



To: submission@nccn.org

Re: Submission Request – Bladder Cancer

Submitted by:

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NCCN Guidelines Panel: Bladder Cancer – September 2018

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™ Monitor Assay** in the discussion section for evaluation of patients with a known history of bladder cancer who are under surveillance.

Specific Change:

- On **MS-12 Surveillance discussion** 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 this assay because the assay is performed in the central laboratory at Pacific Edge Diagnostics USA that is regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP).

Rationale: The Cxbladder urine based assays measure the expression of five genes and calculate an algorithmic score that has 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 of Cxbladder is 95% for recurrent disease with a high risk of progression (all high-grade disease and low-grade, stage \geq T1 disease) compared with 86% for low-grade Ta disease.

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. Of note the recommendation to only incorporate FISH and NMP22 in the discussion is based on literature published prior to the development and commercialization of Cxbladder. More recent literature shows that the sensitivity of both FISH and cytology are considerably lower than their oft-quoted values. Cxbladder on the other hand has sufficient sensitivity and negative predictive value to enhance patient-physician shared decision making and allow clinicians and patients to personalize surveillance evaluations.

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

1. Kavalieris L et al. Performance characteristics of a multigene urine biomarker test for monitoring for recurrent urothelial carcinoma in a multicenter study. *J Urol*. 2017;197(6):1419-26.
2. Lotan Y et al. Clinical comparison of non-invasive urine tests for ruling out recurrent urothelial carcinoma. *Urol Oncol*. 2017; Mar 30.
3. O'Sullivan P et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. *J Urol*. 2012;188(3):741-7.
4. Chow R et al. Urinary biomarkers for diagnosis of bladder cancer: a systemic review and meta-analysis. *Ann Intern Med*. 2015;163(12):922-31.
5. Fancony JJ et al. It may be time to abandon urine tests for bladder cancer. *JNCCN*. 2015;13:1163-66.

Sincerely,

Thomas P. Nifong, MD, Medical Director