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NCCN Guidelines Panel:	Prostate Cancer

On behalf of Myriad Genetic Laboratories, Inc., I respectfully request the NCCN Prostate Cancer Panel to review the enclosed data supporting the use of molecular assays that predict meaningful oncologic endpoints in the initial workup of men with clinically localized prostate cancer.

Specific changes recommended:
On page PROS-1, we request the addition of a footnote associated with the heading "Staging Workup" to read: *"For men with clinically localized disease, consider use of a tumor-based molecular assay that predicts meaningful oncologic endpoints of disease-specific mortality, biochemical recurrence, or metastasis and thus provides more accurate personalized risk stratification."*

Statement of FDA Approval:
The FDA has chosen to exercise its "enforcement discretion" over Laboratory Developed Tests (LDTs) and these tests are routinely performed without FDA premarket approval or clearance.

Rationale:
Page PROS-C states that the NCCN Prostate Cancer Panel and NCCN Prostate Cancer Early Detection Panel remain concerned about over-diagnosis and over-treatment of prostate cancer. Newly diagnosed men can have either aggressive or indolent tumors, and current clinical and pathologic features are limited in their ability to distinguish between the two. As a result, most men will receive definitive treatment, despite the risk of treatment-related complications and the low prostate-cancer mortality with conservative management.

Myriad Genetic Laboratories developed Prolaris®, a novel prognostic test that directly measures tumor biology in order to accurately stratify patients with clinically localized prostate cancer according to disease aggressiveness. The test combines the RNA expression levels of 31 genes involved in cell cycle progression and 15 housekeeping genes to generate a CCP score. The CCP score has been validated as a fundamental characteristic of prostate cancer biology and to be predictive of outcomes. Validation studies were performed on archived tissue specimens from series of prostate cancer patients, for whom outcomes data had been collected prospectively (retrospective-prospective design).

In five published studies (comprised of 8 separate cohorts) on more than 2,100 patients, the CCP score proved to be the most powerful variable in predicting the risk of prostate cancer progression**, as determined by the**

clinically meaningful oncologic endpoints of biochemical recurrence, prostate cancer-specific mortality, and metastasis. [1-5] Evidence that the CCP score provides unique and useful information is assured by its weak correlation with Gleason score and PSA. In addition to the five published studies, data on one additional validation cohort was presented at the American Urological Association meetings, May 16-21, 2014.[6]

In a pivotal clinical utility study, physicians used the risk stratification provided by the CCP test to change their treatment plan in 65% of cases.[8] Overall, there was a 49.5% reduction in recommendations for surgical intervention and a 29.6% reduction in recommendations for radiation treatment. Conversely, physicians increased their use of interventional treatment in 23.4% of cases as warranted by the higher CCP score indicating a more aggressive tumor. The findings of this prospective study are very similar to those previously obtained and published in a retrospective study of case management decisions by physicians participating in a validation study of the CCP test.[7] Together, these results provide convincing evidence that the use of this test addresses a previously unmet need in clinical decision making.

The Center for Medical Technology Policy's effectiveness guidance document on molecular tests in oncology (http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf) supports the use of prospective observational studies to demonstrate clinical utility in specified circumstances, including when "there is genuine uncertainty on the part of the expert medical community regarding the preferred clinical pathway"; this is the case for the treatment of localized prostate cancer. Furthermore, given the long natural history of localized prostate cancer, it is not practical or feasible to conduct prospective trials in which patients are randomized with or without a molecular test and followed for several years to evaluate outcomes based on treatment choice. The time lag associated with conducting such a large randomized controlled study would result in an unacceptable number of missed opportunities to use the test on patients diagnosed during the extended study period. This is particularly concerning given findings from the recent PIVOT study that men with low-risk disease do not benefit from prostatectomy, and the published data herein demonstrating that the use of the CCP test reduces the number of prostatectomies in these men.[8]

Literature support:
A list of citations in support of the proposed addition to the guideline appears below.

We appreciate the panel's consideration of our request. Should you have any questions about the information in our submission, please do not hesitate to contact me.

