Test Specific Guidelines

Cxbladder

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Introduction

Cxbladder testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
Cxbladder Detect	0012M
Cxbladder Monitor	0013M
Cxbladder Triage	0363U

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. [3] However, individuals have reported that cystoscopy is uncomfortable and expensive.[4] In addition, diagnostic accuracy of urinary cytology is subject to cytopathologist expertise and inter-observer variation.[5-6] As a result, investigators are exploring alternative methods, such as Cxbladder, 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 individuals with high grade or late stage bladder cancer.[2]

Test Information

Introduction

The Cxbladder test involves the extraction, purification, and quantification of mRNA of the 5 biomarkers by reverse transcription (RT) quantification polymerase chain reaction (RT-qPCR).[2]

Cxbladder Testing

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 individuals with bladder cancer.

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 individuals with haematuria.[2] According to the manufacturer, this testing is not currently available in the United States.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Cxbladder testing.

American Urological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction

The American Urological Association (AUA, 2020) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (USUF, 2020) stated the following in a joint guideline:[7]

"Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria." (Strong Recommendation; Evidence Level: Grade C)

"Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ." (Expert Opinion)

Additional comments in the general narrative (non-guideline statements) stated:

"While there is insufficient evidence to recommend use of these markers routinely in the evaluation of patients with microhematuria, the potential exists for these markers to improve risk stratification over the clinical variables put forth herein, and thereby improve an individualized approach to microhematuria."

"A prospective randomized trial is currently open that randomizes patients based on clinical risk and marker status (NCT03988309). Patients in the marker arm will have a clinical risk stratification, such that patients with low clinical risk and a negative marker will not have cystoscopy but follow-up only, while those with a positive marker or higher risk based on clinical factors will undergo a standard evaluation with cystoscopy. This marker-based approach will be compared to a standard evaluation in the control arm. Such randomized trials will provide the strength of evidence needed to establish a role for markers in patients with hematuria."

American Urological Association and Society of Urologic Oncology

The American Urological Association (AUA, 2020) and the Society of Urologic Oncology (SUO, 2020) stated the following in a joint guideline:[8]

“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.”

“In surveillance of NMIBC [non-muscle-invasive bladder cancer], a clinician should not use urinary biomarkers in place of cystoscopic evaluation.” (Strong Recommendation; Evidence Strength: Grade B)

“In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance.” (Expert Opinion)

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2021) Clinical Practice Guidelines stated the following regarding the use of available urinary biomarkers:[9]

"Many of these [urinary molecular tests] have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumor markers may be considered during surveillance of high-risk non-muscle invasive bladder cancer. 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 consider this to be a category 2B recommendation."

US Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF, 2011) stated:[10]

"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."

Selected Relevant Publications

The accuracy of CxBladder tests has been evaluated in multiple peer reviewed studies.[1,11-28] Multiple limitations are noted, including indirect, low quality evidence; use of overlapping 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 is also a lack of available studies that have evaluated the effects on 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.[18] 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." [18]

"Given the current evidence, the use of these markers as an adjunct to cystoscopy for the evaluation of hematuria should be considered investigational." [18]

Additional research is needed to assess how Cxbladder testing will be used in the disease management of individuals 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.

Clinical trials may be ongoing. Additional information can be found at https://clinicaltrials.gov.

Criteria

These tests are considered investigational and/or experimental.

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.

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