MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Urinary Tumor Markers for Bladder Cancer**
Policy Number	**2.02.12**
Category	**Technology Assessment**
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Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

Based upon our criteria and assessment of the peer-reviewed literature, the use of urinary tumor markers is considered **investigational** in the diagnosis of, monitoring of, and/or screening for bladder cancer.

Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services

POLICY GUIDELINES

The U.S. Food and Drug Administration (FDA) has approved the following tests Bard BTA Stat test (1995), NMP-22 test (1996), NMP22 BladderChek kit (2002), Vysis UroVysion Bladder Cancer Recurrence kit (2001), and the ImmunoCyt test (2000).

DESCRIPTION

Bladder cancer (transitional cell carcinoma or TCC) typically presents as a tumor confined to the superficial mucosa of the bladder and is treated with transurethral resection. The only symptom of early bladder cancer is hematuria; confirmatory diagnosis of bladder cancer must be made by cystoscopic examination, which is considered to be the "gold standard." There is a 75% incidence of recurrence in bladder cancer patients, and follow-up care includes surveillance cystoscopy and serial evaluations of urine cytology. While urine cytology is a specific test (90-100%), its sensitivity is lower (50-60%) and is considered even lower for low-grade tumors. Therefore, there has been interest in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

Bladder Tumor Antigen (BTA) tests

The BTA stat test is a single-step qualitative test performed on voided urine. It measures human complement factor H-related proteins produced by several human bladder cell lines, but not by other epithelial cell lines. The BTA TRAK test provides a quantitative determination of the same protein. The BTA tests have an improved sensitivity compared to cytology, but lower specificities due to high false-positive rates associated with recent instrumentation, stones, or inflammatory conditions such as benign prostatic hypertrophy (BPH).

ImmunoCyt tests

The ImmunoCyt test uses fluorescence immunohistochemistry with antibodies to a mucin glycoprotein and a carcinoembryonic antigen (CEA). These antigens are found on bladder tumor cells.

Nuclear Matrix Protein (NMP-22) tests

The NMP-22 test is a quantitative test for tumor-related proteins measured in urine. The NMP-22 assay measures nuclear matrix proteins that are involved in DNA replication and RNA synthesis during mitosis. NMP-22 is a protein associated with the nuclear mitotic apparatus. It is thought that this protein is released from the nuclei of tumor cells during apoptosis. Normally, only very low levels of NMP-22 can be detected in the urine, but elevated levels may be associated with bladder cancer. The specificity and sensitivity of NMP-22 are similar to BTA stat.

Fluorescence in situ hybridization (FISH) DNA probe technology tests

FISH DNA probe technology has been used to detect chromosomal abnormalities in voided urine, to assist not only in bladder cancer surveillance, but also in the initial identification of bladder cancer. FISH DNA probe technology is a technique to visualize nucleic acid sequences within cells by creating short sequences of fluorescently labeled, single-strand DNA, called probes, that match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. The sensitivity and specificity of the FISH assay are proposed to be higher than for the BTA tests.

These tests are proposed for use in conjunction with cystoscopy in the surveillance of patients for recurrent bladder cancer, but not intended to replace the procedure. The BTA, NMP-22, and FISH DNA probe technique tests have additionally been proposed as an initial test in patients with signs and symptoms suggestive of bladder cancer.

Multiplex protein-based immunoassay test

Oncuria, DiaCarta, Ltd is a test that received breakthrough device designation from the FDA in 2021 for predicting the response to bacillus Calmette-Guérin (BCG) therapy via midstream voided urine. The Oncuria assay and proprietary algorithms use 10-biomarkers (A1AT & SERPIN A1, ANG, APOE, CA9, IL-8, MMP-9, MMP-10, PAI-1 & SERPIN E1, SDC1, and VEGF-A) to aid in the diagnosing of bladder cancer, monitoring people with early-stage bladder cancer and predicting whether patients with intermediate- to high-risk, early-stage bladder cancer will respond to BCG therapy.

RATIONALE

BTA tests

The sensitivity of the BTA stat test was evaluated in a study of 220 patients with confirmed bladder cancer. Overall sensitivity was 67%, ranging from 51% in those with bladder cancer stage Ta (noninvasive papillary) to 88% in those with higher stages. When categorized according to tumor grade, sensitivity ranged from 42% for those with grade I tumors to 83% for those with grade 3 tumors. A subset of 131 patients also had voided urine cytology performed on the same sample as the BTA. With the exception of those with carcinoma in situ, the BTA test was more sensitive than urine cytology. The combination of the two tests increased the sensitivity slightly compared to the BTA test alone. The most significant improvement was noted in those with carcinoma in situ, in which the sensitivity of the BTA alone was 53%, rising to 80% when combined with the results of cytology.

NMP-22

A study of 231 patients with a history of transitional cell cancer reports collected samples prior to a scheduled cystoscopic examination. Voided urine cytology was also performed in a subset of 200 of the patients. Using an NMP-22 cut off of 6.4

units/ml, the overall sensitivity compared to pathologic diagnosis was 68%. In contrast, the sensitivity of cytology was 31-40%, depending on the definition of a positive cytology examination.

