AssureMDx Testing for Bladder Cancer

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>
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<th>Procedures addressed by this guideline</th>
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What is bladder cancer

Definition

Bladder cancer is one of the most common types of cancer in the U.S., especially among men. It is estimated that there will be more than 80,000 new cases of bladder cancer diagnosed in 2019 (61,700 in men and 18,770 in women).\(^1\) Approximately 90% of patients are older than 55 years and the average age of diagnosis is 73 years.\(^1\)

Bladder cancer is categorized as non-muscle invasive disease (NMID) or muscle invasive disease (MID).\(^2\) Approximately 80% of bladder cancers are NMID, and of those, most are urothelial carcinoma (UC), also called transitional cell carcinoma.\(^2\)-\(^5\) Most cases of UC are low-grade and easily treated; however, UC has a high risk of recurrence (70%), and patients must be monitored for several years after treatment.\(^4\) Diagnostic monitoring usually consists of regular testing of cells in the urine (cytology).\(^2\),\(^6\)

Although the general survival rate is 77%, patients living with bladder cancer experience a sharp decline in quality of life associated with multiple procedures, declining health, and diminished well-being.\(^7\)

The most common symptom of bladder cancer is hematuria. The current standard of care for detection of bladder cancer is cystoscopy, but this procedure is expensive and invasive, and fails to diagnose bladder cancer in up to 20% of cases.\(^8\),\(^9\) In the United States, 11 million hematuria patients are referred to urologists in the United States each year. Only 33% result in an office visit, and only 6% of these undergo cystoscopy. A bladder cancer diagnosis is made in only 3%-23% of those undergoing cystoscopy.\(^10\)

Due to the invasiveness of cystoscopy, there is an estimated 20,000 missed cancer cases among moderate-risk and/or high-risk hematuria patients.\(^11\) In addition, there is excessive use of this invasive procedure in low-risk patients. As a result, there is a clinical need to better select patients for cystoscopies and decrease inappropriate testing.\(^12\)
There is no definitive standard of care for classifying bladder cancer risk. Non-invasive procedures include urinalysis (assessing for blood in urine), urine cytology (assessing for cancer cells in urine), and urine tests for tumor markers (assessing for chromosomal changes or biomarkers).\textsuperscript{13}

Test information

Introduction

AssureMDx is a non-invasive method to analyze tumor markers in the urine of patients with hematuria to identify patients at low risk and high risk for bladder cancer.

The test is intended to assist in deciding who is at low risk for bladder cancer and can avoid cystoscopy, and who may benefit from a cystoscopy.\textsuperscript{14}

AssureMDx is a urine assay that analyzes three mutation markers or chromosomal changes (FGFR3, TERT, and HRAS) and the genetic methylation status of three biomarkers (OTX1, ONECUT2, AND TWIST1). These results, in conjunction with patient age, yield a patient’s risk of bladder cancer (risk profile) and guide the recommendations for cystoscopy. Patients identified at low risk for bladder cancer can avoid an unnecessary cystoscopy. Patients at medium- to high-risk of bladder cancer will proceed with cystoscopy as the gold standard for the diagnosis of bladder cancer.\textsuperscript{14}

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to AssureMDx for bladder cancer.

American Urological Association (AUA)

The current guidelines set forth by the American Urological Association (AUA) recommend cystoscopy for all adults age 35 and older presenting with asymptomatic microhematuria (after ruling out benign causes), and any individual presenting with gross hematuria.\textsuperscript{9}

American College of Physicians (ACP)

Guidelines suggested by the American College of Physicians (ACP) posit that any patient presenting with gross hematuria should receive a referral to a urologist, and any patient presenting with asymptomatic microhematuria should be referred to a urologist, if benign causes are ruled out. Only 9%-25% of patients presenting with hematuria undergo cystoscopy within six months of their initial diagnosis, and this is observed across different patient populations (academic health practice, community health clinic, Medicare-eligible patients).\textsuperscript{11,12}
Literature review

There is insufficient evidence to support the use of the AssureMDx to accurately predict the risk of bladder cancer in patients with hematuria, and thus identify patients for whom cystoscopy is necessary.\textsuperscript{10,11,15} Analytical validity studies are lacking. Clinical validity studies are limited by small study populations and the lack of long-term follow-up regarding the development of bladder cancer at a later date. Although one prospective clinical utility study suggests that recurrence of bladder cancer can be detected by follow-up urine assays, it is unclear if the use of AssureMDx versus conventional cystoscopy leads to changes in health care decision-making and improvement in patient survival.

Additional studies

Additional well-designed studies are needed to add to the evidence base, corroborate the early findings in larger patient populations, and include additional clinical factors such as age, gender, smoking history, and presence of gross versus microscopic hematuria.

Ongoing Clinical Trials

A study with the identifier: NCT03122964 is still in progress and is currently undergoing patient recruitment (updated August 17, 2018).\textsuperscript{16} The primary objective of this study is to evaluate the performance of AssureMDx for the detection of bladder cancer in patients with gross or microscopic hematuria. The secondary objective is to compare the predictive accuracy of a risk model including clinical factors (age, gender, smoking history, gross versus microscopic hematuria) with and without AssureMDx testing.

Criteria

Introduction

Requests for AssureMDx are reviewed using the following criteria.

This test is 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.
References
Introduction

This guideline cites the following references.


