2.04.07 Urinary Tumor Markers for Bladder Cancer

Policy Statement

The use of urinary tumor markers is considered investigational in the diagnosis of, monitoring, and/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.

Coding

The BTA (bladder tumor antigen) stat® and nuclear matrix protein 22 (NMP22) are immunoassay tests.

When performed qualitatively in the physician's office, the following CPT codes may be used to describe the corresponding tests:

- **BTA stat Test**
  - 86294: Immunoassay for tumor antigen, qualitative and semiquantitative (e.g., bladder tumor antigen)

- **NMP22 Test**
  - 86386: Nuclear Matrix Protein 22 (NMP22), qualitative

For clinical laboratories performing a quantitative version of these tests, the following CPT code may be used to describe the test:

- 86316: Immunoassay for tumor antigen; other antigen, quantitative (e.g., CA 50, 72-4, 549), each

There are specific CPT codes for urinary fluorescence in situ hybridization (FISH) testing:

- 88120: Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual

- 88121: Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology

The CertNDx™ test is likely to be reported with the following CPT code:

- 81479: Unlisted molecular pathology procedure

Description

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Bladder cancer has a very high frequency of recurrence and therefore follow-up cystoscopy, along with urine cytology, is done periodically to identify recurrence early. Urine biomarkers that might be used to supplement or supplant these tests have been actively investigated.

Related Policies

- N/A
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### 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 for clinical use:

- **The BTA** stat® 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®** 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, 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.

### Rationale

#### Background

**Urinary Bladder Cancer**

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 (i.e., urinary frequency, urgency, dysuria) may also occur.

#### Diagnosis

The 2012 guidelines from the American Urological Association on the evaluation of microscopic hematuria, which were reviewed and affirmed in 2016, have recommended cystoscopic evaluation of adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with microscopic hematuria and risk factors for developing bladder cancer. Confirmation diagnosis of bladder cancer is made by cystoscopic examination, 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 intravesicual 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 it 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 (e.g., 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.

#### Literature Review

The most recent literature review was performed through April 25, 2017. Following is a summary of the key literature to date.

#### Diagnosis and Management of Individuals with Symptoms or History of Bladder Cancer

**Clinical Context and Test Purpose**

The purpose of using urinary tumor markers in the management in patients who have signs and/or symptoms of bladder cancer (initial or recurrent) is to inform a decision whether to proceed to cystoscopy.

Although patients with a history of urinary bladder cancer have a higher pretest probability of cancer than those with no history, because the evaluation, follow-up, and symptoms are similar,
and many studies have grouped the populations, we have first bundled our discussion of the
diagnosis and management of patients with symptoms and a history of bladder cancer. Where
possible, we separately discuss studies addressing only those with a history of bladder cancer.

The question addressed in this evidence review is: Does the use of urinary tumor markers, in
addition to routine cytology, improve health outcomes for patients with signs and/or symptoms
of or a history of bladder cancer?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are patients with signs and/or symptoms of or a history of
bladder cancer. They may include patients with no prior diagnosis, who present with urinary
symptoms that would be suggestive of bladder cancer, most commonly hematuria, or patients
who have undergone treatment for bladder cancer.

**Interventions**
The interventions of interest are the tests discussed in the Regulatory Status section.

**Comparators**
Patients with microscopic hematuria with no etiology identified after an evaluation for
glomerular disease or infection would typically be recommended for cystoscopy. Patients with a
history of bladder cancer are managed with routine cystoscopies and imaging.

**Outcomes**
The general outcomes of interest are overall survival and disease-specific survival. Beneficial
outcomes are primarily related to detection of disease that would have been missed without the
test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

**Timing**
Although not completely standardized, follow-up for non-muscle-invasive bladder cancer would
typically occur periodically over the course of years.

**Setting**
Testing for urinary tumor markers would typically occur in urologists’ offices.

**Analytic Validity**
All of the U.S. Food and Drug Administration (FDA)—approved tests for urinary tumor markers
involve the use of standard laboratory procedures. No studies specifically reporting on the
analytic validity of the tests discussed were identified.

