Introduction

A tumor marker is a chemical in blood, urine, or tissue that is often made by cancer cells. But just because a tumor marker is found doesn’t necessarily mean a person has cancer. Normal cells often make tumor markers, too. But if cancer is present, much more of the tumor marker is made. There are difficulties in using tumor markers to try to screen for, diagnose, or monitor cancer. Conditions other than cancer can make the level of a tumor marker go up. And, not all cancers create high levels of tumor markers. For these reasons, just looking for high levels of tumor markers isn’t enough to diagnose cancer. This policy specifically discusses tumor markers for bladder cancer. Using tumor marker tests to look for bladder cancer is investigational (unproven). There’s not enough current medical evidence to show that using tumor marker tests compared to standard tests to look for bladder cancer leads to more health benefits. More medical studies are needed.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Service | Investigational
--- | ---
Urinary tumor markers, and panels that measure these markers | The use of urinary tumor markers is considered investigational in the diagnosis of, monitoring, and/or screening for bladder cancer.

Note: Commercial tests include but are not limited to the following: The BTA stat® test and BTA TRAK® test (Polymedco, Cortlandt Manor, NY), Alere NMP22® BladderChek® (Alere), Vysis UroVysion® (Abbott Molecular, ImmunoCyt™ test (DiagnoCure, Quebec City, QC), CertNDx™ (Predictive Laboratories, Lexington, MA), Cxbladder™ (Pacific Edge, New Zealand)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>
| 86294 | Immunoassay for tumor antigen, qualitative or semiquantitative (eg, bladder tumor antigen)  
- May be used to describe the BTA stat test when performed qualitatively in a physician office. |
| 86316 | Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each  
- May be used to describe the BTA or NMP22 test when performed quantitatively in a clinical lab. |
<p>| 86386 | Nuclear Matrix Protein 22 (NMP22), qualitative |
| 88120 | Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual |
| 88121 | Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology |
| 88271 | Molecular cytogenetics; DNA probe, each (eg, FISH) |
| 88291 | Cytogenetics and molecular cytogenetics, interpretation and report |</p>
<table>
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<th>Code</th>
<th>Description</th>
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<td>88299</td>
<td>Unlisted cytogenetic study</td>
</tr>
<tr>
<td>88358</td>
<td>Morphometric analysis; tumor (eg, DNA ploidy)</td>
</tr>
<tr>
<td>88365</td>
<td>In situ hybridization (eg, FISH), per specimen; initial single probe stain procedure</td>
</tr>
<tr>
<td>88367</td>
<td>Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; initial single probe stain procedure</td>
</tr>
<tr>
<td>88368</td>
<td>Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure</td>
</tr>
</tbody>
</table>

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**Related Information**

N/A

**Evidence Review**

**Description**

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Bladder cancer often recurs and therefore follow-up cystoscopy, along with urine cytology, is periodically done to find any recurrence early. Urine biomarkers that might be used to either supplement or replace these tests have been actively investigated.

**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 (eg, urinary frequency, urgency, dysuria) may also occur.
In 2012, the American Urological Association published guidelines on the evaluation of microscopic hematuria in adults. They recommended cystoscopy for adults over age 40, as well as for adults younger than 40 if they had risk factors for developing bladder cancer. These guidelines were reviewed and affirmed by the AUA in 2016. Cystoscopic examination with biopsy is considered to be the criterion standard to diagnose bladder cancer. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. Disease that has not invaded the muscle 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% to 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 cleared by the U.S. Food and Drug Administration clearance, as well as laboratory-developed tests, are summarized in the Regulatory Status section.

**Summary of Evidence**

For individuals who have signs and symptoms of bladder cancer or a history of bladder cancer who receive urinary tumor marker tests, 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. 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 tended to have higher sensitivity but lower or similar specificity compared with cytology. Also, they found that combining tumor marker tests with cytology can improve overall diagnostic accuracy. The decision curve analysis found only a small clinical benefit 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 the 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. Therefore, these tests are considered investigational.

