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NCCN Guidelines Panel:	Prostate Cancer Treatment

Molecular and biomarker analysis of tumor:

On behalf of Myriad Genetic Laboratories, Inc., we respectfully request that the NCCN Prostate Cancer Panel review the enclosed request for modifications to include Prolaris in the Unfavorable Intermediate and High Risk category to provide better risk-stratification within the Prostate Cancer guideline, Version 2.2019 – April 17, 2019.

Specific changes:

1. On PROS-2, under the column "Molecular and biomarker analysis of tumor," change "Not routinely recommended" in the Unfavorable Intermediate and High box to *"Consider if life expectancy ≥ 10 y." Add footnote: "Consider Prolaris for better risk-stratification."*

2. On page PROS-3, Footnote M, change to: "*Consider the use of tumor-based molecular assays (Decipher, Oncotype DX Prostate, Prolaris, ProMark) in men with low or favorable-intermediate risk disease with life expectancy of ≥10 y.* Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN or CAPRA risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy."

3. On page MS-9, under Tumor Multigene Molecular Testing, please modify the following sentence: "Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that (change to) the *consideration of the use of tumor-based molecular assays such as Decipher, Oncotype Dx Prostate, Prolaris, or ProMark in men with clinically localized disease if life expectancy ≥ 10 y is warranted during initial risk stratification.*"

Rationale:

With respect to Specific change #1, intermediate and high-risk disease are heterogeneous disease states of localized prostate cancer with a significant range of possible treatment intensities. Because of such heterogeneity of disease states, molecular testing is currently being used to better stratify risk for men with localized Unfavorable Intermediate or High-Risk prostate cancer, who have a life expectancy of at least 10 years, so that treatment intensities may be more appropriately matched to a patient's risk of progression.

