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OVERVIEW

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. 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

The use of urinary tumor markers is not covered in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.

Commercial Products

The use of urinary tumor markers is considered not medically necessary in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.

COVERAGE

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

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, urinary tract symptoms (i.e., urinary frequency, urgency, dysuria) may also occur. Cigarette smoking is an important risk factor for urothelial carcinoma.

The criterion standard for a confirmatory diagnosis of bladder cancer is cystoscopic examination with biopsy. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. Non-muscle-invasive disease is usually treated with transurethral resection, with or without intravesical therapy, depending on the 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.

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:

- BTA stat® test (Manufacturer: Polymedco) Indication: Qualitative detection of bladder tumor associated antigen in the urine of persons diagnosed with bladder cancer
- BTA TRAK® test (Manufacturer: Polymedco) Indication: Quantitative detection of bladder tumor associated antigen in the urine of persons diagnosed with bladder cancer
- Alere NMP22® (Manufacturer: Alere) Indication: in vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy
- BladderChek® (Manufacturer: Alere) Indication: Adjunct to cystoscopy in patients at risk for bladder cancer
- UroVysion® (Manufacturer: Abbott Molecular) Indication: Aid in the initial diagnosis of bladder cancer (P030052) and monitoring patients with previously diagnosed bladder cancer

For individuals who have signs and/or symptoms of bladder cancer who receive urinary tumor marker tests in addition to cytology, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. The relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have sensitivity ranging from 47% to 85% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a history of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, 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. The 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 have pooled sensitivity ranging from 46% to 84% and pooled specificity ranging from 71% to 91%. The decision analysis found only a small clinical benefit for use 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 using the preferred trial design to evaluate clinical utility were identified; ie, controlled studies prospectively evaluating health outcomes in patients managed with and without use of 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 are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. The relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A 2010 systematic review (conducted for the U.S. Preventive Services Task Force) did not identify any randomized controlled trials, the preferred trial design to evaluate the impact of population based screening, and found only 1 prospective study that the Task Force rated as poor quality. A more recent

retrospective study, assessing a population-based screening program in the Netherlands, reported low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at a population-level risk of colon cancer who receive urinary tests for precancerous polyps, evidence includes a validation study. The relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A urine metabolite assay for adenomatous polyps is at a very early stage of development, with a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

The following CPT codes are not covered for BlueCHiP for Medicare and not medically necessary for Commercial products:

- 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
- 0012M** Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma (~~New code effective 4/1/2018~~)
- 0013M** Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma (~~New code effective 4/1/2018~~)
- 0002U** Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps.

RELATED POLICIES

Proprietary Laboratory Analysis Tests (PLA)

PUBLISHED

Provider Update, March 2020
Provider Update, April 2019
Provider Update, September 2018
Provider Update, June 2018
Provider Update, November 2017
Provider Update, January 2017
Provider Update, August 2015

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