BlueCross BlueShield of Alabama

## Name of Policy:
# Urinary Tumor Markers for Bladder Cancer

Policy #: 433
Category: Medicine

Latest Review Date: March 2014
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) 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.

**Technical performance**

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

**Diagnostic performance**

Urinary bladder 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 diagnostic accuracy studies evaluating urinary tumor markers, as well as systematic reviews of these studies. A 2011 article by Parker and Spiess reviewed the published literature and summarized the sensitivity and specificity 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).

| Test | Sensitivity range (%) | Specificity range (%) |
|---|---|---|
| Cytology | 12 to 79 | 78 to 99 |
| BTA STAT | 50 to 70 | 67 to 78 |
| NMP22 | 50 to 92 | 66 to 87 |
| ImmunoCyt | 67 to 85 | 62 to 85 |
| FISH (UroVysion) | 69 to 92 | 89 to 95 |

FISH, fluorescence in situ hybridization

The UK Health Technology Assessment Program published a systematic review in 2010 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 rests used for initial diagnosis of bladder cancer and tests used to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard. Results of pooled patient-level analyses are:

| | FISH | ImmunoCyt | NMP22 |
|---|---|---|---|
| No. studies | 12 | 8 | 28 |
| No. patients | 3101 | 3041 | 10,565 |
| Sensitivity % (95% CI) | 76 (65-84) | 84 (77-91) | 68 (62-74) |
| Specificity % (95% CI) | 85 (78-92) | 75 (68-83) | 79 (74-84) |

CI, confidence interval

Representative studies focusing on the diagnostic accuracy of urinary tumor markers for the initial detection of bladder cancer are described below:

In 2013, Todenhofer and colleagues published a prospective study including 2,113 individuals suspected of having bladder cancer. All patients underwent cystoscopy and upper urinary tract imaging, and urine samples were analyzed. A total of 502 (24%) of patients were found to have bladder cancer. The sensitivities of cytology, FISH and UCyt+ (also known as ImmunoCyt) for detecting bladder cancer were 80%, 69% and 72%, respectively. Specificities were 83%, 83% and 79%, respectively.

In 2013, Dimashkieh et al retrospectively evaluated UroVysion (FISH) and cytology in 652 patients with hematuria or symptoms of urinary tract obstruction. To be included in the study, patients needed to have either data on histology and/or cystoscopy findings within four months or at least three years of follow-up data after laboratory testing. Cytologic findings were categorized as positive for urothelial cell carcinoma, negative for urothelial cell carcinoma, or atypical urothelial cells. The sensitivity and specificity of FISH for detecting bladder cancer in patients with hematuria/symptoms of urinary tract obstruction were 60% and 93.4% respectively. For urine cytology, the sensitivity and specificity for detecting bladder cancer was 33.3% and 98.5%, respectively in patients not categorized as having atypical cells and 57.8% and 88.6%, respectively, in patients categorized as having atypical cells.

In 2008, Schmitz-Drager and colleagues in Germany prospectively evaluated the UCyt+ test in urine samples obtained from 301 consecutive patients with a first episode of painless hematuria and no history of bladder cancer. Sixty-five patients (22%) patients presented with gross hematuria and 228 (78%) with microhematuria. The sensitivity of the UCyt+ was at least as high as that of the other diagnostic tests, but specificity was lower. Among patients with gross hematuria, sensitivity and specificity were 87% and 96% for cystoscopy, 88% and 80% for UCyt+ and 47% and 91% for cytology. Among patients with microhematuria, sensitivity and specificity were 80% and 99% with cystoscopy, 80% and 89% with UCyt+ and 40% and 97% with cytology.

Representative studies focusing on the diagnostic accuracy of urinary tumor markers for detecting bladder cancer recurrence are described below:

A cross-sectional study from Germany, published by Horstmann and colleagues in 2009, compared the performance of UroVysion, ImmunoCyt and NMP22 used to detect bladder cancer recurrence in a sample of 221 patients diagnosed with non-muscle-invasive transitional cell carcinoma. Patients subsequently underwent cystoscopy as part of regular follow-up (n=49) or

transurethral resection of the bladder (TURB) for suspicion of recurrent disease (n=172). Findings from cystoscopy or TURB were considered the gold standard diagnosis. The investigators evaluated the diagnostic performance of individual markers, urinary cytology, and all possible combinations of markers. When combinations of markers were used, the test was considered positive if at least one marker was positive.

Cytology was the most sensitive single marker (84%) but was less specific than ImmunoCyt (62% and 72%, respectively). The authors commented that the performance of cytology was better than in previous similar studies, and the performance of other single markers was similar to previous studies. All combinations of two tests increased the sensitivity. Sensitivities varied from 94%, with a combination of cytology and NMP22, to 87% for the combination of cytology and UroVysion. Combining two tests generally lowered the specificity. In monitoring patients for bladder cancer recurrence; sensitivity is the more important test characteristic. Still, the combination with the best tradeoff of sensitivity and specificity was cytology and ImmunoCyt, which had a sensitivity of 93% and a specificity of 56%. Combining three tests increased the sensitivity even further. Two combinations attained a sensitivity of 98%, NMP22 and ImmunoCyt combined with either cytology or UroVysion. Specificity of these combinations was low, 31 to 32%. The best tradeoff with three markers was the combination of cytology, ImmunoCyt, and UroVysion, which had a sensitivity of 93% and a specificity of 49%. Combining all four tests did not substantially improve the diagnostic performance.

