Effective September 9, 2016
Policy replaced by Bladder Tumor Marker FISH (MolDX)

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Urinary Tumor Markers for Bladder Cancer

Policy #: 433   Latest Review Date: July 2017
Category: Medicine   Policy Grade: B

Background:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

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

Urinary Bladder Cancer

Urinary bladder cancer, a relatively common form of cancer in the United States, results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma), typically presents as a tumor confined to the superficial mucosa of the bladder. The most frequent symptom of early bladder cancer is hematuria; however, urinary tract symptoms (i.e., urinary frequency, urgency, and dysuria) may also occur.

Diagnosis

The 2012 guidelines from the American Urological Association on the evaluation of microscopic hematuria, which were reviewed and affirmed in 2016, recommend cystoscopic evaluation of adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with microscopic hematuria and risk factors for developing bladder cancer. 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.

Adjunctive testing to urine cytology has used a variety of nuclear and cytoplasmic targets, and a range of molecular pathology and traditional (e.g., immunohistochemistry) methods.

Commercially-available tests that have been cleared by the U.S. Food and Drug Administration (FDA) clearance are summarized in the Regulatory Status section.

Policy:

Effective for dates of service on or after September 7, 2010:

Initial diagnosis:

Blue Advantage will treat the following **urinary bladder tumor markers** as a **covered** benefit 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*;

Blue Advantage will treat the following **urinary bladder tumor marker** as a **non-covered** benefit and as **investigational** in the diagnosis of bladder cancer:

- IMMUNOCYT

Bladder cancer monitoring:

Blue Advantage will treat the following **urinary bladder cancer tumor markers** as a **covered** benefit as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

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

Screening for bladder cancer in asymptomatic persons:

Blue Advantage will treat the **use of urinary bladder cancer tumor markers** as a **non-covered** benefit and as **investigational** for **screening for bladder cancer in asymptomatic persons.**

Blue Advantage will treat the **use of all other bladder cancer tumor markers (including but not limited to, CertNDx, Cxbladder)** as a **non-covered** benefit and as **investigational** in the diagnosis, monitoring, or screening for bladder cancer.

* FDA Approved indications

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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 most recent literature review was performed through April 25, 2017. Following is a summary of the key literature to date.

Diagnosis and Management of Individuals with Symptoms or History of Bladder Cancer
Clinical Context and Test Purpose
The purpose of using urinary tumor markers in the management in patients who have signs and/or symptoms of bladder cancer (initial or recurrent) is to inform a decision whether to proceed to cystoscopy.

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

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

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

Patients
The relevant population(s) of interest is patients with signs and/or symptoms of bladder cancer. These may include patients with no prior diagnosis, who present with urinary symptoms which would be suggestive of bladder cancer, most commonly hematuria, or patients who have undergone treatment for bladder cancer.

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

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

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

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

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

Analytic Validity
All of the FDA-approved tests for urinary tumor markers involve the use of standard laboratory procedures. No studies specifically reporting on the analytic validity of the tests discussed were identified.

Clinical Validity
FDA-Cleared Urinary Tumor Marker Tests (e.g. BTA stat, NMP22 BladderChek, UroVysion, ImmunoCyt)
Studies have evaluated the diagnostic performance of individual markers compared 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.

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

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

Table 1: Diagnostic Accuracy of Urinary Biomarkers Compared with Standard Diagnostic Methods (AHRQ Comparative Effectiveness Report)

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

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

Additional systematic reviews have reported on the diagnostic characteristics of individual tests.

For example, He et al (2016) reported on a systematic review and meta-analysis of studies of uCyt+/ImmunoCyt immunoassay's diagnostic accuracy in detecting cancer as initial diagnosis or recurrence.

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 2. (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)

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

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. Most 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 (see Table 3).

