Name of Policy:
Urinary Tumor Markers for Bladder Cancer

Policy #: 433       Latest Review Date: January 2016
Category: Medicine       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
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.

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, and dysuria) may also occur.

For patients with hematuria, American Urological Association guidelines 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 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. Nonmuscle 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 five-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every three months for one to three years, every six months for an additional two to three 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.

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. Both tests have sensitivities comparable with 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. 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, clinical laboratories that meet Clinical Laboratory Improvement Act standards are marketing urine-based tests. For example, Predictive Laboratories (Lexington, MA) markets a 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. FGFR3 mutations 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 U.S. called Cxbladder™, which tests for 5 urine-based markers.

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;
- Soluble Fas;
- Survivin (can be isolated from urine and also from tumor samples);
- Telomerase;
- Cytokeratin 8, 18, 19, 20
- Quanticyt
Policy:
Initial diagnosis
The following urinary bladder tumor markers meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as an adjunct in the diagnosis of bladder cancer only in conjunction with current standard diagnostic procedures (urine cytology or cystoscopy, with or without biopsy):

- BTA-STAT*, BTA-TRAK*;
- NMP22*, NMP22 BLADDER CHEK*;
- UROVYSION*;

The following urinary bladder tumor marker does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in the diagnosis of bladder cancer:

- IMMUNOCYT

Bladder cancer monitoring
The following urinary bladder cancer tumor markers meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures (urine cytology or cystoscopy, with or without biopsy):

- BTA-STAT*, BTA-TRAK*;
- IMMUNOCYT*;
- NMP22*, NMP22 BLADDER CHEK*;
- UROVYSION*;

The use of all other bladder cancer tumor markers (including but not limited to, CertNDx, Cxbladder) do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in the diagnosis, monitoring, or screening for bladder cancer.

Screening for bladder cancer in asymptomatic persons
The use of urinary bladder cancer tumor markers do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for screening for bladder cancer in asymptomatic persons.

* FDA Approved indications

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.
**Key Points:**
The discussion below focuses on the fundamental attributes of any diagnostic test; its technical performance; its diagnostic performance (sensitivity, specificity, positive and negative predictive values) compared to a gold standard; and data demonstrating how the results of the test can be used to benefit patient outcomes. The most recent literature review was performed through November 1, 2015.

**Technical performance**
All of the FDA-approved tests for urinary tumor markers involve the use of standard laboratory procedures.

**Diagnostic performance**
FDA-Cleared Urinary Tumor Markers (i.e. BTA [Bladder Tumor Antigen] STAT, NMP22 [Nuclear Matrix Protein 22], UroVysion and ImmunoCyt)
Studies have evaluated the diagnostic performance of individual markers compared to urine cytology, the standard urine-based test for bladder tumor diagnosis and surveillance. Cystoscopy and biopsy are generally used as the gold standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared to combinations of markers.

There are a number of systematic reviews of diagnostic accuracy studies, most recently the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review on the diagnosis and treatment of non-muscle-invasive bladder cancer. Selected results of pooled analyses are displayed in Table 1. Diagnostic performance is for findings of studies on initial diagnosis and surveillance of individuals previously treated for bladder cancer, which were combined in the analysis.

<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>ImmunoCyt™ (14 studies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78 (68 to 85)</td>
<td>78 (72 to 82)</td>
<td></td>
</tr>
<tr>
<td>FISH (e.g., UroVysion™) (11 studies)</td>
<td>63 (50 to 75)</td>
<td>87 (79 to 93)</td>
</tr>
</tbody>
</table>

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

The authors also reported in a pooled analysis of 16 studies that the sensitivity of various urinary tumor markers plus cytology was significantly higher than the urinary biomarker alone (80%; 95% confidence interval [CI], 75% to 86% vs 69%; 95% CI, 61% to 76%). There was no significant difference in specificity. The authors did not report a pooled analysis of the diagnostic accuracy of cytology alone.
An earlier comprehensive systematic review published in 2011 by Parker and Spiess summarized the sensitivity and specificity of cytology and of several urine tumor markers in bladder cancer for diagnosis and/or monitoring of recurrence. Selected information from the article is reported in the table below. (Diagnostic accuracy was not reported separately for initial diagnosis versus cancer monitoring).