In 2009, Sullivan and colleagues published a cross-sectional study that compared the urinary tumor markers ImmunoCyt and UroVysion in patients with a history of bladder cancer. A single voided sample was obtained from 100 patients. Immediately after urine collection, patients underwent cystoscopy to identify cancer recurrence. Cystoscopy with biopsy was the gold standard; only biopsy-proven cases were considered positive. The urine sample was divided and used to evaluate cytology, ImmunoCyt and UroVysion; each type of analysis was conducted blindly in a different laboratory. Of the 100 samples, two were considered inadequate for cytology, two were inadequate for ImmunoCyt analysis, and 12 had cell counts too low for UroVysion analysis. Thus, sample size was 98 for cytology and ImmunoCyt and 88 for UroVysion. Sensitivities were 21% for cytology, 76% for ImmunoCyt, and 13% for UroVysion. Specificities were 97% for cytology, 63% for ImmunoCyt, and 90% for UroVysion. Diagnostic performance of the combination of cytology and ImmunoCyt, but not cytology and UroVysion, was reported. In the analysis of two tests, sensitivity was calculated with either test positive and specificity with both tests negative. For the combination of cytology and ImmunoCyt, the sensitivity was 75% and specificity was 63%. The specificity of this combination of tests was similar to that found by Horstmann and colleagues, described above, which was 56%. The combined sensitivity was lower than in the Horstmann study (93%), likely due to the higher sensitivity of urinary cytology found by Horstmann et al. The Sullivan study was limited by a small sample size. Moreover, the study was supported by DiagnoCure, the manufacturer of ImmunoCyt; the Horstmann study did not receive industry funding.

A prospective study by Kamat and colleagues evaluated the accuracy of five bladder cancer surveillance protocols for identifying recurrence in patients with a history of bladder cancer. Four patient management strategies were compared: cystoscopy alone; cystoscopy and NMP22; cystoscopy and UroVysion; and cystoscopy and cytology. In addition, a fifth hypothetical

protocol was evaluated; cystoscopy and contingent strategy in which a UroVysion test was only performed if the NMP22 test was positive. After an initial evaluation, patients were followed with routine cystoscopy every three to six months. For patients with a negative cystoscopy at baseline and in whom a tumor was detected at the first follow-up (i.e., within six months), it was assumed that this was a true result reflecting a missed diagnosis at the initial examination. Cancer was detected in 13 of 200 (6.5%) patients at the baseline evaluation and in 12 of 187 (6.4%) initially negative patients at first follow-up. Each of the patient management strategies described above correctly identified all 13 patients diagnosed with cancer at study entry. The proportion of false-positives at baseline was two of 15 (13%) patients testing positive using cystoscopy alone, 19 of 32 (59%) positives with cystoscopy and NMP22, 30 of 43 (70%) positives with cystoscopy and UroVysion, 14 of 27 (52%) positives with cystoscopy and cytology, and 6 of 19 (32%) positives with cystoscopy and NMP22, followed by UroVysion if the NMP22 test was positive. The number of initial false-positives that were confirmed positive at the first follow-up for each strategy was 0, 1, 5, 2, and 1, respectively. The two invasive tumors (out of 12 total tumors) identified at first follow-up were missed by all five surveillance strategies; urinary tumor markers only detected non-invasive tumors.

Section summary

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 markers tend to have higher sensitivity but not higher specificity than cytology. Combining tumor markers with cytology can improve overall diagnostic accuracy.

Urinary bladder tumor markers for detecting upper urinary tract (UUT) tract 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-TTC). 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.

FGFR3 (Fibroblast Growth Factor Receptor 3) mutations

Several studies have evaluated urine-based assays for identifying FGFR3 mutations. A 2012 study was published by Fernandez and colleagues; 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%.

Other urinary bladder tumor markers

A 2009 review article on potential new tumor markers comments that bladder cancer tumor markers is a rapidly evolving field in which new markers are constantly identified. The review concluded, "1) there exists a dizzying number of markers identified using newer expertise, and 2) much more work will need to be done to delineate which markers may be clinically applicable and which will be discarded."

Regarding the variety of other potential tumor markers in bladder cancer, most of the published studies evaluating them have included small numbers of patients and were preliminary investigations. Literature searches identified one meta-analysis and several larger prospective studies on additional markers. The meta-analysis, published in 2012 by Ku and colleagues, addressed using urine survivin as a marker for diagnosing bladder cancer and used cystoscopy and/or histopathology as a reference standard. They 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% confidence interval [CI]: 0.74-0.80) and a pooled specificity of 0.92 (95% CI: 0.90-0.93). In a pre-planned 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.

