Medical Coverage Policy | Urinary Biomarkers for Cancer Screening, Diagnosis and Surveillance

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 08|07|2024

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

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans

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. Refer to the Coding section for details.

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. Refer to the Coding section for details.

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

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.

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 approved or cleared by the U.S. Food and Drug Administration (FDA) as well as laboratory-developed tests 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 and monitoring patients with previously diagnosed bladder cancer
- Bladder EpiCheck® (Manufacturer: Nucleix) Indication: Monitoring for tumor recurrence inconjunction with cystoscopy in patientswith previously diagnosed NMIBC

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. 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 82% 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 52% 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. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The clinical data supporting a urine metabolite assay for adenomatous polyps includes 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 code(s) are not covered for Medicare Advantage Plans 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

This code can be used for CxBladder™ Detect (Pacific Edge Diagnostics USA, Ltd.)

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

This code can be used for CxBladder™ Monitor (Pacific Edge Diagnostics USA, Ltd.)

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

This code can be used for PolypDX™ (Atlantic Diagnostic Laboratories, LLC, Metabolomic Technologies, Inc.)

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.

This code can be used for Cxbladder™ Triage (Pacific Edge Diagnostics USA, Ltd.)

0363U Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, andCXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma (**New Code Effective 1/1/2023**)

This code can be used for Cxbladder Detect+ (Pacific Edge Diagnostics USA, Ltd.)

0420U Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma (**New Code Effective 1/1/2024**)

The following CPT code(s) are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when filed with one of the ICD-10-CM codes listed below.
Note: This CPT code can be used for testing for more conditions/diagnoses than are referenced in this policy. Please see the Related Policies section for other not covered and not medically necessary conditions/diagnoses.

86316 Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each

ICD-10-CM

C67.0-C67.9
D09.0
D49.4
K63.5
R31.9
Z83.71
Z85.51
Z86.010 (Code Deleted Effective 9/30/2024)
Z86.0100 (New Code Effective 10/1/2024)
Z86.0101 (New Code Effective 10/1/2024)
Z86.0102 (New Code Effective 10/1/2024)
Z86.0109 (New Code Effective 10/1/2024)

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services
Medical Necessity
Proprietary Laboratory Analysis Tests (PLA)
Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
Serum Tumor Markers for Breast and Gastrointestinal Malignancies

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Provider Update, October 2024
Provider Update, March 2023, November 2023
Provider Update, April 2022
Provider Update, March 2021
Provider Update, March 2020

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