For individuals who are asymptomatic and do not have an increased risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The 2010 systematic review (conducted for the U.S. Preventive Services Task Force [USPSTF]) did not identify any RCTs, which is the preferred trial design to evaluate the impact of population-based screening, and found only 1 prospective study that USPSTF 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. Therefore these tests are considered investigational.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 2 physician specialty societies and 5 academic medical centers while the policy was under review in 2012. There was unanimous agreement that urinary tumor markers approved by the Food and Drug Administration may be considered medically necessary as an adjunctive test in the diagnosis and monitoring of bladder cancer in conjunction with standard diagnostic procedures. In contrast, there was mixed support, but no consensus, on the incremental value of urinary tumor markers compared with urinary
cytology alone and for whether urinary tumor markers lead to changes in patient management. There was unanimous agreement that the use of urinary tumor markers is investigational to screen for bladder cancer in asymptomatic subjects.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (v.2.2017) bladder cancer guidelines include consideration for checking urinary urothelial tumor markers every 3 months along with urine cytology for the first 2 years of follow-up for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation).²⁰

**American Urological Association**

The 2016 guidelines from the American Urological Association and Society of Urologic Oncology addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review completed by the Agency for Health Care Research and Quality.²¹ Statements on the use of urine markers after the diagnosis of bladder of cancer are summarized in Table 1.

**Table 1. Guidelines for Urine Tumor Markers After the Diagnosis of Bladder Cancer**

<table>
<thead>
<tr>
<th>Guidance Statement</th>
<th>SOR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation.”</td>
<td>Strong</td>
<td>B</td>
</tr>
<tr>
<td>“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.”</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>“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™).”</td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

LOE: level of evidence; NMIBC: non-muscle-invasive bladder cancer; SOR: strength of recommendation.
The 2012 guidelines from the American Urological Association (reviewed and affirmed in 2016) on the evaluation of microscopic hematuria in adults recommended cystoscopic evaluation for the following individuals:\(^1\):

- Older than age 40 with microscopic hematuria; and
- Younger than age 40 with microscopic hematuria and risk factors for developing bladder cancer.

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force 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 based on insufficient evidence (grade I).\(^2\)

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

The following urinary tumor marker tests have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and in clinical use:

- The BTA stat\(^\circledast\) test (Polymedco, Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that has been shown to be produced by several human bladder cell lines but not by other epithelial cell lines. The BTA stat\(^\circledast\) 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\(^\circledast\) test (Polymedco, Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both Polymedco tests have sensitivities comparable with that of cytology for high-grade tumors and better than cytology for low-grade tumors.
• The nuclear matrix protein 22 (NMP22) urine immunoassay (Alere NMP22® BladderChek®; Alere) tests for NMP22, a protein associated with the nuclear mitotic apparatus, which may be released from the nuclei of tumor cells during apoptosis. Elevated urine levels have been associated with bladder cancer. NMP22 may be detected in the urine using an immunoassay.

• Vysis UroVysion® (Abbott Molecular) is a commercially available fluorescence in situ hybridization (FISH) test. FISH is a molecular cytogenetic technology that can be used with either DNA or RNA probes to detect chromosomal abnormalities. DNA FISH probe technology involves the creation of short sequences of fluorescently labeled, single-strand DNA probes that match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. DNA FISH probes have been used to detect chromosomal abnormalities in voided urine to assist in bladder cancer surveillance and in the initial identification of bladder cancer.

• The ImmunoCyt™ test (DiagnoCure, Quebec City, QC) uses fluorescence immunohistochemistry to detect antibodies to a mucin glycoprotein and a carcinoembryonic antigen. These antigens are found on bladder tumor cells. DiagnoCure ceased operations in 2016.

With the exception of the ImmunoCyt™ test, which is only cleared for monitoring bladder cancer recurrence, all tests are FDA-cleared as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients.

In addition to FDA-cleared tests, clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Urine-based tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

For example, Predictive Laboratories (Lexington, MA) markets the CertNDx™ test; it assesses fibroblast growth factor receptor 3 (FGFR3) variants. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. FGFR3 variants may be associated with lower grade bladder tumors that have a good prognosis. In addition, Pacific Edge (New Zealand) is marketing a test in the United States called Cxbladder™, which tests for 5 urine-based markers.