Word changes are requested for Specific change #2 and #3 so that there is consistency with statements in the column titled "Molecular and biomarker analysis of tumor" on page PROS-2, where it states "Consider if life expectancy ≥ 10 y." Such consistency is important for providers and clinicians.
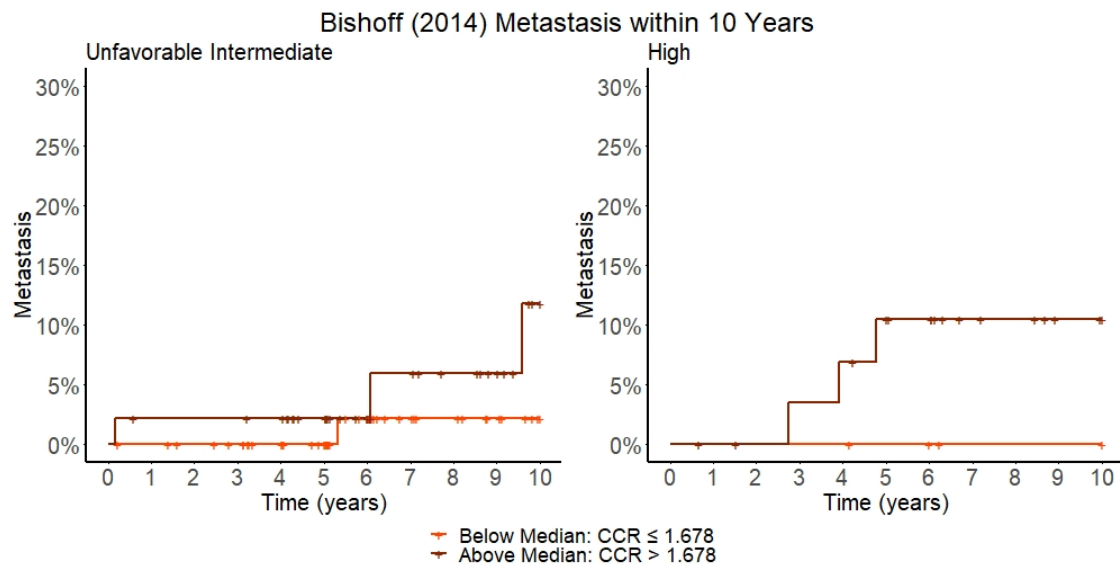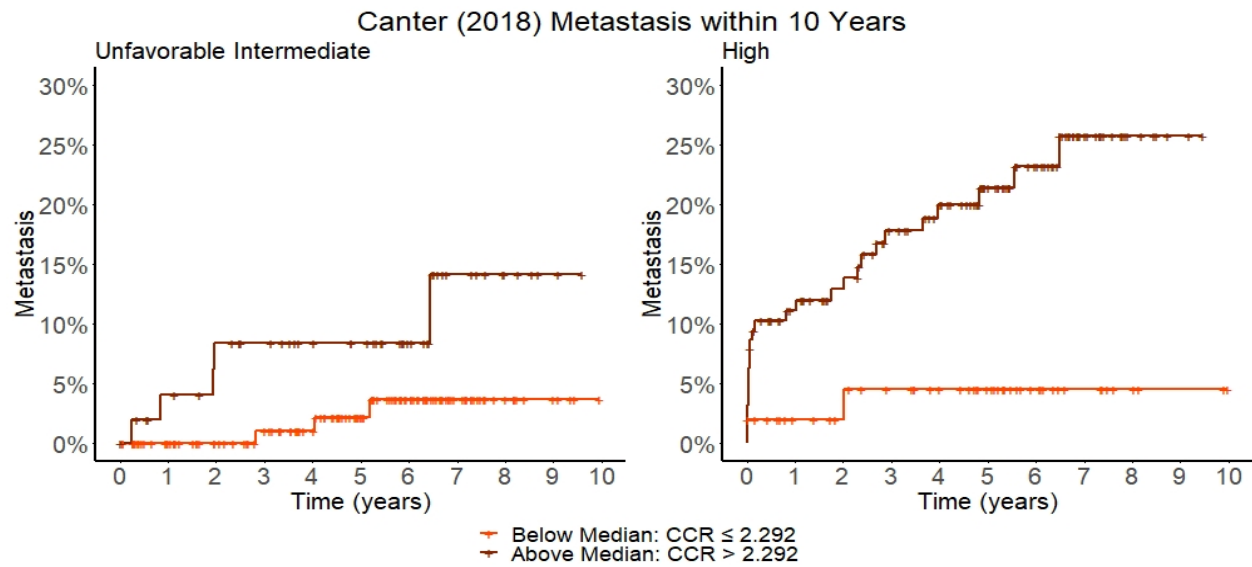
Since the first mention of tumor-based molecular assays in the 2015 NCCN Prostate Cancer guidelines, data have been published in support of the Prolaris® test, a 46-gene RNA-expression assay that directly measures tumor cell growth characteristics to generate a cell-cycle progression (CCP) score. In multiple published studies, the CCP score proved to be an independent and powerful variable for predicting the risk of lethal prostate cancer across all risk categories, including unfavorable intermediate and high risk, as determined by the clinically meaningful oncologic endpoints of prostate cancer-specific mortality (PCM), metastasis, and biochemical recurrence after radical prostatectomy.[1-10]

