

Corporate Medical Policy

Urinary Tumor Markers for Bladder Cancer AHS – G2125

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Description of Procedure or Service

A. Definitions

Tumor biomarkers are proteins detected in the blood, urine, or other body fluids that are either produced by the tumor itself or in response to its presence used to help detect, diagnose, and manage some types of cancer (Hottinger & Hormigo, 2011).

B. Background

Worldwide, there were approximately 540,000 cases of bladder cancer and 190,000 deaths related to bladder cancer (Fitzmaurice et al., 2017). In the United States, there are approximately 79,000 cases per year and 17,000 deaths (Siegel, Miller, & Jemal, 2017). Bladder cancer commonly presents as painless hematuria, and is heterogeneous, with 70% of patients presenting with superficial tumours (Chou & Dana, 2010), 50 – 70% of which recur despite treatment but are generally not life threatening, and 30% presenting as aggressive muscle-invasive disease associated with a high risk of metastases (Kaufman, Shipley, & Feldman, 2009).

Cystoscopy is the gold standard for examination for bladder cancer although it does not detect all malignancies nor does it visualize the upper urinary tract. Furthermore, cystoscopy although minimally invasive, can be uncomfortable and promote anxiety, which can lead to suboptimal compliance with management recommendations. Urine biomarkers could have a significant role in determining which individuals require cystoscopy as well as determining those who might need evaluation of the upper urinary tract (Mitra, Birkman, & Penson, 2017).

Cytology of voided urine or bladder washings is commonly used as an adjunct to cystoscopy, particularly to detect lesions that might be missed by cystoscopy. While bladder wash urine cytology has a high sensitivity for high-grade papillary tumors and carcinoma in situ, it has relatively low sensitivity for low-grade tumors (Mitra et al., 2017).

Urine has the potential to contain a variety of molecular markers that may be associated with neoplasia along with cells for cytology. A number of urine markers (table 1) and additional techniques to analyze cells shed in urine (table 2) have been evaluated (Mitra et al., 2017):

Urinary Tumor Markers for Bladder Cancer AHS – G2125

Table 1

Target	Sensitivity	Specificity	False positive in
Bladder tumor antigen	50 to 90 percent	90 percent	Urinary tract infection, hematuria, calculi, BPH, prior intravesical treatment
Nuclear matrix protein (NMP) 22	42 to 100 percent	70 to 91 percent	Inflammation
NMP 52	97 percent	94 percent	
Bladder cancer associated nuclear matrix protein 4 (BLCA-4)	89 to 96 percent	95 to 100 percent	
BLCA-1	80 percent	87 percent	
Survivin	64 to 100 percent	93 to 100 percent	
Cytokeratin (CK) 8 and CK 18	35 to 79 percent	68 percent	
CK 19	43 to 96 percent	70 percent	Urinary tract infection, calculi, post-BCG
Fibrin degradation products (FDP)	70 percent	68 to 86 percent	
Hyaluronic acid, hyaluronidase	82 to 100 percent	81 to 90 percent	

Table 2

Target	Sensitivity	Specificity	False positive in
Nuclear morphology abnormalities	59 to 69 percent	73 to 93 percent	
Cytokeratin 20	78 to 87 percent	55 to 80 percent	Urinary tract infection, calculi, post-BCG
Telomerase	70 to 100 percent	60 to 70 percent	Infection
Microsatellite DNA	72 to 97 percent	80 to 100 percent	BPH, inflammation
Chromosomal abnormalities (chromosomes 3, 7, 17, and 9p21)	69 to 87 percent	89 to 96 percent	BPH, inflammation, hematuria
Carcinoembryonic antigen (CEA), mucoproteins	70 to 80 percent	60 to 70 percent	BPH, inflammation, hematuria
DD23 antibody	70 to 87 percent	60 percent	
Lewis X antigen	80 to 85 percent	80 to 85 percent	BPH

However, because of the lower disease prevalence in a screening population, even in those at increased risk, the use of biomarkers for screening is not cost effective or recommended (Lotan et al., 2009). Despite the promise of urine biomarkers, cystoscopy remains the procedure of choice both for initial diagnosis and for surveillance in previously treated patients.

