Submitted by:
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Date of Request: July 31, 2017
NCCN Guidelines Panel: Bladder Cancer – September 2017

On behalf of Pacific Edge Diagnostics, I respectfully request the NCCN Bladder Cancer Guideline Panel to review the enclosed data for inclusion of the Cxbladder™ Assays in the evaluation of the following patient populations: 1) hematuria patients at risk for bladder cancer; and 2) patients with a known history of bladder cancer who are under surveillance for recurrence of the disease.

Specific Changes:

- **BL-1:** include the Cxbladder™ assays as a component of the Initial Evaluation. Specifically, below the bullet “Consider cytology”, add a new bullet with “Consider Cxbladder™”.

- **BL-E:** include the Cxbladder™ assays in the list corresponding to “Urine Tests - Consider urinary urothelial tumor markers”. Specifically, on MS-10 Surveillance replace “Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization (FISH) or nuclear matrix protein 22 in monitoring for recurrence” with “Consideration may be given to urinary biomarker testing by fluorescence in situ hybridization (FISH), nuclear matrix protein 22, or Cxbladder™ mRNA gene expression in monitoring for recurrence”.

FDA Clearance: FDA clearance is not required for these assays because the assays are performed in the central laboratory at Pacific Edge Diagnostics USA, regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP).

Rationale: **BL-1:** The American Urological Association has encouraged the development of sensitive serum or urine based tests to allow patients with asymptomatic microscopic hematuria to have more personalized work-ups, which may lessen the need for intensity of initial evaluation as well as monitoring, inclusive of follow-up visits and the frequency of cystoscopy. The Cxbladder urine based assays measure the expression of five genes and incorporate patient characteristics into algorithmic scores that have sufficient sensitivity and negative predictive value to enhance patient-physician shared decision making and allow clinicians and patients to prioritize full work-up for the higher risk patients while judiciously avoiding unnecessary procedures in low risk patients. The Cxbladder assays have been published in peer reviewed journals which demonstrate their ability to identify patients with hematuria who have a low probability of having urothelial cancer, showing 82% overall sensitivity and 97% NPV with a 100% sensitivity for detecting tumors stage 1 or greater. **BL-E/MS-10:** The current guidelines acknowledge that FISH and nuclear matrix protein 22 (NMP22) should be considered in the surveillance
of high risk patients with urothelial carcinoma, given their higher sensitivity for detecting urothelial carcinoma as compared to urinary cytology. The Cxbladder urine based assays have been shown in a prospective non-interventional study to be superior to FISH and NMP22 in the detection of recurrent urothelial carcinoma. The sensitivity of Cxbladder (91%) significantly outperformed cytology (22%), FISH (33%), NMP22 ELISA (26%), and NMP22 BladderChek (11%). Sensitivity is 95% for recurrent disease with a high risk of progression (all high-grade disease and low-grade, stage ≥T1 disease) compared with 86% for low-grade Ta disease. The Cxbladder NPV of 96% is superior to all comparator assays.

The following articles are submitted in support of the proposed changes to the NCCN guidelines:

**Surveillance studies:**

**Primary detection studies:**
3. Kavalieris L et al. A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. *BMC Urol.* 2015;15(23).

**Utility studies:**

**Additional Information:** Studies show that compliance with guidelines advocating cystoscopy is poor in both the primary detection and surveillance of bladder cancer. Non-invasive urine molecular tests for urothelial carcinoma having both high sensitivity and negative predictive value may be useful for detection and management of bladder tumors and to further stratify surveillance schedules for lower risk patients in this setting.

**Compliance studies:**

Sincerely,

Thomas P. Nifong, MD, Medical Director