We analyzed cohorts from two publications, Bishoff et al[2] and Canter et al[3], that included 659 patients at intermediate and high-risk categories. In this analysis, the CCP score was found **to have a significant Hazard Ratio** for progression to metastases in 10-years after adjusting for CAPRA (see table below). This table also shows improvement in c-index from a CAPRA only model to a CCR-based model that incorporates both CCP score and CAPRA.
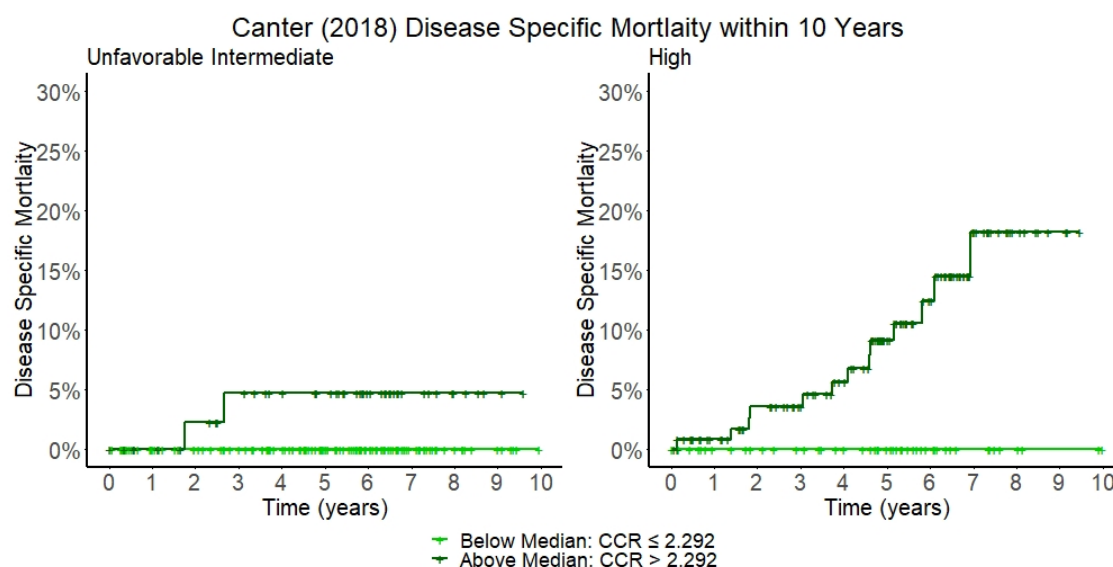
Cohort (events/n)	Bivariate CCP HR (95% HR) p-value	CAPRA c-index (%)	CCP c-index (%)	CCR c-index (%)
Canter (37/444)	2.09 (1.54, 2.82) p = 8.4×10^{-6}	81.8	73.9	84.6
Bishoff (7/215)	2.67 (1.31, 5.43) p = 0.008	62.1	73.5	76.0

- **HR example**: the HR per unit score for CCP is 2.09, p-value 8.4×10^{-6} for progression to metastasis after adjusting for CAPRA in Canter et al[3].

- **C-index example**: the c-index in same study improves from 0.82 (CAPRA) to 0.85 (CCR).

To illustrate potential discrimination above and below a CCR threshold, the Kaplan-Meier plots are provided below. For example, Canter et al[3] shows that the median CCR score (2.29) separates unfavorable-intermediate risk men into two groups with ~4% risk of metastasis vs. ~14% risk of metastasis in 10-years. These figures also demonstrate added risk discrimination by Prolaris within high-risk men.
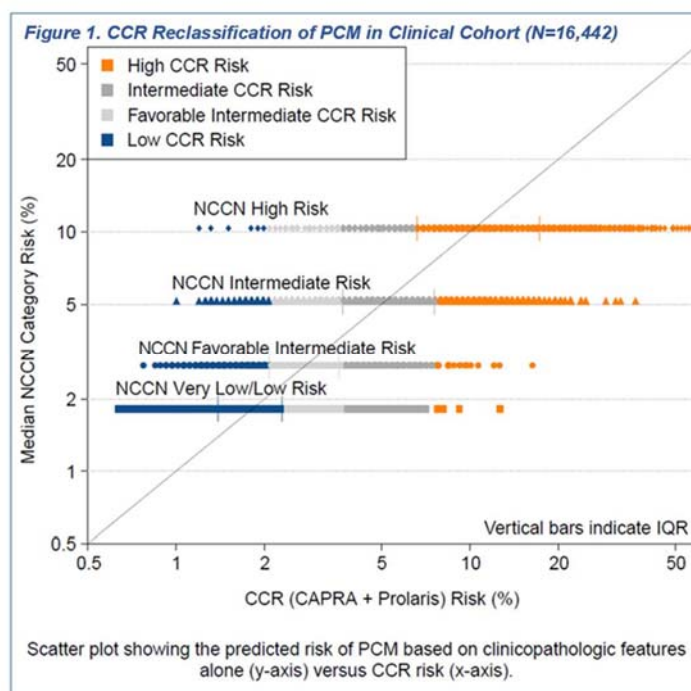
Canter (2018) Metastasis within 10 Years