Table 2: Sensitivity and Specificity Ranges of Selected Biomarkers (Parker and Spiess, 2011)

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

FISH, fluorescence in situ hybridization

In addition, in 2010, the UK Health Technology Assessment Program published a systematic review of studies on the diagnostic performance of several urine biomarkers. The review included 71 studies on the test performance of cytology and urine biomarkers. A majority of the studies 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.

Table 3. Results of Pooled Patient-Level Analyses in the UK HTA

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

CI, confidence interval; FISH: fluorescence in situ hybridization

Section Summary: Diagnostic Performance 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 (i.e. FGFR3 mutations, Cxbladder)
Fibroblast Growth Factor Receptor 3 mutations
Several studies have evaluated urine-based assays for identifying fibroblast growth factor receptor 3 (FGFR3) mutations. A 2012 study was published by Fernandez et al; several authors were employees of Predictive Biosciences, the manufacturer of the CertNDx test. The study
included 323 individuals who had been treated for bladder cancer; 48 of these had a 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 mutation testing and were excluded from further analysis. FGFR3 mutations were detected in 15 samples, five from patients with cancer recurrence and 10 from individuals without evidence of disease. This resulted in a sensitivity of 5 of 48 (10%) and a specificity of 258 of 268 (96%). When results of FGFR3 mutation analysis were combined with the findings of other tests (matrix metalloproteinase 2 (MMP2), Twist 1 and Nid2 methylation), the markers had a 92% sensitivity (44 of 48) and 51% specificity (136 of 268) for detecting cancer recurrence.

In a retrospective study, Rieger-Christ and colleagues compared the accuracy of FGFR3 mutation analysis, cytology and the combination of the two in identifying bladder tumors. The study included 192 patients with bladder cancer, 72 who underwent TURB (Group A) and 120 who underwent cystectomy (Group B). Urine samples were collected prior to surgery. DNA preparations were screened for FGFR3 mutations using single-strand conformation polymorphism (SSCP) and DNA sequencing. (The study did not appear to use the CertNDx test). Cytology results were available for 62 of 72 (86%) in the TURB group and 62 of 120 (52%) in the cystectomy group. 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 the combination of FGFR3 and cytology, the sensitivity was 78% for Group A and 93.5% for Group B.

In addition, Zuiverloon and colleagues have applied FGFR3 mutation analysis to the detection and prediction of bladder cancer recurrence. The research team, based in the Netherlands, developed an assay to identify common FGFR3 mutations in urine samples. A study published in 2010 identified the FGFR3 mutation status of tumors in 200 patients with low-grade non-muscle invasive bladder cancer. FGFR3 mutations 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 found. The sensitivity of the assay to detect concomitant recurrences was 26 of 45 (58%). After at least 12 months of follow-up from the time of the last urine sample, an additional 34 recurrences were identified. Overall, 85 of 105 (81%) FGFR3-positive urine samples were associated with a bladder cancer recurrence compared to 41 of 358 (11%) FGFR3-negative urine samples. In a Cox time-to-event analysis, an FGFR3-positive urine was associated with a 3.8-fold higher risk of having a recurrence (p<0.0001). Another study by this research team was published in 2012. A total of 716 urine samples were collected from 136 patients with non-muscle invasive bladder cancer (at least three samples per patient were required for study entry. During a median of three years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity of FGFR3 for detecting a recurrence was 201 of 408 (49%) and 124 of 187 (66%), respectively. In comparison, the sensitivity of cytology was 211 of 377 (56%) and the specificity was 106/185 (57%). Combining FGFR3 and cytology increased sensitivity to 76% but lowered specificity to 42%.

Cxbladder

In 2015, Breen et al compared Cxbladder to three other urinary marker tests (UroVysion, FISH, NMP22) using samples from five datasets. The datasets included 939 patients, 89 of whom had urothelial carcinoma (UC). In addition to cytology, between one and three additional diagnostic
tests were performed on each sample; a single study (124 samples, 9 cancers) performed all three
tests. Cxbladder was obtained in 746 (79.4%) of samples. The authors proposed a "methodology
for comparative analysis and ranking" to evaluate the different tests despite their not being
performed in 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
divided by the sum of the two 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 Cxbladder has
higher sensitivity but lower specificity than the other tests. For example, in the comparison of
Cxbladder 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%). Cxbladder 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 Cxbladder.

