that CCP score was associated with BCR and metastasis and that the association with BCR remained significant after adjusting for other prognostic clinical variables.

- Tosoain et al. [8] assessed men who underwent radical prostatectomy for Gleason score ≤6 prostate cancer. CCP added significantly to the prediction of biochemical recurrence in multivariate analysis, both in the overall cohort and in the subset of men meeting NCCN low risk criteria.

- Koch et al.[7] evaluated CCP score discrimination between systemic disease and local recurrence in patients with biochemical recurrence after radical prostatectomy. The CCP score was found to be a significant predictor of systemic disease (p=0.0060).

- Finally, a second validation study demonstrating that Prolaris accurately predicts the 10-year risk of prostate cancer metastasis after definitive therapy was recently presented at the American Urological Association 2017 annual meeting.[10] Among 767 men with localized prostate cancer (40% of whom were African American), CCP was a significant predictor of metastatic disease following initial definitive therapy such as RP or EBRT (HR/unit score=2.76;p=$2.8x10^{-11}$), with no difference in predictive performance between races or treatment groups.

Because of the above data, we request that the use of the Prolaris Post-RP test be reflected in the initial management algorithm as part of monitoring following initial definitive therapy. We believe that this change will allow for improved stratification for monitoring recurrence, especially with regards to PSA frequency.

Literature support: A list of all publications supporting the use of Prolaris to predict biochemical recurrence, prostate cancer-specific mortality, and metastasis is provided below.

Sincerely,

Todd Cohen, MD.
VP of Medical Affairs, Urology
Myriad Genetic Laboratories, Inc.

Johnathan Lancaster, MD, PhD.
Chief Medical Officer
Myriad Genetic Laboratories, Inc.

References:

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3. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol*. 2013 Apr 10;31(11):1428-34.
4. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013 Aug 1;86(5):848-53.
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6. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2015; 113:382–9.
7. Koch MO, Cho JS, Kaimakliotis HZ, et al. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomark. 2016 Jun 7;17(1):83-8.
8. Tosoian JJ, Chappidi MR, Bishoff JT, et al: Prognostic utility of biopsy-derived cell cycle progression score in patients with National Comprehensive Cancer Network low-risk prostate cancer undergoing radical prostatectomy: implications for treatment guidance. *BJU Int* 2017; 120:808-4.
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10. Bardot S, Reid J, Latsis S, et al: Evaluating the prognostic utility of the CCP score for predicting prostate cancer aggressiveness in African American men. *J Urol* 194, issue 4, e346 (abstract MP28-19).