Among the prospective studies evaluating potential tumor markers, Eissa and colleagues in Egypt aimed to determine the ability of HYAL1 and survivin to identify malignant bladder tumors. A total of 278 patients underwent urine analysis and cystoscopy, and 100 healthy volunteers who did not undergo cystoscopy served as controls. Among patients, 166 were found to have bladder cancer, and 112 had benign bladder lesions. Using qualitative real-time polymerase chain reaction (RT-PCR) analysis, HYAL1 was identified in 153 (92%) malignant samples and 12 (11%) of benign samples, and survivin in 126 (76%) of malignant samples and 12 (11%) of benign samples. HYAL1 and survivin were not identified in any of the control samples. Using the best cutoffs for discriminating the malignant and non-malignant groups, the sensitivity of HYAL1 was 92.2% at 94.3% specificity. This was higher than a comparable analysis of survivin, which had 75.9% sensitivity and 94.3% specificity. Using semi-quantitative RT-PCR analysis, the sensitivity of HYAL1 was 91% and of survivin was 95.9%; specificity in both cases was 100%.

Similarly, Passerotti and colleagues in Brazil evaluated urinary hyaluronate for diagnosing transitional cell carcinoma (TCC). Urine samples were taken from 350 patients prior to surgery (cystoscopy, cystectomy or transurethral resection for bladder cancer). Postoperatively, a total of 160 patients (46%) were found to have TCC. Using area under the curve analysis, the investigators identified the optimal urinary hyaluronan cutoff to be 13.0 ug; with this cutoff, the test had a sensitivity of 82.3% and a specificity of 81.2% for identifying the presence of TCC. Moreover, a 2010 study by Li and colleagues in China prospectively evaluated the cytokeratin 20 (CK20) test for detecting urothelial carcinoma. Diagnostic accuracy of CK20 was compared to cytology and the ImmunoCyt test, using cystoscopy with histological diagnosis as the reference standard. The study included 169 patients who were hospitalized for a urological condition; 22 healthy individuals were included as controls. Thirty-four of 169 (20%) patients were excluded from the analysis due to missing data. Of the remaining 135 patients, 93 had urothelial carcinoma (primary tumors in 68 and recurrent tumors in 25), 26 had other urogenital malignancies, and 16 had benign lesions. A total of 132 patients had findings available on all three tests. The sensitivity of liquid-based cytology alone was 49.4% and the specificity was 91.1%. The combination of cytology and CK20 yielded a sensitivity of 81.6% and a specificity of 88.9%. When all three tests were used together (any positive test scored as positive), the sensitivity was 90.8% and the specificity was 84.4%. It is worth noting that the ImmunoCyt test is FDA-approved for use in patients already diagnosed with bladder cancer, not for initial diagnosis. The authors did not specify whether or not all study participants, who were inpatients in a department of urology, had previously received a diagnosis for their condition.

Section summary
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 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
There is a lack of evidence that health outcomes are improved in patients managed with 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 urinary tumor marker testing for patients with nonmuscle invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

**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 poor. 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 4 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 1 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 (eg, sensitivity) cannot be calculated.

Section summary

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**

Numerous studies have evaluated the accuracy of the urinary tumor markers BTA STAT, NMP22, UroVysion and ImmunoCyt for diagnosing and/or monitoring bladder cancer. These urinary tumor markers tend to have higher sensitivity but not higher specificity than cytology and combining tumor markers with cytology can improve overall diagnostic accuracy. There is insufficient evidence that urinary tumor markers improve the accuracy of initial diagnosis of upper urinary tract disease or monitoring patients with a history of urinary tract disease for upper tract recurrence. There is little evidence on the impact of urinary bladder tumor marker tests on patient management, e.g., the frequency of cystoscopy, or on the impact of tests on health outcomes. Moreover, there is also a lack of evidence on the impact of screening asymptomatic individuals for bladder cancer using urinary tumor markers. Therefore, use of urinary tumor markers for screening asymptomatic individuals for bladder cancer is considered investigational.

**Practice Guidelines and Position Statements**
National Comprehensive Cancer Network (NCCN) 2014 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."

In 2011, the U.S. Preventive Services Task Force concluded 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. This statement replaced a 2004 recommendation against routine screening for bladder cancer.

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."

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."

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

## 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 ImmunoCyt™ test, also marketed as UCyt+™ (DiagnoCure Inc., Quebec).

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

## 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:

| | |
|---|---|
| **86294** | Immunoassay for tumor antigen; qualitative or semiquantitative (e.g., bladder tumor antigen) |
| **86316** | Immunoassay for tumor antigen; other antigen, quantitative, each |
| **86386** | Nuclear Matrix Protein 22 (NMP22), qualitative (**Effective 01/01/2012)** |
| **88120** | Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual **(Effective 01/01/2011)** |
| **88121** | 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)** |
| **88299** | Unlisted cytogenetic study |

## Previous Coding:

CPT Codes:

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

| | |
|---|---|
| **88271** | Molecular cytogenetics, DNA probe, each (e.g., FISH) |
| **88367** | Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology |
| **88368** | Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual |

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## 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

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*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.*