Sincerely,

Michael Brawer, MD
Vice President of Medical Affairs, Urology
Myriad Genetic Laboratories, Inc.

References:

1. 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.
2. 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.
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.
5. 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 Feb 6. pii: S0022-5347(14)00248-1. doi: 10.1016/j.juro.2014.02.003. [Epub ahead of print]
6. Cuzick J, Stone S, Yang ZH, et al. Validation of a 46-gene cell cycle progression (CCP) RNA signature for predicting prostate cancer death in a conservatively managed watchful waiting needle biopsy cohort. Accepted for presentation at the American Urological Association meeting May 16-21, 2014 in Orlando FL.
7. Shore N, Concepcion R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. *Curr Med Res Opin*. 2013 Dec 23. [Epub ahead of print] (doi:10.1185/03007995.2013.873398)
8. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: Results from an ongoing registry. *Curr Med Res Opin*. 2014 Feb 28. [Epub ahead of print] doi:10.1185/03007995.2014.899208

Table 1. Prolaris Clinical Validation Studies

	COHORT, SPECIMEN TYPE	PRIMARY ENDPOINT	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS		ABILITY OF PROLARIS TO PREDICT ENDPOINT*
Published:							
Cuzick 2011[1]	**Cohort 1, Post-prostatectomy:** U.S. men, radical prostatectomy from 1985-95; tumor registry. N=353	Biochemical recurrence	HR=1.89	$p=5.6 \times 10^{-9}$	HR=1.77	$p=4.3 \times 10^{-6}$	Prolaris and PSA were most predictive
	Cohort 2, Transurethral resection of the prostate: Conservatively managed U.K. patients diagnosed after TURP form 1990-1996. N=337	10-year mortality	HR=2.92	$p=6.1 \times 10^{-22}$	HR=2.57	$p=8.2 \times 10^{-11}$	Prolaris most predictive
Cuzick 2012[2]	**Cohort 3, Biopsy:** Conservatively managed U.K. patients diagnosed by needle biopsy from 1990-1996. N=349	10-year mortality	HR=2.02	$p=8.6 \times 10^{-10}$	HR=1.65	$p=2.6 \times 10^{-5}$	Prolaris most predictive
Cooperberg 2013[3]	**Cohort 4, Post-prostatectomy:** Contemporary cohort of U.S. men, radical prostatectomy from 1994-2006. N=413	Biochemical recurrence	HR=2.1	$p=2.2x\ 10^{-6}$	HR=2.01	$p=5.7 \times 10^{-5}$	Prolaris most predictive
Freedland 2013[4]	**Cohort 5, Biopsy:** U.S. men, external beam radiation therarpy (EBRT) from 1991-2006. N=141	Biochemical recurrence	HR=2.55	p=0.0017	HR=2.11	p=0.034	Prolaris most predictive
Bishoff 2014[5]	**Combined Cohorts 6-8** Cohort 6, Biopsy: German men, radical prostatectomy from 2005-2006. N=283 Cohort 7, Biopsy: U.S. men, radical prostatectomy from 1994-2005. N=176 Cohort 8, Biopsy: U.S. men, radical prostatectomy from 1997-2004. N=123	Biochemical recurrence	HR=1.60	$p = 2.4 \times 10^{-7}$	HR=1.47	$p= 4.7 \times 10^{-5}$	Prolaris and PSA were most predictive
		Metastatic disease	HR=5.35	$p = 2.1 \times 10^{-8}$	HR=4.19	$p= 8.2 \times 10^{-6}$	Prolaris most predictive
Accepted for presentation at American Urological Association, May 2014:							
Cuzick 2014[6]	**Cohort 9, Biopsy:** Contemporary cohort of conservatively managed U.K. patients diagnosed by needle biopsy from 1990-2004. N=757	Disease Specifc Mortality	HR=2.32	$p = <10^{-17}$	HR=1.86	$p= < 10^{-6}$	Prolaris most predictive

* In multivariate analysis. Variables retaining their predictive significance in multivariate analysis provide information not captured by other variables.