**Clinical Validity**
FDA-Cleared Urinary Tumor Marker Tests (e.g., BTA stat, NMP22 BladderChek, UroVysion,
ImmunoCyt)
Studies have evaluated the diagnostic performance of individual markers compared with urine
cytology, the standard urine-based test for bladder tumor diagnosis and surveillance.
Cystoscopy and biopsy are generally used as the criterion standard comparison. Of particular
interest are the relative performance of individual markers and the performance of individual
markers compared with combinations of markers.

We identified several systematic reviews of diagnostic accuracy studies. Most recently, Chou et
al (2015) reported on a systematic review and meta-analysis of studies of the diagnostic
accuracy of urinary biomarkers for the diagnosis or follow-up of non-muscle-invasive bladder
cancer, which was done as part of an Agency for Healthcare Research and Quality
Comparative Effectiveness Review on the diagnosis and treatment of non-muscle-invasive
bladder cancer.2 Reviewers included 57 studies reported in 60 publications; 8 studies involved
diagnostic testing, 16 involved surveillance for previously treated bladder cancer, and 19 involved mixed populations.

Selected results of pooled analyses are displayed in Table 1. Diagnostic performance is reported for findings of studies on initial diagnosis and surveillance of individuals previously treated for bladder cancer, which were combined in the analysis.

### Table 1. Diagnostic Accuracy of Urinary Biomarkers Compared With Standard Diagnostic Methods (AHRQ Comparative Effectiveness Report)

<table>
<thead>
<tr>
<th>Test</th>
<th>Pooled Sensitivity (95% CI), %</th>
<th>Pooled Specificity (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat (2 studies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test (2 studies)</td>
<td>64 (58 to 69)</td>
<td>77 (73 to 81)</td>
</tr>
<tr>
<td>Qualitative test (4 studies)</td>
<td>58 (39 to 75)</td>
<td>88 (78 to 94)</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test (19 studies)</td>
<td>69 (62 to 75)</td>
<td>77 (70 to 83)</td>
</tr>
<tr>
<td>Qualitative test (4 studies)</td>
<td>58 (39 to 75)</td>
<td>88 (78 to 94)</td>
</tr>
<tr>
<td>FISH (e.g., UroVysion) (11 studies)</td>
<td>63 (50 to 75)</td>
<td>87 (79 to 93)</td>
</tr>
<tr>
<td>ImmunoCyt (14 studies)</td>
<td>78 (68 to 85)</td>
<td>78 (72 to 82)</td>
</tr>
</tbody>
</table>

CI: confidence interval; FISH: fluorescence in situ hybridization.

Additional systematic reviews have reported on the diagnostic characteristics of individual tests. For example, He et al (2016) reported on a meta-analysis of studies of ImmunoCyt/uCyt+ immunoassay’s diagnostic accuracy in detecting cancer as initial diagnosis or recurrence.3

An earlier comprehensive systematic review published by Parker and Spiess (2011) summarized the sensitivity and specificity of cytology and of several urine tumor markers in bladder cancer for diagnosis and/or monitoring of recurrence.4 Reported sensitivity and specificity data are listed in Table 2. (Diagnostic accuracy was not reported separately for initial diagnosis versus cancer monitoring.)

### Table 2. Sensitivity and Specificity Ranges of Select Biomarkers (Parker and Spiess)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity Range, %</th>
<th>Specificity Range, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>12-79</td>
<td>78-99</td>
</tr>
<tr>
<td>BTA stat</td>
<td>50-70</td>
<td>67-78</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td>50-92</td>
<td>66-87</td>
</tr>
<tr>
<td>FISH (UroVysion)</td>
<td>69-92</td>
<td>89-95</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>67-85</td>
<td>62-85</td>
</tr>
</tbody>
</table>

FISH: fluorescence in situ hybridization.

In addition, in 2010, the U.K. Health Technology Assessment Program published a systematic review of studies on the diagnostic performance of several urine biomarkers.5 Reviewers included 71 studies on the test performance of cytology and urine biomarkers. Most included patients both with and without a history of bladder cancer, or included only patients with a history of bladder cancer. Few studies were identified that focused on the evaluation of urinary markers for the initial diagnosis of bladder cancer. Pooled analyses of study findings combined results of tests used for initial diagnosis of bladder cancer and tests used to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard (see Table 3).