FISH Technology

A comparison of cystoscopy with biopsy or tumor resection to urine cytology and FISH analysis in urine sample of 86 patients reported finding overall sensitivity of FISH to be 80.4% vs. 63.8% for urine cytology. Sensitivities reported by tumor grades 1, 2 and 3 were 53.3%, 83.3% and 100% for FISH and 25%, 66% and 94.7% for urine cytology, respectively. Two multicenter trials compared FISH to the BTA Stat test and voided urine cytology. In the first study of 176 patients with known transitional cell carcinoma (TCC), sensitivities were 71% for FISH, 50% for BTA Stat, and 26% for cytology. In the second study of 275 healthy volunteers and patients with conditions other than TCC, the specificity of FISH was 94.5%.

While the 2007 American Urological Association's best practices policy indicates that, despite their present and future potential, the critical evaluation and comparison of urine-based markers is beyond the scope of the current guideline involving the management of non-muscle invasive bladder cancer.

ImmunoCyt immunohistochemical assay

A multi-center study using the ImmunoCyt assay in 341 patients with a history of bladder cancer reported sensitivity and specificity similar to the other medically appropriate markers in this policy. Overall sensitivity was 81% and specificity was 75%. For most grades and stages of tumors, the ImmunoCyt assay was more sensitive than urine cytology. As with other markers for bladder cancer, the low specificity of this test (dealing with false-positive results) can be problematic.

Studies have been published with other potential tumor markers in bladder cancer. These potential new markers include telomerase, soluble FAS, TATI (tumor-associated trypsin inhibitor), soluble e-cadherin, and BLCA-1 and BLCA-4 (bladder cancer specific biomarkers). Studies describing these markers generally involve limited numbers of patients. Therefore, additional studies are needed before their use would be considered medically appropriate. There have not been clinical trials to demonstrate that any of these markers can change the current role or frequency of cystoscopy in monitoring patients with bladder cancer. There are also limited studies that compare one marker to another.

The U.S. Preventive Services Task Force (USPSTF) concluded that tumor markers do not have a proven role in screening of asymptomatic persons for early detection of bladder cancer. The August 2011 USPSTF and 2019 recommendation statement, Screening for Bladder Cancer, conclude that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults**.**

Multiplex protein-based immunoassay test (Oncuria, DiaCarta Ltd)

There are three clinical trials that are currently recruiting (NCT03193541, NCT03193528, NCT 03193515) these three large multicenter, international prospective clinical trials will include first-event diagnosis and disease recurrence monitoring (Hirasawa et al., 2021). The diagnostic performance of Oncuria was performed by Hirasawa et al. (2021), the test was evaluated in a multi-institutional cohort of 362 prospectively collected subjects presenting for bladder cancer evaluation. The parallel measurement of 10 biomarkers (A1AT, APOE, ANG, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) was performed in an independent clinical laboratory. Bladder cancer status was confirmed by cystoscopy and tissue biopsy. The hybrid signature achieved an overall sensitivity of 0.93, specificity of 0.93, PPV of 0.65 and NPV of 0.99 for bladder cancer classification. Sensitivity values of the diagnostic panel for high-grade bladder cancer, low-grade bladder cancer, MIBC and NMIBC were 0.94, 0.89, 0.97 and 0.93, respectively. Additional studies are needed to evaluate the value of the test in clinical decision making.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
86294 **(E/I)**	Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)
86386 **(E/I)**	Nuclear Matrix Protein 22 (NMP22), qualitative
88120 **(E/I)**	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121 **(E/I)**	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
88367 *	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), using computer-assisted technology, per specimen; initial single probe stain procedure (*with C67.0-C67.9, D09.0, D49.4, R31.0-R31.9, Z85.51) **(E/I for listed diagnosis codes)**
88373	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each additional single probe stain procedure (list separately in addition to code for primary procedure)
88368	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure (List separately in addition to code for primary procedure) (*with C67.0-C67.9, D09.0, D49.4, R31.0-R31.9, Z85.51) **(E/I for listed diagnosis codes)**
88369	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each additional single probe stain procedure (list separately in addition to code for primary procedure)
0012M **(E/I)**	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
0013M **(E/I)**	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
0363U **(E/I)**	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 (includes Cxbladder triage, Pacific Edge Diagnostic USA) *(Effective 1/01/2023)*
0365U **(E/I)**	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of bladder cancer (Oncuria® Predict, DiaCarta Clinical Lab, DiaCarta, Inc) *(Effective 04/01/2023)*

Code	Description
0366U **(E/I)**	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer (Oncuria® Predict, DiaCarta Clinical Lab, DiaCarta, Inc) *(Effective 04/01/2023)*
0367U **(E/I)**	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection (Oncuria® Predict, DiaCarta Clinical Lab, DiaCarta, Inc) *(Effective 04/01/2023)*
0420U **(E/I)**	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 *(Effective 01/01/2024)*
0452U **(E/I)**	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer *(Effective 07/01/2024)*
0465U **(E/I)**	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative *(Effective 07/01/2024)*

HCPCS Codes

Code	Description
No codes	

ICD10 Codes

Code	Description
C67.0-C67.9	Malignant neoplasm of bladder (code range)
D09.0	Carcinoma in situ of bladder
D49.4	Neoplasm of unspecified behavior of bladder
R31.0-R31.9	Hematuria (code range)
Z85.51	Personal history of malignant neoplasm of bladder

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*Key Article

KEY WORDS

Bladder tumor antigen, BTA, Fibrin/fibrinogen degradation (FDP), ImmunoCyt, NMP-22.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Urinary Markers for Bladder Cancer.