Urinary Tumor Markers for Bladder Cancer

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, 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 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 for the urologic evaluation of asymptomatic microhematuria, a cystoscopy should be performed on all patients aged 35 years and older. Confirmatory diagnosis of bladder cancer must be made by cystoscopic examination, which is considered to be the criterion 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 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%–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.

Tests cleared by the U.S. Food and Drug Administration (FDA):

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.
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Both tests have sensitivities 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. Vysis UroVysion® (Abbott Molecular) is a commercially available FISH test.

The ImmunoCyt™ test (Scimedx Corporation. Denville, NJ) 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.

In addition to the FDA-cleared tests, Predictive Biosciences (Lexington, MA) is marketing a urine-based test, called CertNDx™ to assess Fibroblast Growth Factor Receptor 3 (FGFR3) mutations. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. It is being offered through Predictive Bioscience’s network of Clinical Laboratory Improvement Amendment (CLIA) laboratories. FGFR3 mutations may be associated with lower-grade bladder tumors that have a good prognosis.

Pacific Edge Diagnostics USA (Hersey, PA.) is marketing a urine-based test called Cxbladder™. Five biomarkers of interest, MDK, HOXA13, CDC2 (CDK1), IGFBP5, and CXCR2 are quantified by a different probe and the relationship between the individual biomarkers is determined by a mathematical equation. According to the company’s website, “The calculated outcome provides a measure of the probability of the presence of urothelial carcinoma (UC).”

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

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

### Other urinary markers

A number of other urinary tumor markers, not currently commercially available in the United States, are under investigation. These include:
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- BLCA-1 and BCLA-4;
- Hyaluronic acid and hyaluronidase;
- Lewis X antigen;
- Microsatellite markers;
- Soluble Fas;
- Survivin (can be isolated from urine and also from tumor samples);
- Telomerase;
- Cytokeratin 8, 18, 19, 20;
- Quanticyt

Regulatory Status

The following 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 Alere Waltham, MA.
- The Vysis UroVysion® Bladder Cancer Kit (Abbott Molecular), a FISH test.
- The ImmunoCyt™ test, also marketed as UCyt+™ (Scimedx Corporation. Denville, NJ).

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.

At this time, CertNDx™ (Predictive Biosciences) and CxBladder (Pacific Edge Diagnostics USA) have not received FDA approval.

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 evaluation

The following urinary bladder tumor markers may be considered medically necessary as an adjunct...
Urinary Tumor Markers for Bladder Cancer

in the diagnostic exclusion of bladder cancer only in conjunction with current standard diagnostic procedures for patients who have an atypical or equivocal cytology:

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

Bladder cancer surveillance

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®*
- 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 routine screening for bladder cancer in low or high risk individuals.

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.

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 for patients who have an atypical or equivocal cytology, and other markers are considered investigational.

The existing evidence does not support the use of urinary tumor markers to routinely screen for bladder cancer due to the low prevalence of disease without signs or symptoms 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 individuals without signs or symptoms of bladder cancer.
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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, 88369, 88373, 88374, 88377, 81599*

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**


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


Medical Director – 10/2010

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

Urinary Tumor Markers for Bladder Cancer


Specialty Matched Consultant Advisory Panel review 12/2012

Medical Director review 3/2013


Specialty Matched Consultant Advisory Panel review 11/2013

Medical Director review 11/2013


Policy Implementation/Update Information


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 re-formatted; no change to policy intent. (btw)

4/1/13 Specialty Matched Consultant Advisory Panel review 12/2012. Removed the following statement from the “When not Covered” section: “Urinary bladder tumor markers are considered investigational for screening for bladder cancer in asymptomatic patients.” Revised statement in the “When Covered” section: “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 for patients who have an atypical or equivocal cytology…” Revised headers in “When Covered” from “Bladder cancer monitoring” to “Bladder cancer surveillance” and “Initial Diagnosis” to “Initial Evaluation.” Medical Director review 3/2013. (mco)
Urinary Tumor Markers for Bladder Cancer

5/14/13 Description section updated. References updated. No changes to Policy Statements. (mco)

12/10/13 Description section updated to include new test “CxBladder.” “CxBladder added to the “When not Covered” section. Unlisted CPT code 81599 added to “Billing/Coding” section. Specialty Matched Consultant Advisory Panel review 11/2013. Medical Director review 11/2013. (mco)

4/29/14 References updated. No changes to Policy Statements. (mco)


12/30/14 Added codes 88369, 88373, 88374, and 88377 to Billing/Coding section for effective date 1/1/2015. (sk)

4/28/15 Reference added. (sk)

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. (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 and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.