### Table 3. Results of Pooled Patient-Level Analyses (Mowatt et al, 2010)

<table>
<thead>
<tr>
<th>Variables</th>
<th>FISH</th>
<th>ImmunoCyt</th>
<th>NMP22</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>12</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>No. of patients</td>
<td>3101</td>
<td>3041</td>
<td>10,565</td>
</tr>
<tr>
<td>Sensitivity (95% confidence interval)</td>
<td>76% (65% to 84%)</td>
<td>84% (77% to 91%)</td>
<td>68% (62% to 74%)</td>
</tr>
<tr>
<td>Specificity (95% confidence interval)</td>
<td>85% (78% to 92%)</td>
<td>75% (68% to 83%)</td>
<td>79% (74% to 84%)</td>
</tr>
</tbody>
</table>

FISH: fluorescence in situ hybridization.
Subsection Summary: Clinical Validity of FDA-Cleared Urinary Tumor Marker Tests
Numerous studies have evaluated the accuracy of the urinary tumor markers BTA stat, NMP22, UroVysion, and ImmunoCyt for diagnosing and/or monitoring bladder cancer. Several systematic reviews of these studies have been published. In studies on the initial diagnosis of bladder cancer and/or detection of recurrent bladder cancer, urinary tumor marker tests were found to have reasonably high sensitivity and specificity compared with standard diagnostic approaches. In the systematic review that included a comparison with cytology, urinary tumor markers tended to have higher sensitivity but similar or lower specificity. Combining tumor markers with cytology can improve overall diagnostic accuracy.

Laboratory-Developed Tests Marketed in the United States
Fibroblast Growth Factor Receptor 3 Variants
Several studies have evaluated urine-based assays for identifying fibroblast growth factor receptor 3 (FGFR3) variants.

A 2012 study was published by Fernandez et al; several coauthors were employees of Predictive Biosciences, the manufacturer of the CertNDx test. The study included 323 individuals who had been treated for bladder cancer; 48 had recurrence of bladder cancer and the remaining 275 had no current evidence of disease. Seven patients without disease did not have sufficient DNA for FGFR3 variant testing and were excluded from further analysis. FGFR3 variants were detected in 15 samples, 5 from patients with cancer recurrence and 10 from patients without evidence of disease. This resulted in a sensitivity of 5 (10%) of 48 and a specificity of 258 (96%) of 268. When results of FGFR3 variant analysis were combined with the findings of other tests (matrix metalloproteinase 2 [MMP2], Twist 1, Nid2 methylation), the markers had a 92% (44/48) sensitivity and 51% (136/268) specificity for detecting cancer recurrence.

In a retrospective study, Rieger-Christ et al (2003) compared the accuracy of FGFR3 variant analysis, cytology, and the combination of both in identifying bladder tumors. The study included 192 patients with bladder cancer, 72 who underwent transurethral resection of the bladder (group A) and 120 who underwent cystectomy (group B). Urine samples were collected before surgery. DNA preparations were screened for FGFR3 variants using single-strand conformation variant and DNA sequencing. (The study did not appear to use the CertNDx test.) Cytology results were available for 62 (86%) of 72 in the group A and 62 (52%) of 120 in group B. Sensitivity of the FGFR3 test alone was 68% for group A and 24% for group B. The sensitivity of cytology alone was 32% for group A and 90% for group B. For combination FGFR3 plus cytology, the sensitivity was 78% for group A and 93.5% for group B.

In addition, Zuiverloon et al (2010) applied FGFR3 variant analysis to the detection and prediction of bladder cancer recurrence. The research team, based in the Netherlands, developed an assay to identify common FGFR3 variants in urine samples. They identified tumor FGFR3 variant status in 200 patients with low-grade non-muscle-invasive bladder cancer. FGFR3 variants were identified in 134 (67%) patients. The 134 patients with an FGFR3-mutant tumor provided 463 urine samples, and 45 concomitant histologically proven recurrences of bladder cancer were detected. The sensitivity of the assay to detect concomitant recurrences was 26 (58%) of 45. After at least 12 months of follow-up from the last urine sample, an additional 34 recurrences were identified. Overall, 85 (81%) of 105 FGFR3-positive urine samples were associated with a bladder cancer recurrence compared with 41 (11%) of 358 FGFR3-negative urine samples. Using a Cox time-to-event analysis, an FGFR3-positive urine test was associated with a 3.8-fold higher risk of recurrence (p<0.001). Another study by this research team was published in 2013. A total of 716 urine samples were collected from 136 patients with non-muscle-invasive bladder cancer (at least 3 samples per patient were required for study entry). During a median of 3 years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity and specificity of FGFR3 for detecting a recurrence were 201 (49%) of 408 and 124 (66%) of 187, respectively. In comparison, the sensitivity of cytology was 211 (56%) of 377 and the specificity was 106 (57%) of 185. Combining FGFR3 and cytology increased sensitivity to 76% but lowered specificity to 42%.
Cxb bladder

