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August 13, 2018

NCCN Guidelines Panel: Prostate Cancer Early Detection

On behalf of Exosome Diagnostics, Inc., I respectfully request the NCCN (Prostate cancer Early Detection Panel) to review the enclosed additional data for inclusion of the non-invasive (non-DRE), simple urine-based exosome 3-gene expression assay (ExoDx Prostate(*IntelliScore*) or EPI) to further define the probability of high-grade Gleason score 7 prostate cancer on an initial biopsy for men presenting with a PSA 2-10 ng/mL.

Specific changes: 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, in press.
2. McKiernan J, et al., A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. *JAMA Oncol.* 2016; 2: 882-889.
3. Donovan M, 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 results. *Prostate Cancer Prostatic Dis.* 2015; 18: 370-375.
4. Motamedinia P et al., Urine Exosomes for non-invasive assessment of gene expression and mutations of prostate cancer. *PLoS One.* 2016; 4: e0154507.
5. Nilsson J et al., Prostate cancer-derived urine exosomes: a novel approach to biomarkers for prostate cancer. *Br. J Cancer.* 2009; 19:1603-1607.