

Submitted by:  
Michael J. Donovan PhD, MD  
Exosome Diagnostics, Inc  
266 Second Avenue, Suite 200  
Waltham, MA. 02451  
212-241-4868  
[Michael@exosomedx.com](mailto:Michael@exosomedx.com)  
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NCCN Guidelines Panel: Prostate Cancer Early Detection

On behalf of Exosome Diagnostics, Inc., I respectfully request the NCCN (Prostate cancer Early Detection Panel) review the enclosed recently published second validation study for the ExoDx Prostate (Intelliscore) or EPI test along with proposed language to update the current language regarding the EPI test for use in the 2018 and 2019 guideline updates.

Specific changes:

Consideration #1:

Update the following statement in current guideline (MS-21, Page 29)

*“Based on reasons discussed above (see Additional Biomarker Tests), the panel considers EPI to be investigational at the present time, but will review additional information as it becomes available.”*

The additional data reported from the 2<sup>nd</sup> prospective multi-institutional validation study (noted above) renders the EPI test **no longer investigational** and we request that the sentence be removed from the final V2.2018 Guideline text.

Consideration #2:

Replace the existing paragraph in V1.2018 highlighted above by the following paragraph summarizing the performance of EPI in the 2<sup>nd</sup> validation study in men aged 50+ with PSA 2-10 ng/ml (“grey zone”) undergoing initial prostate biopsy.

**“A second independent prospective multi-center validation study performed at 14 sites between May 2016 – August 2017 in 503 patients within the intended use population demonstrated an AUC of 0.70 and confirms the performance in the first study (AUC 0.71). The AUC for EPI (0.70) was higher than the AUC for PSA (0.58), PCPT-RC (0.63) and ERSPC-RC (0.59).**

**The investigators propose the EPI assay as a secondary or “reflex test” for risk stratification in conjunction with PSA screening.”**

Consideration #3:

Revise the following statement in the current V1.2018 Guidelines (MS-21, Page 29)

*"In the McKiernan study, the algorithm was developed for the first time in 255 patients and then validated in the extended screening group of 519 patients, representing only 48% of the validation cohort after multiple exclusions. The majority of exclusions were for urine volume >49 mL, assay failure, and application outside the intended use population".*

Substitute with the following (changes in bold type):

*"In the McKiernan study, the **previously developed** algorithm (see reference below) was **confirmed in a training set of 255 patients** and then validated in the extended **validation cohort** of 519 patients."*

The text ... *"representing only 48% of the validation cohort after multiple exclusions. The majority of exclusions were for urine volume >49 mL, assay failure, and application outside the intended use population"* is a misleading interpretation of data from the JAMA Oncology paper. The total validation cohort of 1064 patients included multiple cohorts – intended use cohort (519), prior biopsy cohort and patients outside the age range and PSA levels of the intended use population (PSA 2-10 ng/dl and age 50 years plus).

Reference:

Donovan MJ, Noerholm M, Bentink S et al: A molecular signature of PCA3 and ERG exosomal RNA from non-DRE urine is predictive of initial prostate biopsy result.

Prostate Cancer Prostatic Dis. 2015;18(4): 370-5.

Consideration #4:

Revision of the new "Footnote I" (UPDATES-1, Page 4) (see below) to include EPI (suggested text in bold).

*"Footnote "i" is new to the page. "Biomarkers that improve the specificity of detection are not, as yet, recommended as first line screening tests. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, **EPI score greater than 15.6** or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy."*

Recommend the EPI non-DRE urine test in patients with PSA between 2-10 ng/mL who have not yet had a biopsy. Based on the clinical data EPI including the two prospective validation studies in high impact journals, the EPI test should not be regarded as investigational.

FDA Clearance: The EPI test is an uncleared and unapproved In Vitro Diagnostic assay and best defined as a Clinical Laboratory Improvement Amendments (CLIA)-certified, laboratory derived test (LDT).

Rationale: Overtreatment of clinically insignificant prostate cancer is a concern for early detection protocols. Furthermore, the recent emphasis on the ability to discriminate high grade Gleason 7 prostate cancer from Gleason 6 and benign disease processes further supports the evidence that only a small percentage of men with low grade Gleason 6 or low volume Gleason 7 (3+4) prostate cancer will progress. Aggregate evidence from recent randomized trials suggests that optimal prostate cancer early detection methods would preferentially identify patients with high grade tumors for biopsy while avoiding biopsy in men without cancer or with low grade disease. It is thought that such an approach would have the potential to maintain mortality reduction while reducing biopsy-associated morbidities and over-treatment of indolent cancer.

We have previously submitted a series of publications including the original validation study (McKiernan et al, JAMA Oncol, 2016) supporting the clinical and analytic validation of the EPI test and now include a second validation study which was just recently accepted in August, 2018 for publication in the European Urology.

The following curated references are submitted in support of this proposed change. We would like to further acknowledge the contributions of NCCN panel members as co-authors in both published validation studies.

1. McKiernan J. et al. A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with PSA 2-10ng/mL at initial biopsy. European Urology, 2018, published online.