In 2015, Breen et al compared Cxb bladder to 3 other urinary marker tests (UroVysion, fluorescence in situ hybridization [FISH], NMP22) using samples from 5 datasets. The datasets included 939 patients, 89 of whom had urothelial carcinoma (UC). In addition to cytology, between 1 and 3 additional diagnostic tests were performed on each sample; a single study (124 samples, 9 cancers) performed all 3 tests. Cxb bladder results were obtained in 746 (79.4%) of samples. The authors proposed a "methodology for comparative analysis and ranking" to evaluate the different tests despite not all tests being performed on all samples. The approach required imputing results in studies not conducting particular tests using different imputation methods.

Next, a signal-to-noise ratio (SNR) for each test was calculated as the mean difference in a test result for patients with or without UC and dividing by the sum of the 2 standard deviations. Although similar to a standard effect size, the summed standard deviations do not account for small sample sizes (e.g., UC samples), making the SNR somewhat difficult to interpret. Analysis of the imputed data suggested Cxb bladder has higher sensitivity but lower specificity than the other tests. For example, in the comparison of Cxb bladder and cytology, sensitivities were 73.6% (95% CI, 65.1% to 81.7%) versus 46.0% (95% CI, 36.3% to 55.8%) and specificities were 81.7% (95% CI, 78.7% to 84.4%) versus 95.3% (95% CI, 93.7% to 96.6%), respectively. Cxb bladder was also accompanied by the largest point estimate (presumably a median but not stated) ranking for the SNR. However, the novel methodology and the absence of reported confidence intervals for the rankings limit any conclusions about the relative diagnostic accuracy of Cxb bladder.

**Subsection Summary: Clinical Validity of Laboratory-Developed Tests**

We found several diagnostic performance studies on FGFR3 or Cxb bladder for identifying or monitoring bladder cancer. These studies generally showed that the markers had higher sensitivity than cytology. Specificity was compared with cytology in an analysis of Cxb bladder data and found to be lower. We identified few studies; those we did identify did not provide enough evidence that the diagnostic accuracy of these markers is sufficiently high to replace cytology.

**Urinary Tumor Markers in Individuals with a History of Bladder Cancer**

No studies were identified that specifically address the diagnostic accuracy of urinary tumor markers for diagnosing UUT cancers in patients with a history of bladder cancer. Several studies have addressed the accuracy of urinary tumor markers for diagnosing upper urinary tract (UUT) diseases in mixed populations with suspected disease and a history of bladder cancer or UUT cancer. For example, Lodde et al (2001) in Austria evaluated the accuracy of ImmunoCyt for detecting UUT transitional cell carcinoma (UUT-TCC). The study included 37 patients with signs or symptoms suggestive of UUT-TCC; 14 (38%) patients had a history of bladder cancer. Sixteen (43%) of 37 patients were found to have UUT-TCC. All patients also underwent cystoscopy, renal ultrasonography, and intravenous excretory urography. Using voided urine samples, ImmunoCyt had a 75% sensitivity and a 95% specificity for identifying UUT-TCC. This compares to a sensitivity of 50% and specificity of 100% for cytology. Using ureteral urine samples, ImmunoCyt had a sensitivity of 91% and cytology had a sensitivity of 82%. Both tests had 100% specificity using ureteral urine. Combination ImmunoCyt plus cytology had a sensitivity of 88% in voided urine samples and a sensitivity of 100% in ureteral urine.

