Jonathan I. Epstein, M.D.
Professor
Departments of Pathology, Urology and Oncology
The Reinhard Professor of Urologic Pathology
Director, Surgical Pathology

Department of Pathology
The Harry and Jeanette Weinberg Building
401 N. Broadway / Room 2242
Baltimore MD 21231-2410
410-955-5043 / Fax 443-287-3818
jepstein@jhmi.edu

JOHNS HOPKINS
MEDICINE
JOHNS HOPKINS
MEDICAL INSTITUTIONS

5/1/2015

Name	Jonathan Epstein, MD Professor, Departments of Pathology, Urology, & Oncology
Organization	Johns Hopkins Medical Institutions
Address	401 N. Broadway Street, Rm 2242, Baltimore MD
Phone	(410) 955-5043
Email	jepstein@jhmi.edu
NCCN Guidelines Panel	Prostate Cancer Early Detection

On behalf of Metamark Genetics Laboratories, I respectfully request the NCCN Prostate Cancer Panel to review the data below supporting the expansion of the Discussion section of the v1. 2015 Guideline to include additional molecular assays that have been validated to predict adverse pathology, providing more accurate risk stratification for men with clinically localized prostate cancer.

Specific changes recommended:
In the Discussion section, under Molecular Testing (MS-4), we request the addition of information on the ProMark prostate biopsy prognostic test (assay information and references below).

Statement of FDA Approval:
ProMark is classified as a laboratory developed test (LDT) pursuant to the Clinical Laboratory Improvement Amendments program administered by the Centers for Medicare and Medicaid Services. Although the FDA has enforcement oversight of medical devices, including in vitro diagnostic tests, in the case of LDTs it has expressly chosen to exercise "enforcement discretion" allowing these tests to be routinely performed without premarket approval or clearance.

Rationale:
The NCCN Prostate Cancer Panel has already recognized molecular assays to improve risk stratification in men with clinically localized prostate cancer and inform decisions on active surveillance or treatment. The Molecular Testing discussion (MS-4) of the NCCN Prostate Cancer Guidelines version 1.2015 states:

> *'American men continue to under select active surveillance for very low or low risk prostate cancer largely due to uncertainty in the risk of disease progression, an*

uncertainty that could be reduced by a molecular biomarker that can be measured accurately and reproducibly and provide prognostic or predictive information beyond NCCN risk group assignment and currently available tables and nomograms.'

Page Pros-1 states that:

'Men with clinically localized disease could consider the use of a tumor-based molecular assay to better stratify risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease specific mortality after radical prostatectomy'

ProMark is a prognostic assay developed and validated specifically to minimize sampling error and to predict adverse pathology within the prostate based on prostate biopsy tissue. The assay is intended for use in men with clinically localized Gleason 3+3 and 3+4 prostate cancer at the time of biopsy, for whom a decision of pursuing active surveillance or immediate treatment needs to be made.

Promark uses an automated, quantitative multiplex immunofluorescence method to measure the protein levels of 8 biomarkers (DERL1, HSPA9, CUL2, FUS, SMAD4, PDSS2, pS6, and YBX1) directly on sections of prostate biopsy tissue. The biomarkers individually correlate with adverse pathology and by combination using a trained algorithm predict an individual patient's probability that his cancer has not extended beyond the prostate or has histological features of aggressive tumors.

The development and validation of ProMark involved more than 1200 prostate cancer patients across four studies. These studies were conducted using archived tissue specimens from a series of prostate cancer patients for whom outcomes data had been collected prospectively (retrospective-prospective design). As demonstrated in these studies, ProMark provides a risk prediction independent of clinical and pathological findings. The validation study met its primary endpoint, separating favorable from non-favorable pathology (AUC, 0.68, $P<0.0001$, odds ratio=20.9) as an independent measure of risk. Moreover, when combined with established risk stratification methods (e.g. NCCN) the ProMark score provides additional information to refine the individual patient's prostate risk assessment. At a risk score ≤ 0.33, predictive values for favorable pathology in very low and low-risk NCCN were 95%, 81.5%, and 87.2%, respectively, higher than for these current risk classification groups themselves (80.3%, 63.8%, and 70.6%, respectively). The predictive value for non-favorable pathology was 76.9% at biomarker risk scores >0.8 across all risk groups. Increased biomarker risk scores correlated with decreased frequency of favorable cases across all risk groups. These compelling data support the inclusion of ProMark alongside the currently noted prognostic tests within the NCCN guideline to stratify risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease specific mortality after radical prostatectomy.

ProMark is currently in clinical use across the US to aid in the management decisions of men with localized prostate cancer.

Literature support:
Below is a list of citations supporting the proposed addition of ProMark to the Prostate Cancer Guidelines.

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,

Jonathan Epstein, MD
Professor of Pathology, Urology, Oncology
The Reinhard Professor of Urological Pathology
The Johns Hopkins Medical Institutions

REFERENCES

1. Shipitsin M, Small C, Giladi E, Siddiqui S, Choudhury S, Hussain S, et al. Automated quantitative multiplex immunofluorescence in situ imaging identifies phospho-S6 and phospho-PRAS40 as predictive protein biomarkers for prostate cancer lethality.
Proteome Science 2014.

2. Shipitsin M, Small C, Choudhury S, Giladi E, Friedlander S, Nardone J, et al. Identification of proteomic biomarkers predicting prostate cancer aggressiveness and lethality despite biopsy-sampling error. British Journal of Cancer. 2014.

3. Saad F, Shipitsin M, Choudhury S, et al. Distinguishing aggressive versus nonaggressive prostate cancer using a novel prognostic proteomics biopsy test, ProMark. J Clin Oncol. 32:5s, 2014 (suppl; abstr 5090)

4. Saad F, Shipitsin M, Blume-Jensen P, Berman D,et al. Development and Clinical Validation of an in situ Biopsy Based Multi-Marker Assay for Risk Stratification in Prostate Cancer. Clinical Cancer Research. 2015.