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

Variables	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; FISH: fluorescence in situ hybridization;

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

Laboratory-Developed Tests Marketed in the United States
Fibroblast Growth Factor Receptor 3 Variants
Several studies have evaluated urine-based assays for identifying fibroblast growth factor receptor 3 (FGFR3) variants. A 2012 study was published by Fernandez et al; several 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 variant testing and were excluded from further analysis. FGFR3 variants 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 variant 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 et al (2003) compared the accuracy of FGFR3 variant analysis, cytology and the combination of both in identifying bladder tumors. The study included 192 patients with bladder cancer, 72 who underwent transurethral resection of the bladder (Group A) and 120 who underwent cystectomy (Group B). Urine samples were collected prior to surgery. DNA preparations were screened for FGFR3 variants 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 et al (2010) have applied FGFR3 variant analysis to the detection and prediction of bladder cancer recurrence. The research team, based in the Netherlands, developed an assay to identify common FGFR3 variants in urine samples. A study published in 2010 identified the FGFR3 variant status of tumors in 200 patients with low-grade non-muscle invasive bladder cancer. FGFR3 variants were identified in 134 (67%) patients. The 134 patients with an FGFR3-mutant tumor provided 463 urine samples, and 45 concomitant histologically proven recurrences of bladder cancer were 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<0.001). 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.

Subsection Summary: Clinical Validity of Laboratory-Developed Tests
We found several diagnostic performance studies 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.

Urinary Tumor Markers in Individuals with a History of Bladder Cancer
No studies were identified that specifically addressed the diagnostic accuracy of urinary tumor markers for diagnosing UUT cancers in patients with a history of bladder cancer. Several studies have addressed the accuracy of urinary tumor markers for diagnosing UUT diseases in populations that were a mixed group of patients with suspected disease and a history of bladder cancer or UUT cancer. For example, Lodde et al in Austria evaluated the accuracy of ImmunoCyt for detecting UUT transitional cell carcinoma (UUT-TCC). The study included 37 patients with signs or symptoms suggestive of UUT-TCC; 14 patients (38%) had a history of bladder cancer. Sixteen of 37 patients (43%) were found to have UUT-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 UUT-TCC. This compares to a sensitivity of 50% and specificity of 100% for cytology. Using ureteral urine samples, ImmunoCyt had a sensitivity of 91% and cytology had a sensitivity of 82%. Both tests had 100% specificity using ureteral urine. 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 et al 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 UUT disease. Patients underwent cystoscopy after urine collection. Seventeen patients (20%) had a history of urinary tract urothelial carcinoma and 8 (9%) had a history of bladder cancer. The remaining patients had signs or symptoms of disease such as hematuria. The sensitivity of FISH for diagnosing urinary tract carcinoma was 79% and the sensitivity of cytology was 45%. Specificity was 98% for FISH and 100% for cytology. When findings from cytology and FISH were combined, the sensitivity was 86% and the specificity was 98%. Neither study separately reported findings for detection of recurrence in patients with a history of urinary tract cancer, or for patients with a negative cystoscopy.

In 2012, Picozzi et al published a meta-analysis of studies that reported data related to UUT 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 urinary tract in the studies ranged from 0.75% to 6.4% and, among the cancers detected, 64.6% were advanced and 35.6% were metastatic. The Picozzi review also reported on the diagnostic yield of protocols used to follow patients after treatment for bladder cancer. As reported in the review, in 14 studies, 63 of 166 patients (38%) with UUT recurrence were identified by follow-up investigations and in the remaining 103 (62%) of patients, diagnosis was based on symptoms. In 9 studies that used urine cytology, 10 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 2000 urine cytology examinations or 800 radiologic examinations were performed to identify 1 patient with urinary tract 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 urinary tract imaging compared with symptoms because the data on this subject were poor. The Picozzi review did not discuss the use of urinary tumor markers for diagnosis of UUT recurrence.