In 2011, Xu et al in China reported on the diagnostic accuracy of FISH (UroVysion) for detecting upper tract UC. The study included urine specimens from 85 patients suspected of having UUT disease. Patients underwent cystoscopy after urine collection. Seventeen (20%) patients had a history of upper tract UC and 8 (9%) had a history of bladder cancer. The remaining patients had signs or symptoms of disease such as hematuria. The sensitivity of FISH for diagnosing urinary tract carcinoma was 79% and the sensitivity of cytology was 45%. Specificity was 98% for FISH and 100% for cytology. When findings from cytology and FISH were combined, the sensitivity was 86% and the specificity was 98%. Neither study separately reported findings for detection of recurrence in patients with a history of urinary tract cancer or for patients with a negative cystoscopy.
In 2012, Picozzi et al published a meta-analysis of studies that reported data on UUT recurrence following radical cystectomy for bladder cancer. Upper tract recurrence was defined as any documented recurrence in the renal collecting system or ureter. Reviewers identified 27 studies (total N=13,185 participants). The overall prevalence of urinary tract in the studies ranged from 0.75% to 6.4% and, among the cancers detected, 64.6% were advanced and 35.6% were metastatic. The Picozzi review also reported on the diagnostic yield of protocols used to follow patients after treatment for bladder cancer. As reported in the review, in 14 studies, 63 (38%) of 166 patients with UUT recurrence were identified by follow-up investigations and in the remaining 103 (62%) of patients, diagnosis was based on symptoms. In 9 studies that used urine cytology, 10 (9%) of 112 patients with recurrence were identified by positive cytology. In 13 studies that used upper tract imaging, 40 (25%) of 161 patients with recurrence were identified by imaging. Put another way, approximately 2000 urine cytology examinations or 800 radiologic examinations were performed to identify 1 patient with urinary tract recurrence. Reviewers stated that they were unable to determine whether there was a survival advantage in patients whose tumors were identified by cytology or urinary tract imaging compared with those detected by symptoms because the data on this subject were poor. The Picozzi review did not discuss the use of urinary tumor markers for diagnosis of UUT recurrence.

Section Summary: Urinary Tumor Markers in Individuals with a History of Bladder Cancer
No studies were identified that focused specifically on the use of urinary tumor markers for detecting UUT recurrences in patients with a history of bladder cancer. Several studies have evaluated urinary tumor markers for detecting UUT disease in samples of patients both with and without a history of urinary carcinoma. Available studies generally found that urinary tumor markers had higher sensitivity but not higher specificity than cytology, and combining urinary markers and cytology improved diagnostic accuracy.

Clinical Utility
Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the schedule of cystoscopies will be altered unless the sensitivity of urinary marker(s) approaches 100%. Some have suggested that consideration be given to lengthening the intervals of cystoscopy in patients with low levels of an accurate marker and low-grade bladder cancer. In addition, while urinary tumor markers might not alter the schedule of cystoscopies, if their results suggest a high likelihood of tumor recurrence, the resulting cystoscopy might be performed more thoroughly, or investigation of the UUT might be initiated. Direct evidence that outcomes are improved or not worsened with an altered schedule would be useful.

No controlled studies were identified that prospectively evaluated health outcomes in patients managed with and without the use of urinary tumor marker tests. In addition, we found no published studies comparing different cystoscopy protocols, used in conjunction with urinary markers, to monitor recurrence. We did find uncontrolled prospective and retrospective studies.

A 2011 study by Shariat et al used a decision curve analysis to assess the impact of urinary marker testing using the NMP22 assay on the decision to refer for cystoscopy and concluded that the marker did not aid clinical decision making in most cases. The study included 2222 patients with non-muscle-invasive bladder cancer and negative cytology, at various stages of surveillance. Patients with positive urinary cytology were excluded, because standard practice is to refer those patients for cystoscopy. According to the study protocol, all patients underwent cystoscopy, and 581 (26%) were found to have disease recurrence; of these, 234 (40%) had disease progression. NMP22 level was found to be significantly associated with both disease recurrence and progression (p<0.001 for both).