Section Summary: Diagnostic Performance of Laboratory-Developed Tests
Several diagnostic performance studies were identified on FGFR3 or Cxbladder 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 Cxbladder
data and found to be lower. Few studies were available and they did not provide sufficient
evidence that the diagnostic accuracy of these markers is sufficiently high to replace cytology

Other Urinary Bladder Tumor Markers
Most of the published studies evaluating other potential tumor markers them have included small
numbers of patients and were preliminary investigations. Examples include a study by Passerotti
et al on urinary hyalurinate, a study by Abd El-Hakim on survivin and a study by Li et al on the
cytokeratin 20 test. One meta-analysis was identified. This was a 2012 meta-analysis by Ku et al
that examined literature on urine survivin as a marker for diagnosing bladder cancer and used
cystoscopy and/or histopathology as a reference standard. The investigators identified 14 studies,
three of which were conducted in the United States and three of which identified recruitment as
prospective. A meta-analysis of data from the studies found a pooled sensitivity for the urine
survivin test of 0.77 (95% CI, 0.74 to 0.80) and a pooled specificity of 0.92 (95% CI, 0.90 to
0.93). In a preplanned subgroup analysis comparing the diagnostic accuracy of survivin and
cytology, a pooled analysis of data from six studies found that survivin had a significantly better
sensitivity than cytology, but a significantly lower specificity; the sensitivity and specificity of
cytology for diagnosing bladder cancer was 0.43 and 0.98, respectively.

Section Summary: Other Urinary Bladder Tumor Markers
Studies have evaluated various other potential urinary tumor markers but there is insufficient
evidence on the diagnostic accuracy of any particular marker.

Impact of Urinary Tumor Marker Tests on Patient Care
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/markers approaches 100%. However, some authors 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 upper urinary tract might be instigated.

No controlled studies were identified that prospectively evaluated health outcomes in patients who were managed with and without the use of urinary tumor marker tests. In addition, there were no published studies to date comparing different cystoscopy protocols, used in conjunction with urinary markers, to monitor recurrence.

A 2011 study by Shariat and colleagues used a decision-curve analysis to assess the impact of urinary marker testing using the NMP22 test on the decision to refer for cystoscopy and concluded that the marker did not aid clinical decision making in most cases. The study included 2,222 patients with nonmuscle-invasive bladder cancer and negative cytology, at various stages of surveillance. (Patients with positive urinary cytology were excluded, since standard practice is to refer these 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 or recurrence at which a patient or clinician would opt for cystoscopy. The investigators found only a small clinical net benefit of 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 a 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 2013 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 nonmuscle 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 three to six months. A total of 243 patients who met the above criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy two to six months after reflex FISH. The cystoscopy was 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 nonmuscle invasive bladder cancer.
Section Summary: Impact of Urinary Tumor Marker Tests on Patient Care
There is a lack of evidence that health outcomes are improved in patients managed with only urinary tumor marker tests compared to those managed without tumor marker tests and 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 using only urinary tumor marker testing for patients with nonmuscle invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

