Medical Coverage Policy | Urinary Tumor Markers for Bladder Cancer

EFFECTIVE DATE: 10|01|2015
POLICY LAST UPDATED: 09|19|2017

OVERVIEW
This policy documents the coverage determination for Urinary Tumor Markers for Bladder Cancer. The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Moreover, bladder cancer has a very high frequency of recurrence and therefore follow-up cystoscopy, along with urine cytology, is done periodically to identify recurrence early. Urine biomarkers that might be used to either supplement or supplant these tests have been actively investigated.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
BlueCHiP for Medicare and Commercial Products
The use of urinary tumor markers is considered not medically necessary in the diagnosis of, monitoring, and/or screening for bladder cancer as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND
Urinary bladder cancer, a relatively common form of cancer in the United States, results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma), typically presents as a tumor confined to the superficial mucosa of the bladder. The most frequent symptom of early bladder cancer is hematuria; however, UT symptoms (i.e., urinary frequency, urgency, dysuria) may also occur.

Guidelines from the American Urological Association from 2012 on the evaluation of microscopic hematuria, which were reviewed and affirmed in 2016, recommend cystoscopic evaluation of adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with microscopic hematuria and risk factors for developing bladder cancer. Confirmatory diagnosis of bladder cancer is made by cystoscopic examination, considered to be the criterion standard, and biopsy. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. Nonmuscle invasive disease is usually treated with transurethral resection, with or without intravesical therapy, depending on depth of invasion and tumor grade. However, a 50% to 75% incidence of recurrence has been noted in these patients, with 10% to 15% progressing to muscle invasion over a 5-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every 3 months for 1 to 3 years, every 6 months for an additional 2 to 3 years, and then annually thereafter, assuming no recurrence.

While urine cytology is a specific test (from 90%-100%), its sensitivity is lower, ranging from 50% to 60% overall and is considered even lower for low-grade tumors. Therefore, interest has been reported in

identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

Adjunctive testing to urine cytology has used a variety of nuclear and cytoplasmic targets, and a range of molecular pathology and traditional (eg, immunohistochemistry) methods.

Commercially-available tests that have been cleared by the U.S. Food and Drug Administration (FDA) clearance are summarized in the Regulatory Status section.

In addition to FDA-cleared tests, clinical laboratories that meet Clinical Laboratory Improvement Act standards are marketing urine-based tests. For example, Predictive Laboratories (Lexington, MA) markets a test called CertNDx™, to assess fibroblast growth factor receptor 3 (*FGFR3*) variants. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. *FGFR3* variants may be associated with lower grade bladder tumors that have a good prognosis. In addition, Pacific Edge (New Zealand) is marketing a test in the United States called Cxbladder™, which tests for 5 urine-based markers.

REGULATORY STATUS

Urinary tumor marker tests cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and in clinical use include:

- The BTA stat® test (Polymedco, Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that was shown to be produced by several human bladder cell lines but not by other epithelial cell lines. The BTA stat® test is an in vitro immunoassay intended for the qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer.

- The BTA TRAK® test (Polymedco, Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both tests have sensitivities comparable with that of cytology for high-grade tumors and better than cytology for low-grade tumors.

- Nuclear matrix protein 22 (NMP22) urine immunoassay. NMP22 is a protein associated with the nuclear mitotic apparatus, which may be released from the nuclei of tumor cells during apoptosis. Elevated urine levels may have been associated with bladder cancer. NMP22 may be detected in the urine using an immunoassay.

- Vysis UroVysion® (Abbott Molecular) is a commercially available fluorescence in situ hybridization (FISH) test. Fluorescence in situ hybridization (FISH) is a molecular cytogenetic technology which can be used with either DNA or RNA probes to detect chromosomal abnormalities. DNA FISH probe technology involves the creation of short sequences of fluorescently labeled, single-strand DNA probes which match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. DNA FISH probes have been used to detect chromosomal abnormalities in voided urine to assist in bladder cancer surveillance and in the initial identification of bladder cancer.

- ImmunoCyt™ test (DiagnoCure, Quebec City, QC) uses fluorescence immunohistochemistry with antibodies to a mucin glycoprotein and a carcinoembryonic antigen. These antigens are found on bladder tumor cells.

With the exception of the ImmunoCyt™ test, which is only cleared for monitoring bladder cancer recurrence, all tests are FDA-cleared as adjunctive tests for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients, in conjunction with standard procedures.

For individuals who have signs and symptoms of bladder cancer or a history of bladder cancer who receive urinary tumor marker tests, the evidence includes a number of diagnostic accuracy studies, meta-analyses, as well as a decision curve analysis and retrospective study examining the clinical utility of urinary tumor marker tests. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The diagnostic accuracy studies found that urinary tumor marker tests tended to have higher sensitivity but lower or similar specificity compared with cytology. Also, they found that combining tumor marker tests with cytology can improve overall diagnostic accuracy. The decision analysis found only a small clinical benefit of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies of the preferred design to evaluate clinical utility were identified; that is, controlled studies prospectively evaluating health outcomes in patients managed with and without use or urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have no signs or symptoms or history of bladder cancer who receive urinary tumor marker tests, the evidence includes a 2010 systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The systematic review (conducted for the U.S. Preventive Services Task Force) did not identify any RCTs, the preferred trial design to evaluate the impact of population-based screening, and found only 1 prospective study that USPSTF rated as poor quality. A more recent retrospective study, reporting on a population-based screening program in the Netherlands, had low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore, these services are considered not medically necessary for BlueCHiP for Medicare and Commercial products.

CODING

BlueCHiP for Medicare and Commercial Products

The following CPT codes are considered not medically necessary:

86294 Immunoassay for tumor antigen, qualitative or semi quantitative (e.g., bladder tumor antigen)
86386 Nuclear Matrix Protein 22 (NMP22), qualitative
88120 Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121 Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology

RELATED POLICIES

None

PUBLISHED

Provider Update, November 2017
Provider Update, January 2017
Provider Update, August 2015

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