In the analysis, the clinical net benefit of the NMP22 test was evaluated by summing the benefits (true positives), subtracting the harms (false positives), and weighing these values by the “threshold probability,” defined as the minimum probability of bladder cancer recurrence at which a patient or clinician would opt for cystoscopy. The investigators found only a small
clinical net benefit for the NMP22 test over the strategy of “cystoscopy for all patients,” and this benefit occurred only at threshold probabilities over 8%. For example, for patients with at least a 15% risk of recurrence, using a model containing age, sex, and NMP22, 229 (23%) cystoscopies could be avoided, 236 (90%) recurrences would be identified, and 25 (15%) recurrences would be missed. Thus, for clinicians or patients who would opt for cystoscopy even if patients had a low risk of recurrence (e.g., 5%), NMP22 would not add clinical benefit and the optimal strategy would be to offer cystoscopy to all at-risk patients. The authors attributed the low clinical net benefit to the high risk of bladder cancer recurrence in patients with negative cytology.

A 2014 study by Kim et al examined data on the FISH test with the aim of determining whether the urinary marker could modify the surveillance schedule in patients with non-muscle-invasive bladder cancer who had suspicious cytology but a negative surveillance cystoscopy. The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every 3 to 6 months. A total of 243 patients who met the previous criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy 2 to 6 months after reflex FISH. Cystoscopy findings were positive in 17 (7%) patients. FISH results were not significantly associated with the results of the next cystoscopy (odds ratio [OR], 0.84; 95% CI, 0.26 to 2.74; p=1.0). Because of this lack of short-term association between FISH results and cystoscopy, the authors concluded that FISH has limited ability to modify the surveillance schedule in non-muscle-invasive bladder cancer.

Section Summary: Clinical Utility of Diagnosis and Management of Individuals with Symptoms or History of Bladder Cancer

There is a lack of direct evidence that health outcomes improve in patients managed with urinary tumor marker tests compared with those managed without tumor marker tests. And there is a lack of direct evidence that cystoscopy protocols can be changed when urinary tumor marker tests are used. The available studies have found low potential clinical benefit of urinary tumor marker testing for patients with non-muscle-invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

Urinary Markers for Screening Asymptomatic Individuals for Bladder Cancer

Clinical Context and Test Purpose
The purpose of screening testing with urinary markers in asymptomatic individuals at population-level risk is to detect disease at an earlier stage than it would present otherwise at a stage when treatment would allow improved outcomes.

The question addressed in this evidence review is: Does population-level screening with urinary markers for bladder cancer improve outcomes in asymptomatic individuals?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population(s) of interest are individuals without signs and/or symptoms of bladder cancer.

Interventions
The interventions of interest are tests discussed in the Regulatory Status section.

Comparators
At present, there is no standard population-level screening for bladder cancer. Patients typically present with signs and/or symptoms, such as hematuria.

Outcomes
The general outcomes of interest are overall survival and disease-specific survival. Beneficial outcomes are primarily related to detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.
Timing
Although it is not completely standardized, follow-up for non-muscle-invasive bladder cancer would typically occur periodically over the course of years.

Setting
Testing for urinary tumor markers would typically occur in urologists’ offices.

The ideal study for evaluating the effectiveness of a screening program is a randomized controlled trial (RCT) comparing outcomes in patients who did and did not participate in a screening program. In 2010, the U.S. Preventive Services Task Force updated its evidence review on screening adults for bladder cancer. The quality of evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only 1 prospective study, rated as poor quality. The systematic review did not identify any studies evaluating the sensitivity or specificity of diagnostic tests for bladder patients in asymptomatic average-risk patients. Moreover, reviewers did not identify any suitable studies on whether treatment of screen-detected bladder cancer reduces disease-specific morbidity and mortality, or on potential harms of screening for bladder cancer. Reviewers concluded: “major gaps in evidence make it impossible to reach any reliable conclusions about screening.”