Below Median: CCR ≤ 2.292
Above Median: CCR > 2.292

Bishoff (2014) Metastasis within 10 Years

Below Median: CCR ≤ 1.678
Above Median: CCR > 1.678

Finally, Kaplan-Meier plots are included below to illustrate discrimination above and below the CCR median threshold of 2.29 for PCM. In Canter et al[3], there were **no PCM events in either unfavorable intermediate or high-risk patients** below the median CCR threshold.

Canter (2018) Disease Specific Mortlaity within 10 Years

Legend:
- Below Median: CCR ≤ 2.292
- Above Median: CCR > 2.292

Also, we analyzed real-world experience of 16,442 patients clinically tested with Prolaris[11]. Prostate cancer mortality (PCM) risk was assigned based on patients' CCR score, a combined clinical cell cycle risk (CCR) score threshold that incorporates the CCP score with clinical information (CAPRA risk stratification). Patients whose PCM risks were outside of interquartile range (IQR) of their NCCN risk category were reclassified according to whether their PCM risks fell within the IQR of another NCCN risk category.

Figure 1 shows the results of calculating patient's risk of PCM based on CCR in the clinically tested patients. 24% of the NCCN unfavorable intermediate risk category were reclassified to a lower risk and 25% were reclassified to a higher risk category. For men in NCCN high-risk category, 25% were reclassified to the favorable/unfavorable intermediate risk category. This reclassification by CCR can be applied to better guide medical management or treatment intensity such as determining whether patients can be safely treated by a single modality therapy vs. multi-modality therapy.

Figure 1. CCR Reclassification of PCM in Clinical Cohort (N=16,442)

Scatter plot showing the predicted risk of PCM based on clinicopathologic features alone (y-axis) versus CCR risk (x-axis).

 Summary:

The broad range of recommended interventions for intermediate and high-risk men is reflective of the heterogeneous metastatic potential and lethality of prostate cancer. The clinical uncertainty and availability of treatment options highlights the need for improved disease risk stratification beyond clinical and pathological features for men with unfavorable intermediate and high-risk disease. As such, our request for the inclusion of Prolaris to unfavorable intermediate and high-risk disease to provide for

enhanced risk stratification would allow for more informed decisions regarding potential treatment selection.

Literature support: A list of all publications supporting the use of Prolaris to predict lethal prostate cancer and risk stratification is referenced below.

Sincerely,

Todd Cohen, MD.   Johnathan Lancaster, MD, PhD.
VP of Medical Affairs, Urology   Chief Medical Officer
Myriad Genetic Laboratories, Inc.   Myriad Genetic Laboratories, Inc.

References:

1. Bishoff JT, Freedland SJ, Gerber L, et al: Prognostic utility of the CCP score generated from biopsy in men treated with prostatectomy. *J Urol* 2014 Aug: 192(2):409-14.
2. Canter DJ, Reid, Latsis M, et al: Comparing the prognostic utility of the cell cycle proliferation score for predicting clinical outcomes in African American and non-African American men with localized prostate cancer. *Eur Urol* 2019; 75:515-22.
3. Cuzick J, Swanson GP, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol*. 2011 Mar;12(3):245-55.
4. Cuzick J, Berney DM, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2012 Mar 13;106(6):1095-9.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. Lin DW, Crawford ED, Keane T, et al: Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. Urol Oncol 2018 Jun;36(6):310.e7-310.e13. doi:10.1016/j.urolonc.2018.03.011. Epub Apr 11, 2018.
11. Stone S, Reid J, Brawer M: Patient NCCN Risk Classification Based on Combined Clinical Cell Cycle Risk (CCR) Score. Poster presented at: Genitourinary Cancers Symposium (ASCO-GU); 2017 Feb 17; Orlando, FL.