

Corporate Medical Policy

Urinary Tumor Markers for Bladder Cancer

File Name: urinary_tumor_markers_for_bladder_cancer
Origination: 5/2011
Last CAP Review: 4/2012
Next CAP Review: 4/2013
Last Review: 4/2012

Description of Procedure or Service

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Moreover, bladder cancer has a very high frequency of recurrence and therefore requires follow-up cystoscopies, along with urine cytology, as periodic surveillance to identify recurrence early. Consequently, urine biomarkers that might be used to either supplement or supplant these tests have been actively investigated.

Background

Urinary bladder carcinoma, the fourth most common cancer in men and the ninth most common cancer in women, 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 common symptom of early bladder cancer is hematuria; however, urinary tract symptoms (i.e., urinary frequency, urgency and dysuria) may also occur. Most urologists follow the American Urological Association (AUA) guidelines for hematuria, which recommend cystoscopic evaluation of all adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with risk factors for developing bladder cancer. Confirmatory diagnosis of bladder cancer must be made by cystoscopic examination, which is considered to be the gold standard, and 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 depth of invasion and tumor grade. However, a 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 50–60% 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.

Commercially Available Bladder Tumor Markers

The BTA (bladder tumor antigen) stat® test, (Polymedco Inc., 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 Inc., Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both tests have sensitivities

Urinary Tumor Markers for Bladder Cancer

comparable to that of cytology for high-grade tumors and better than cytology for low-grade tumors.

Nuclear matrix protein 22 (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, and elevated levels may be associated with bladder cancer. NMP-22 may be detected in the urine using an immunoassay.

Fluorescence in situ hybridization (FISH) DNA probe technology has also 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, which match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. UroVysion® (Vysis Inc., Downers Grove, IL) is a commercially available FISH test.

The ImmunoCyt™ test (DiagnoCure Inc., Quebec) uses fluorescence immunohistochemistry with antibodies to a mucin glycoprotein and a carcinoembryonic antigen (CEA). These antigens are found on bladder tumor cells. The test is used for monitoring bladder cancer in conjunction with cytology and cystoscopy.

The following table reflects the sensitivities and specificities of urine tumor markers in bladder cancer as reported in publications.

Sensitivities and specificities of selected urine-based tumor markers in bladder cancer

Commercially available marker	Sensitivity (%) mean/ range	Specificity (%) mean/ range
Cytology	48/ 16-89	96/ 81-100
Hematuria dipstick	68/ 40-93	68/ 51-97
BTA <i>stat</i> ®	68/ 53-89	74/ 54-93
BTA TRAK®	61/ 17-78	71/ 58-89
NMP22®	75/ 32-92	75/ 51-94
NMP22®BladderChek®	55.7	85.7
ImmunoCyt™	74/ 39-100	80/ 73-84
UroVysion™	77/ 73-81	98/ 96-100

Other urinary markers

A number of other urinary tumor markers, not currently commercially available in the United States, are under investigation. These include:

- BLCA-1 and BCLA-4;
- Hyaluronic acid and hyaluronidase;
- Lewis X antigen;
- Microsatellite markers;
- Solubla Fas;
- Survivin (can be isolated from urine and also from tumor samples);
- Telomerase;
- Cytokeratin 8, 18, 19, 20;
- Quanticyt

Urinary Tumor Markers for Bladder Cancer

Regulatory Status

As of March 2010, 6 urinary tumor marker tests have been cleared by the U.S. Food and Drug Administration (FDA) and are in clinical use. These tests are:

- The quantitative BTA TRAK® and the qualitative point-of-care BTA (bladder tumor antigen) stat® test, both by Polymedco Inc., Cortlandt Manor, NY.
- The quantitative immunoassay NMP22® and the qualitative, point-of-care test NMP22® BladderChek®, both by MatriTech Inc., Newton, MA.
- The UroVysion® Bladder Cancer Kit (Vysis Inc., Downers Grove, IL), a FISH test.
- 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.

Related Policies

None

****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 to be medically necessary because the medical criteria and guidelines shown 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 are covered

Initial diagnosis

The following urinary bladder tumor markers may be considered medically necessary as an adjunct in the diagnosis of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA *stat*®*, BTA TRAK®*;
- NMP22®*, NMP22 Bladder Chek®*;
- UroVysion™*.