Urinary Bladder Tumor Markers for Detecting Upper Urinary Tract (UUT) Disease in Patients with a History of Bladder Cancer and a Negative Cystoscopy
No studies were identified that specifically addressed the diagnostic accuracy of urinary tumor markers for diagnosing upper tract cancers in patients with a history of bladder cancer. Several studies have addressed the accuracy of urinary tumor markers for diagnosing upper urinary tract diseases. However, the populations included in this study were either patients with suspected disease or a mixed group of patients with suspected disease and a history of bladder cancer or upper urinary tract cancer. For example, Lodde and colleagues in Austria evaluated the accuracy of ImmunoCyt for detecting upper urinary tract transitional cell carcinoma (UT-TCC). The study included 37 patients with signs or symptoms suggestive of UT-TCC; 14 patients (38%) had a history of bladder cancer. Sixteen of 37 patients (43%) were found to have UT-TCC. All patients also underwent cystoscopy, renal ultrasonography and intravenous excretory urography. Using voided urine samples, ImmunoCyt had 75% sensitivity and 95% specificity for identifying UT-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. The combination of ImmunoCyt and cytology had a sensitivity of 88% in voided urine samples and a sensitivity of 100% in ureteral urine. In 2011, Xu and colleagues in China reported on the diagnostic accuracy of UroVysion FISH for detecting upper tract urothelial carcinoma. The study included urine specimens from 85 patients suspected of having upper urinary tract disease. Patients underwent cystoscopy after urine collection. Seventeen patients (20%) had a history of UT urothelial carcinoma and eight (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 UT 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 and colleagues published a systematic review of studies that reported data related to upper urinary tract recurrence following radical cystectomy for bladder cancer. Upper tract recurrence was defined as any documented recurrence in the renal collecting system or ureter. The authors identified 27 studies with a total of 13,185 participants. The overall prevalence of UT 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 of 166 patients (38%) with upper urinary tract recurrence were identified by follow-up investigations and in the remaining 103 (62%) of patients, diagnosis
was based on symptoms. In nine studies that used urine cytology, 10 of 112 (9%) patients with recurrence were identified by positive cytology. In 13 studies that used upper tract imaging, 40 of 161 (25%) patients with recurrence were identified by imaging. Put another way, approximately 2,000 urine cytology examinations or 800 radiological examinations were performed to identify one patient with UT recurrence. The authors stated that they were not able to determine whether there was a survival advantage in patients whose tumors were identified by cytology or UT imaging compared to 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
No studies were identified that focused specifically on the use of urinary tumor markers for detecting upper urinary tract recurrences in patients with a history of bladder cancer. Several studies have evaluated urinary tumor markers for detecting upper urinary tract 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.

Urinary Markers for Screening Asymptomatic Individuals for Bladder Cancer
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 (USPSTF) published an updated evidence review on screening adults for bladder cancer. The quality of direct evidence that screening for bladder cancer reduces morbidity or mortality was low. There were no RCTs, and only one prospective study, which was rated as being 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, the review 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. The authors concluded that “major gaps in evidence make it impossible to reach any reliable conclusions about screening.”

Several uncontrolled studies evaluating screening protocols have been published. In 2013, Bangma et al reported on a population-based program with men in The Netherlands. The purpose of the study was to evaluate the feasibility of screening using urine-based markers and to examine performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least one positive home hematuria test underwent screening for four urine-based molecular markers. Men with at least one positive urine-based test were recommended to undergo cystoscopy. Out 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 cystoscopy. Cancer was diagnosed in four of 1747 men who underwent screening (three bladder cancers and one 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 two cancers (one bladder cancer and one kidney cancer) had been diagnosed in men who completed the protocol; these were considered to be false negatives. Considering these data, the sensitivity of any urine-based marker was 80% (95% CI, 28.4-99.5) 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 one case of atypia. Follow-up at a mean of 12 months was obtained for 1309 of 1502 (87%) screened patients. No additional cancers were diagnosed in the group that had had positive BladderChek tests. Two participants with negative BladderChek screen had been diagnosed with bladder cancer; both tumors were less than 1cm. Because no follow-up tests were done on participants who initially tested negative, it cannot be known 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 that had previously undergone urinalysis. Study limitations include lack of follow-up testing on approximately 20% of participants who tested positive and lack of early cystoscopy and incomplete one- 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
There are 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
The evidence for urinary tumor marker tests in patients who have signs and symptoms of bladder cancer or a history of bladder cancer 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 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 of the preferred design to evaluate clinical utility were identified; that is,
controlled studies prospectively evaluating health outcomes in patients managed with and without use or urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers.

The evidence for urinary tumor marker tests in individuals with no signs or symptoms or history of bladder cancer includes a 2010 systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The systematic review (conducted for the U.S. Preventive Services Task Force [USPSTF]) did not identify any RCTs, the preferred trial design to evaluate the impact of population-based screening, and found only one prospective study that USPSTF rated as poor quality. A more recent retrospective study, reporting on a population-based screening program in the Netherlands, had low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence on the use of urinary tumor markers as an adjunct in the diagnosis of and monitoring of bladder cancer has consistently demonstrated these markers having higher sensitivities but lower specificities than cytology. Combining tumor markers with cytology can improve overall diagnostic accuracy.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) 2015 bladder cancer guideline included the following statement regarding monitoring patients with high-grade bladder tumors:

“...Urine molecular tests for urothelial tumor markers are now available. Most of these tests have a better sensitivity for detecting bladder cancer than urine cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information which is useful for detection and management of non-muscle invasive bladder tumors. Therefore, The NCCN Bladder Cancer panel members consider this a category 2B recommendation.”