C. Applicable Federal Regulations

Urinary tumor marker tests cleared by the FDA and in clinical use include:

Urinary Tumor Markers for Bladder Cancer AHS – G2125

1. The quantitative BTA TRAK® and the qualitative point-of-care BTA (bladder tumor antigen) stat® test, both by Polymedco Inc., Cortlandt Manor, NY.
2. The quantitative immunoassay NMP22® and the qualitative, point-of-care test NMP22® BladderChek®, both by Matritech Inc., Newton, MA.
3. The UroVysion® Bladder Cancer Kit (Vysis Inc., Downers Grove, IL), a FISH test.
4. The ImmunoCyt™ test, also marketed as UCyt+™ (DiagnoCure Inc., Quebec).

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.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Urinary Tumor Markers for Bladder Cancer when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Urinary Tumor Markers for Bladder Cancer is covered

1. Reimbursement is allowed for urinary biomarkers (bladder tumor antigen (BTA) test, nuclear matrix protein (NMP22) test, or fluorescence in situ hybridization (FISH) UroVysion Bladder Cancer test):
 - a. as an adjunct in the diagnostic exclusion of bladder cancer for patients who have an atypical or equivocal cytology
 - b. as an adjunct in the monitoring of bladder cancer
2. Reimbursement is allowed for the use of fluorescence immunocytology (ImmunoCyt/uCyt) as an adjunct to cystoscopy or cytology in the monitoring of persons with bladder cancer.

When Urinary Tumor Markers for Bladder Cancer is not covered

1. Reimbursement is not allowed for urinary biomarkers (bladder tumor antigen (BTA) test, nuclear matrix protein (NMP22) test, or fluorescence in situ hybridization (FISH) UroVysion Bladder Cancer test) for screening of bladder cancer, evaluation of hematuria, and diagnosing bladder cancer in symptomatic individuals, and all other indications.
2. Reimbursement is not allowed for the use of fluorescence immunocytology (ImmunoCyt/uCyt) in the evaluation of hematuria, diagnosing bladder cancer, or for screening for bladder cancer in asymptomatic persons and all other indications.
3. Reimbursement is not allowed for the use of all other urinary biomarkers, including but not limited to quantitative mRNA (Cxbladder).

Policy Guidelines

A. Guidelines and Recommendations

Chou et al (Chou et al., 2015) conducted a meta-analysis which found that “Across biomarkers, sensitivities ranged from 0.57 to 0.82 and specificities ranged from 0.74 to 0.88. Positive likelihood ratios ranged from 2.52 to 5.53, and negative likelihood ratios ranged from 0.21 to 0.48 (moderate SOE for quantitative NMP22, qualitative BTA, FISH, and ImmunoCyt; low SOE for others). For some biomarkers, sensitivity was higher for initial diagnosis of bladder cancer than for diagnosis of recurrence. Sensitivity increased with higher tumor stage or grade. Studies that directly compared the accuracy of quantitative NMP22 and qualitative BTA found no differences in diagnostic accuracy (moderate SOE); head-to-head studies of other biomarkers were limited. Urinary biomarkers plus cytologic evaluation were more sensitive than biomarkers alone but missed about 10% of bladder cancer cases.” The authors concluded that “Urinary biomarkers miss a substantial proportion of patients with bladder cancer and are subject to false-positive results in others. Accuracy is poor for low-stage and low-grade tumors.”

Meleth et al (2014) prepared an assessment for the Agency for Healthcare Research and Quality that stated “although UroVysion is marketed as a diagnostic rather than a prognostic test, limited evidence from two small studies (total N=168) rated as low or medium risk of bias supported associations between test result and prognosis for risk of recurrence. We found no studies that directly assessed the impact of a test of interest on both physician decision-making and downstream health outcomes to establish clinical utility. We attempted to construct an indirect chain of evidence to answer the overarching question, but we were unable to do so. Even in the cases where the tests seemed to add value in determining prognosis (i.e., evidence of clinical validity), we found no evidence that using the test was related to improved outcomes for patients.”