Several uncontrolled studies have reported findings of screening studies. In 2013, Bangma et al reported on a population-based program with men in The Netherlands. The study evaluated the feasibility of screening using urine-based markers and examined performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least 1 positive home hematuria test underwent screening for 4 urine-based molecular markers. Men with at least 1 positive urine-based test were recommended to undergo cystoscopy. Of 6500 men invited to participate in screening, 1984 (30.5%) agreed and 1747 (88.1%) underwent hematuria testing. Of these, 409 (23.4%) tested positive for hematuria and 385 (94%) underwent urine-based marker testing. The number of men testing positive for each marker was 14 (3.6%) for NMP22, 33 (8.6%) for microsatellite analysis, 6 (1.6%) for FGFR3, and 40 (10.4%) for CH3. Cystoscopy was recommended for 75 men, and 71 actually underwent the procedure. Cancer was diagnosed in 4 (0.002%) of 1747 men who underwent screening (3 bladder cancers, 1 kidney cancer). Although men in the study who tested negative on screening tests did not receive further testing, the investigators were able to link participants’ data to a Dutch cancer registry data. They determined that 2 cancers (1 bladder cancer, 1 kidney cancer) had been diagnosed in men who completed the protocol; they were considered false negatives. Considering these data, the sensitivity of any urine-based marker was 80% (95% CI, 28.4% to 99.5%) and the specificity was 95.9% (95% CI, 94.9% to 96.8%). The sensitivity and specificity of the FDA-approved NMP22 test was 25% (95% CI, 0.63% to 80.6%) and 96.6% (95% CI, 94.2% to 98.2%). The screening program had low diagnostic yield.

In 2009, Lotan et al published a prospective study in which 1502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure were screened. The study used the NMP22 BladderChek test and was supported by the test manufacturer. Individuals with positive BladderChek tests underwent additional testing, beginning with urinalysis. Those found to have infection on urinalysis were treated and their urine was retested; others who tested positive received cystoscopy and cytology. Individuals with a negative BladderChek test did not have to undergo additional testing. Eighty-five (5.7%) of the 1502 participants had a positive BladderChek test. Two of the 85 patients were found to have bladder cancer (noninvasive), yielding a positive predictive value of 2.4%. There was also 1 case of atypia. Follow-up at a mean of 12 months was obtained for 1309 (87%) of 1502 screened patients. Two participants with negative BladderChek test had been diagnosed with bladder cancer; both tumors were less than 1 cm. Because no follow-up tests were done on participants who initially tested negative, it is unclear whether these were false-negative findings or new cancers. The authors report that the cancer prevalence in this population was lower than expected, which could be...
due in part to the large proportion who had previously undergone urinalysis. Study limitations included lack of follow-up testing on approximately 20% of participants who tested positive and lack of early cystoscopy and incomplete 1-year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Section Summary: Urinary Markers for Screening Asymptomatic Individuals for Bladder Cancer
We found no RCTs evaluating the impact of screening for bladder cancer on health outcomes in asymptomatic individuals. There is also insufficient observational evidence on the diagnostic accuracy of urinary tumor markers used to screen asymptomatic individuals for bladder cancer.

Summary of Evidence
For individuals who have signs and/or 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 tend to have higher sensitivity but lower or similar specificity than cytology. Also, they found that combining tumor marker tests with cytology can improve overall diagnostic accuracy. The decision analysis found only a small clinical benefit for use 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; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without 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.

For individuals who are asymptomatic and at a population-level 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 randomized controlled trials, 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.

Supplemental Information
Clinical Input from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, 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 from Blue Cross Blue Shield Association, input was received through 2 physician specialty societies and 5 academic medical centers 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 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 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 et al

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 cancer are summarized in Table 4.

Table 4. 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>
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<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 recommended cystoscopic evaluation for the following individuals:

- Older than age 40 with microscopic hematuria
- 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).22

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.

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.

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
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<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td></td>
<td>86294</td>
<td>Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)</td>
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<tr>
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<td>86316</td>
<td>Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each</td>
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<td>86386</td>
<td>Nuclear Matrix Protein 22 (NMP22), qualitative</td>
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<td>88120</td>
<td>Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual</td>
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<td>88121</td>
<td>Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology</td>
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</tbody>
</table>

**ICD-10 Procedure**

None

**ICD-10 Diagnosis**

All Diagnoses

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>12/07/2006</td>
<td>Policy Adopted - BCBSA MPP</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/07/2011</td>
<td>Policy title change from Urinary Tumor Markers for Bladder Cancer</td>
<td>Medical Policy Committee</td>
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<tr>
<td></td>
<td>Policy revision with position change</td>
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<td>01/21/2011</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<tr>
<td>12/14/2012</td>
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<td>Medical Policy Committee</td>
</tr>
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</table>
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.