Bladder cancer monitoring

The following urinary bladder cancer tumor markers may be considered medically necessary as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA *stat*®*, BTA TRAK®*;

Urinary Tumor Markers for Bladder Cancer

- Immunocyt™*;
- NMP22® *, NMP22 Bladder Chek®*;
- UroVysion™.*

*** FDA Approved indications**

When Urinary Tumor Markers for Bladder Cancer are not covered

The following urinary bladder tumor markers are considered investigational in the initial diagnosis of bladder cancer:

- ImmunoCyt™, UCyt+™

Urinary bladder cancer tumor markers are considered investigational for screening for bladder cancer in asymptomatic persons.

All other bladder cancer tumor markers not addressed under “When Urinary Tumor Markers for Bladder Cancer are covered” are considered investigational in the diagnosis, monitoring, or screening for bladder cancer.

*** FDA Approved indications**

Policy Guidelines

For the purpose of this policy, standard diagnostic procedures for bladder cancer consist of urine cytology and cystoscopy, with or without biopsy.

Numerous well-designed studies have evaluated the diagnostic performance of the FDA-approved urinary tumor markers. Overall, studies have found reasonable sensitivities and specificities, and a recent study found that that one or two of these urinary tumor markers can enhance the sensitivity of urinary cytology. Studies describing other, non-FDA approved markers generally involve limited numbers of patients, and they have not been compared to urinary cytology or the commercially available tests. Based on the available evidence, the FDA-approved urinary markers are considered medically necessary for their approved indications when used in conjunction with standard diagnostic procedures, and other markers are considered investigational.

The existing evidence does not support the use of urinary tumor markers to screen for bladder cancer due to the low prevalence of asymptomatic disease in the general population and the lack of evidence that early treatment of screen-detected bladder cancer improves health outcomes. A recent prospective study also found a low yield when the BladderChek test was used in an industry-sponsored trial to screen high-risk asymptomatic individuals.

Urinary Tumor Markers for Bladder Cancer

Billing/Coding/Physician Documentation Information

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.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86294, 86316, 86386, 88120, 88121, 88271, 88299, 88367, 88368

The UroVysion Bladder Cancer Kit is a FISH test. Some examples of coding that laboratory companies use for this test include:

CPT codes 88271(x4) with 88274,

CPT code 88367 (x4); and

CPT code 88368 (x4)

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

Original Policy named: Tumor Markers

BCBSA Medical Policy Reference Manual - 7/10/98

Medical Policy Advisory Group - 3/99

Specialty Matched Consultant Advisory Panel - 6/2001

Conference call with the American Society of Clinical Oncology (ASCO) - 7/2001 (clarification of 2000 ASCO guidelines)

Medical Policy Advisory Group with presentation by Specialty Matched Consultant - 9/6/2001 (clarification of 2000 ASCO guidelines)

Specialty Matched Consultant Advisory Panel - 6/2003

BCBSA Medical Policy Reference Manual. 2.04.07, 2/25/2004

Specialty Matched Consultant Advisory Panel - 4/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.07, 6/27/05

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.07, 10/10/06

Specialty Matched Consultant Advisory Panel - 4/2007

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.07, 6/12/08

Specialty Matched Consultant Advisory Panel - 4/2009

Urinary Tumor Markers for Bladder Cancer

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.07. 5/13/2010

Medical Director – 10/2010

Tumor Marker Policy Separated – New Name Urinary Tumor Markers for Bladder Cancer

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.07, 5/12/11

Specialty Matched Consultant Advisory Panel – 4/2012

Policy Implementation/Update Information

- 5/24/11 “Tumor Marker” policy separated, policy name changed to “Urinary Tumor Markers for Bladder Cancer”. Specialty Matched Consultant Advisory Panel review 4/27/11. “Description” section revised. No change to policy intent in relation to bladder cancer. Added CPT codes 88120 and 88121 to “Billing/Coding” section. Reference added. (btw)
- 8/16/11 Reworded 8th bullet in “Description”, under Other Urinary Markers to indicate “Cytokeratin 8, 18, 19, 20”. Reference added. (btw)
- 1/1/12 Added new 2012 CPT code, 86386, to the “Billing/Coding” section. (btw)
- 5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. The When Not Covered section reformatted, no change to policy intent. (btw)

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