**National Academy of Clinical Biochemistry Laboratory Medicine**

The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend use of any of the FDA-approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients. The guideline stated:

“At this time, no tumor markers tests can be recommended for use in the diagnosis and clinical management of bladder cancer. This includes tests for making a differential diagnosis, assessing prognosis, staging of the disease or monitoring patients for the early detection of recurrent disease. There are no prospective clinical trial data that establish the utility of any of the FDA cleared markers or the proposed markers for increasing survival time, decreasing the cost of treatment or improving the quality of life of bladder cancer patients.”
American Urological Association
The American Urological Association’s 2007 guideline on management of bladder cancer included the following statement regarding urine-based markers for bladder cancer: “Despite their present and future potential, the critical evaluation and comparison of urine-based markers is beyond the scope of the current guideline involving the management of nonmuscle invasive 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 graded as an “I” recommendation, indicating insufficient evidence.

Key Words:
Bladder Tumor Antigen, BTA Test, FISH, Bladder Cancer Testing, ImmunoCyt, NMP-22, Tumor Marker, Bladder Cancer, UroVysion, BTA Stat, CertNDx, FGFR3, Cxbladder

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

- 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 ImmunoCytTM test, also marketed as UCyt+TM (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.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>86294</td>
<td>Immunoassay for tumor antigen; qualitative or semiquantitative (e.g., bladder tumor antigen)</td>
</tr>
<tr>
<td>86316</td>
<td>Immunoassay for tumor antigen; other antigen, quantitative, each</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>86386</td>
<td>Nuclear Matrix Protein 22 (NMP22), qualitative (Effective 01/01/2012)</td>
</tr>
<tr>
<td>88120</td>
<td>Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual (Effective 01/01/2011)</td>
</tr>
<tr>
<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 (Effective 01/01/2011)</td>
</tr>
<tr>
<td>88299</td>
<td>Unlisted cytogenetic study</td>
</tr>
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</table>

**Previous Coding:**

CPT Codes:

Prior to 2011, examples of coding that laboratory companies used for FISH testing:

<table>
<thead>
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<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>88271</td>
<td>Molecular cytogenetics, DNA probe, each (e.g., FISH)</td>
</tr>
<tr>
<td>88367</td>
<td>Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology</td>
</tr>
<tr>
<td>88368</td>
<td>Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual</td>
</tr>
</tbody>
</table>

**References:**


Policy History:
Medical Policy Group, June 2010 (3)
Medical Policy Administration Committee, July 2010
Available for comment July 2-August 16, 2010
Medical Policy Group, December 2010 (1): 2 new CPT codes added effective 1/1/2011
Medical Policy Group, June 2011; Updated Description, Key Points, & References
Medical Policy Group, July 2011 (1): Added “prior to July 1, 2010” policy statements concerning bladder cancer from policy 195
Medical Policy Group, August 2011 (1): Added CertNDx tumor marker test to investigational portion of policy statement; Key Points, Key Words and References updated related to CertNDx
Medical Policy Administration Committee, August 2011
Medical Policy Group, November 2011 (1): Added CPT 86386
Medical Policy Group, March 2012 (1): Clarification to policy statement; standard diagnostic procedures include urine cytology or cystoscopy with or without biopsy
Medical Policy Group, September 2013 (1): Update to Description, Key Points and References; no change to policy statement
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 (1): Update to Description, Key Points and References; no change to policy statement
Medical Policy Panel, March 2015
Medical Policy Group, March 2015 (3): Updates to Key Points and References; no change to policy statement.
Medical Policy Panel, December 2015
Medical Policy Group, January 2016 (3): Updates to Key Points, Key Words and References. Added “Cxbladder” to the investigational policy statement for all other bladder tumor markers.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.