Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cxbladder Detect</td>
<td>0012M</td>
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<tr>
<td>Cxbladder Monitor</td>
<td>0013M</td>
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<tr>
<td>Cxbladder Triage</td>
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<tr>
<td>Cxbladder Resolve</td>
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</tbody>
</table>

What is Cxbladder

Definition

Cxbladder is a family of non-invasive urinary biomarker tests manufactured by Pacific Edge Diagnostics. Cxbladder was developed as an alternative or adjunct to conventional tests for the initial diagnosis of bladder cancer or for later disease recurrence.\(^1\,^2\)

- Bladder cancer is typically diagnosed using a combination of cytologic evaluation of urine, imaging tests, and cystoscopy. However, patients have reported that cystoscopy is uncomfortable and expensive, and as a result, investigators are exploring alternative methods to detect bladder cancer.
- The following tests are included in the Cxbladder family:\(^2\)
  - Cxbladder Triage: used to rule out bladder cancer at an early stage.\(^2\)
  - Cxbladder Detect: used to assess the probability of bladder cancer.\(^2\)
  - Cxbladder Monitor: used to assess the probability of disease recurrence.\(^2\)
  - Cxbladder Resolve: used to identify patients with high grade or late stage bladder cancer.\(^2\)
Test information

- According to the manufacturer, levels of messenger RNA (mRNA) of five biomarker genes, including MDK, HOXA13, CDC2, IGFBP5, CXCR2, are believed to be in higher concentrations in urine samples of patients with bladder cancer.
- The Cxbladder test involves the extraction, purification, and quantification of mRNA of the 5 biomarkers by reverse transcription (RT) quantification polymerase chain reaction (RT-qPRC).²
  - Cxbladder Triage
    - Combines bladder cancer risk factors as well as urinary biomarkers to rule out the presence of bladder cancer.²
  - Cxbladder Detect
    - Analyzes five urinary biomarkers to identify bladder cancer.²
  - Cxbladder Monitor
    - Combines clinical information and urinary biomarkers to assess the chance that bladder cancer has recurred.²
  - Cxbladder Resolve
    - Used to identify high grade or late stage bladder cancer in patients with haematuria.²

Guidelines and evidence

The National Comprehensive Cancer Network (NCCN)

- The National Comprehensive Cancer Network (2018) Clinical Practice Guidelines state the following regarding the use of available urinary biomarkers:³
  - “Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization or nuclear matrix protein 22 in monitoring for recurrence.”
  - “For cTa high grade, cT1, and Tis, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6- month intervals for the first 2 years, and at increasing intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high grade tumors (see Follow-up in the algorithm). Urine molecular tests for urothelial tumor markers are now available. Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information that is useful for detection and
management of non-muscle-invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation."

The American Urological Association (AUA)

The American Urological Association (2016) states:4

- Urinary biomarkers are insufficiently accurate to replace cystoscopy for diagnosis/surveillance, though some appear to have predictive ability for assessing response to intravesical BCG and may help interpret indeterminate cytology.
- “At the time of first disease evaluation and treatment, none of the existent risk stratification tools or urinary biomarkers are sufficiently sensitive and specific to predict which patient will have an early tumor recurrence. Therefore, the most reliable way to know whether patients are at risk for early recurrence is by cystoscopic evaluation.”

US Preventive Services Task Force (USPSTF)

In 2011, the U.S. Preventive Services Task Force updated its 2004 evidence review with regard to bladder cancer screening, and reported the following:5

- “no study evaluated the sensitivity or specificity of tests for hematuria, urinary cytology, or other urinary biomarkers for bladder cancer in asymptomatic persons without a history of bladder cancer. The positive predictive value of screening is less than 10% in asymptomatic persons, including higher-risk populations. No study evaluated harms associated with treatment of screen-detected bladder cancer compared with no treatment.”
- “screening tests that might be feasible for primary care include tests for hematuria, urinary cytology, and other urinary biomarkers. The U.S. Preventive Services Task Force (USPSTF) last reviewed the evidence on bladder cancer screening in 2004 but found insufficient evidence to guide a recommendation.”

Peer Reviewed Literature

The accuracy of CxBladder tests has been evaluated in multiple peer reviewed studies.1-12 Multiple limitations are noted, including indirect, low quality evidence; use of overlapping patient populations; non-blinded analysis; small sample sizes; short follow-up period, and/or bias in study design. For some tests in the suite, there is a lack of peer reviewed literature. There are no available studies that evaluated the effects on patient-relevant outcomes (survival, quality of life) of Cxbladder testing.

Sathianathen and colleagues carried out a systematic meta-analysis of published studies of urinary biomarker assays used to evaluate the clinical significance of primary hematuria.13 The Cxbladder assay was included in the review. The authors concluded that:
• “The current diagnostic performance of biomarkers are inadequate to replace cystoscopy in the primary hematuria setting.” 13
• “Given the current evidence, the use of these markers as an adjunct to cystoscopy for the evaluation of hematuria should be considered investigational.” 13

Additional research is needed to assess how Cxbladder testing will be used in the disease management of patients with cancer. Questions persist regarding if Cxbladder has sufficient clinical utility to replace invasive cystoscopy or if Cxbladder has the potential to augment or clarify uncertain results obtained using conventional diagnostic methods.

Ongoing Clinical Trials

The Cxbladder Monitoring Study: A Clinical, Non-Intervention Study of the Cxbladder Urine Test for the Detection of Recurrent Urothelial Carcinoma (UC). 14

• NCT02700659
• Primary outcome measures
  o “Proportion of participants with bladder cancer who are correctly identified as having cancer (true positives) and no cancer (true negatives) by the Cxbladder test.”
    • “The Cxbladder test results will be compared to that of cystoscopy, which is the gold standard method for diagnosing urothelial cancer; the true positive and true negative rates will be measured, along with the false positive and false negative rates of the test. The results will be reported as sensitivity and specificity of the Cxbladder test for detecting urothelial cancer in patients with recurrent disease.”
  o “Probability that patients identified as having cancer and no cancer by the Cxbladder test truly have cancer (positive predictive value; PPV), and truly have no cancer (negative predictive value; NPV) respectively.”

Criteria

• These tests are considered investigational and/or experimental.
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