Lotan and Choueiri (2017) stated that “most urine-based molecular markers are more sensitive than urine cytology in the detection of urothelial cancer, especially for low-grade tumors, but the specificity of molecular markers is inferior to that of urine cytology.” The authors further stated that “none of these markers have sufficient sensitivity to replace cystoscopy in the assessment of an individual suspected to have bladder cancer, and their clinical use has not been recommended by consensus panels. There is a potential benefit for surveillance in patients with a history of urothelial cancer by reducing the interval for cystoscopy. There is evidence that markers, such as Urovysion FISH assay, may help management of patients with atypical findings on cytology or cystoscopy. Furthermore, urine markers may help in predicting outcomes for patients being treated with intravesical immunotherapy.”

Mitra et al (2017) published a review of urinary biomarkers for the detection of bladder cancer. Regarding potential application of biomarkers in diagnosis, the authors stated that “The diagnosis of bladder cancer ultimately requires a histologic diagnosis, which usually comes from a biopsy that is obtained at cystoscopy. Cytology may provide strong evidence for the presence of malignancy, and a positive cytology should prompt further investigation. Urine biomarkers could have a significant role in determining which individuals require cystoscopy, as well as determining those who might need evaluation of the upper urinary tract.” Regarding the use of biomarkers for surveillance, the authors noted that “Cystoscopy is the gold standard for surveillance in patients with a history of bladder cancer. Because it does not detect all recurrences nor does it visualize the upper urinary tract, a biomarker test should accompany cystoscopy in order to minimize the risk of missing a high-grade tumor.”

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Urinary Tumor Markers for Bladder Cancer AHS – G2125

Regarding surveillance of bladder cancer, the National Comprehensive Cancer Network (NCCN, 2017) bladder cancer guidelines recommended that “Consideration may be given to FDA approved urinary biomarker testing by fluorescence in situ hybridization (FISH) or nuclear matrix protein 22 in monitoring for recurrence”

National Academy of Clinical Biochemistry Laboratory Medicine

The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend use of any Food and Drug Administration (FDA)–approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients.²⁵ The guideline stated:

“At this time, no tumor markers tests can be recommended for use in the diagnosis and clinical management of bladder cancer. This includes tests for making a differential diagnosis, assessing prognosis, staging of the disease or monitoring patients for the early detection of recurrent disease. There are no prospective clinical trial data that establish the utility of any of the FDA cleared markers or the proposed markers for increasing survival time, decreasing the cost of treatment or improving the quality of life of bladder cancer patients.”

American Urological Association

The American Urological Association’s (Davis et al., 2012) guideline on the Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults recommends that: “The use of urine cytology and urine markers (Nuclear Matrix Protein 22 [NMP22], bladder tumor antigen [BTA]-stat, and UroVysion fluorescence in situ hybridization assay [FISH]) is NOT recommended as a part of the routine evaluation of the asymptomatic microhematuria patient.”

The American Urological Association and Society of Urologic Oncology (Chang et al., 2016) joint guidelines on Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer recommend:

“In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation.

In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance.

In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™).”

The authors further stated that “At present, urinary biomarkers are insufficiently accurate to replace cystoscopy for diagnosis/surveillance, though some appear to have predictive utility for assessing response to intravesical BCG and may help interpret indeterminate cytology.”

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (Moyer, 2011) concluded in 2011 that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was graded as an “I” recommendation, indicating insufficient evidence.

Billing/Coding/Physician Documentation Information

Urinary Tumor Markers for Bladder Cancer AHS – G2125

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 86294, 86316, 86386, 88120, 88121, 88271, 88299, 88365

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Urinary Tumor Markers for Bladder Cancer AHS – G2125

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Policy Implementation/Update Information

- 1/1/19 New policy developed. BCBSNC will provide coverage for urinary tumor markers for bladder cancer when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)
- 10/1/19 Policy statement revised to read: BCBSNC will provide coverage for Urinary Tumor Markers for Bladder Cancer when it is determined the medical criteria or reimbursement guidelines below are met. Wording revised in the When Covered section. "Medically necessary" changed to read "Reimbursement is allowed..." Wording revised in the Not Covered section. "Investigational" changed to read "Reimbursement is not allowed..." Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019.
- 10/15/19 Medical Director review. Statement added that reimbursement for the use of all other urinary biomarkers, including but not limited to quantitative mRNA (Cxbladder), is not allowed. Notification given 10/15/2019 for effective date 12/31/2019. (sk)
- 12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment

Urinary Tumor Markers for Bladder Cancer AHS – G2125

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.