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

Clinical Utility
Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the schedule of cystoscopies will be altered unless the sensitivity of urinary marker/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. <u>Direct evidence that outcomes are improved or not worsened with an altered schedule would be useful.</u>

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. <u>We did find uncontrolled prospective and retrospective studies.</u>

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 non-muscle-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 non-muscle invasive bladder cancer who had suspicious cytology but a negative surveillance cystoscopy. The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every three to six months. A total of 243 patients who met the <u>previous</u> 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 non-muscle invasive bladder cancer.

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

There is a lack of direct evidence that health outcomes 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

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

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

Comparators

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

Outcomes

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

Timing

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

Setting

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

The ideal study for evaluating the effectiveness of a screening program is a randomized controlled trial (RCT) comparing outcomes in patients who did and did not participate in a screening program. In 2010, the U.S. Preventive Services Task Force (USPSTF) published an

updated evidence review on screening adults for bladder cancer. The quality of direct evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only one prospective study, 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 have reported findings of screening studies. 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 of Evidence
For individuals who have signs and/or symptoms of bladder cancer or a history of bladder cancer who receive urinary tumor marker tests, the evidence includes a number of diagnostic accuracy studies, meta-analyses, as well as a decision curve analysis and retrospective study examining the clinical utility of urinary tumor marker tests. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The diagnostic accuracy studies found that urinary tumor marker tests tend to have higher sensitivity but lower or similar specificity than cytology. Also, they found that combining tumor marker tests with cytology can improve overall diagnostic accuracy. The decision analysis found only a small clinical benefit for use of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies using the preferred trial design to evaluate clinical utility were identified; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without use of urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers.

For individuals who are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The 2010 systematic review (conducted for the U.S. Preventive Services Task Force [USPSTF]) did not identify any randomized controlled trials, the preferred trial design to evaluate the impact of population-based screening, and found only 1 prospective study that USPSTF rated as poor quality. A more recent retrospective study, assessing a population-based screening program in the Netherlands, reported low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes

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

American Urological Association et al

The 2016 guidelines from the American Urological Association addressed the diagnosis and treatment of non-muscle invasive bladder cancer, based on a systematic review completed by the Agency for Health Care Research and Quality. Statements about the use of urine markers after the diagnosis of bladder of cancer are summarized in Table 4.

Table 4: American Urological Association Guidelines for Urine Tumor Markers after the Diagnosis of Bladder Cancer

Guidance Statement	Strength of Recommendation	Level of Evidence
"In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation."	Strong recommendation	Grade B
"In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance."		Expert opinion
"In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)."		Expert opinion

NMIBC: non-muscle invasive bladder cancer

Guidelines from the American Urological Association from 2012 (reviewed and affirmed in 2016) on the evaluation of microscopic hematuria recommend cystoscopic evaluation for the following individuals:

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

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force concluded in 2011 that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was 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:
The following urinary tumor marker tests cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for clinical use:

- The BTA stat® test (Polymedco, Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that 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, 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.

- The nuclear matrix protein 22 (NMP22) urine immunoassay (Alere NMP22® BladderChek®; Alere) tests for NMP22,   a protein associated with the nuclear mitotic apparatus, which may be released from the nuclei of tumor cells during apoptosis. Elevated urine levels have been associated with bladder cancer. NMP22 may be detected in the urine using an immunoassay.

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

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

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

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

For example, Predictive Laboratories (Lexington, MA) markets the CertNDx™ test; it assesses fibroblast growth factor receptor 3 (FGFR3) variants. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. FGFR3 variants may be associated with lower grade bladder tumors that have a good prognosis.

In addition, Pacific Edge (New Zealand) is marketing a test in the United States called Cxbladder™, which tests for five urine-based markers.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

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:

Adopted for Blue Advantage, July 2010
Available for comment July 23-September 6, 2010
Medical Policy Group, December 2010
Medical Policy Administration Committee, August 2011
Medical Policy Group, November 2011
Medical Policy Group, March 2012
Medical Policy Group, September 2013
Medical Policy Group, March 2014
Medical Policy Group, March 2015
Medical Policy Group, January 2016