**References**


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## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>06/25/98</td>
<td>Add to Medicine Section - New Policy</td>
</tr>
<tr>
<td>09/01/98</td>
<td>Replace Policy - Policy updated.</td>
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<tr>
<td>12/21/00</td>
<td>Replace Policy - New CPT coding information added.</td>
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<tr>
<td>12/11/01</td>
<td>Replace Policy - New information on NMP-22 added and title changed from Bladder Tumor Antigen.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Policy updated; policy statement unchanged; references added.</td>
</tr>
<tr>
<td>08/09/05</td>
<td>Replace Policy - Policy updated with literature review; references added; policy statement revised to indicate the use of bladder cancer tumor markers involving immunoassay tests NMP-22 or BTA stat® as medically necessary as an adjunct in the diagnosis of bladder cancer. Information on fluorescence in situ hybridization (FISH) added; additional policy statement indicating FISH as medically necessary added. Finally, added investigational policy statements for use of these tests for screening in asymptomatic persons.</td>
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<tr>
<td>01/10/06</td>
<td>Replace Policy - Policy updated with the addition of ICD-9 code 599.7; no change to policy statement. Going to OAP 2/16/06.</td>
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<tr>
<td>03/28/06</td>
<td>Code Change - Coding updated only, no other changes</td>
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<tr>
<td>06/30/06</td>
<td>Update Scope and Disclaimer - No other changes</td>
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<tr>
<td>11/14/06</td>
<td>Replace Policy - Literature review update completed and information added on ImmunoCyt along with policy statement of medically necessary for this indication in the monitoring of patients with bladder cancer, remaining investigational for all other uses. Comments added regarding other tumor markers currently under study, however, remaining investigational. References added. Code S3701 removed from policy. Policy reviewed and recommended by OAP on 2/16/06.</td>
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<tr>
<td>11/11/08</td>
<td>Replace Policy - Policy updated with literature search, no change to the policy statement. References added. Reviewed and recommended by OAP on 5/22/08.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
</tr>
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<tr>
<td>03/10/09</td>
<td>Code Update - Code 88291 added.</td>
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<tr>
<td>07/14/09</td>
<td>Replace Policy - Policy updated with literature search. Policy statement has been reworded for clarification however; intent of policy statements remains unchanged. Statements have been modified to include FDA-approved uses. References and code added.</td>
</tr>
<tr>
<td>8/10/10</td>
<td>Replace Policy - Policy updated with literature review from April 2009 through March 2010. Policy statements unchanged. Rationale rewritten; new references 1, 4-5, 7-12, 14-15 added; other references have been renumbered or removed.</td>
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<tr>
<td>07/12/11</td>
<td>Replace Policy - Policy updated with literature search from March 2010 through March 2011. References 7, 13, 14, 17 and 22 added; other references renumbered and/or updated. Policy statements unchanged. ICD-10 codes added to policy. CPT coding for FISH testing also updated.</td>
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<td>09/11/12</td>
<td>Replace policy. Policy updated with literature search through March 2012. Policy changed to investigational for diagnosing, monitoring and/or screening for bladder cancer. References 1, 6-8, 10, 12, 15 and 20 added; other references renumbered or removed. Clinical input added. Policy update effective 2/11/13 subsequent to provider notification.</td>
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<tr>
<td>05/28/13</td>
<td>Replace policy. Policy updated with literature search through January 31, 2013. Policy statement unchanged. References 3, 4, 8-10 and 14 added; other references renumbered or removed.</td>
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<tr>
<td>05/12/14</td>
<td>Annual Review. Policy updated with literature review through February 4, 2014. Policy statement unchanged. References 4, 23. and 25 added; other references renumbered or removed.</td>
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<td>12/08/14</td>
<td>Update Related Policies. Remove 2.03.501 as it was archived.</td>
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<tr>
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<td>Archive Policy. Policy updated with literature review through February 10, 2015. References 3, 5, 15 added. Policy statement unchanged. This service costs more to review than to allow.</td>
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<td>02/09/16</td>
<td>Reinstate policy. Claims volumes and cost have increased substantiating a need for the policy.</td>
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<tr>
<td>11/10/16</td>
<td>Minor formatting update. All coding information added to Policy Guidelines section.</td>
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</table>

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Email AppealsDepartmentInquiries@Premera.com

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https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


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Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormacion. Daytoy a pakdaar mabalbin nga adda ket naglaon iti napateg nga impormasion maijanggep iti aplikasyonno wenno coverage babaen ti Premera Blue Cross. Daytoy ket mabalbin dagiti importante a pelta iti daytoy a pakdaar. Mabalbin nga adda rumbeng nga aramideng nga adda sangkay dagiti partialik a naituding nga adda alway napo tapapagatalinedyo iti tegaay ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganayo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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