Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Urinary Biomarkers for Bladder Cancer

Description/Background

Urinary Bladder Cancer

Urinary bladder cancer, a relatively common form of cancer in the U.S., results in significant morbidity and mortality.[1] Bladder cancer 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 (ie, urinary frequency, urgency, dysuria) may also occur.

Diagnosis

The criterion standard for a confirmatory diagnosis of bladder cancer is cystoscopic examination with biopsy.[1] At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. The non-muscle-invasive disease is usually treated with transurethral resection, with or without intravesical therapy, depending on the depth of invasion and tumor grade. However, a 50% to 75% incidence of recurrence has been noted in these patients, with 10% to 15% progressing to muscle invasion over a 5-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every 3 months for 1 to 3 years, every 6 months for an additional 2 to 3 years, and then annually thereafter, assuming no recurrence.

While urine cytology is a specific test (from 90% to 100%), its sensitivity is lower, ranging from 50% to 60% overall and it is considered even lower for low-grade tumors.[1] Intravesical bladder cancer treatment can also confound interpretation of urine cytology. Therefore, interest has been reported in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

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

Commercially available tests cleared by the U.S. Food and Drug Administration (FDA) as well as laboratory-developed tests are summarized in the Regulatory Status section.

Regulatory Status

Table 1 lists urinary tumor marker tests approved or cleared for marketing by FDA. The FDA approved or cleared tests are indicated as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer surveillance of bladder cancer patients.

Table 1. FDA-Approved or -Cleared Urinary Tumor Marker Tests

Test	Manufacturer	Type	Detection	Indication
BTA *stat*®	Polymedco	Point of care immunoassay	Human complement factor H-related protein	Qualitative detection of bladder tumor- associated antigen in the urine of persons diagnosed with bladder cancer
BTA TRAK®	Polymedco	Reference laboratory immunoassay	Human complement factor H-related protein	Quantitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer
Alere NMP22®	Alere	Immunoassay	NMP22 protein	in vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy
BladderChek®	Alere	Point of care immunoassay	NMP22 protein	Adjunct to cystoscopy in patients at risk for bladder cancer
UroVysion®	Abbott Molecular	FISH[a]	Cell-based chromosomal abnormalities	Aid in the initial diagnosis of bladder cancer (P030052) and monitoring patients with previously diagnosed bladder cancer (K033982)
Bladder EpiCheck®	Nucleix	RT-PCR	DNA methylation biomarkers	Monitoring for tumor recurrence in conjunction with cystoscopy in patients with previously diagnosed NMIBC

FISH: fluorescence in situ hybridization; NMIBC: non-muscle invasive bladder cancer;

IHC: immunohistochemistry; NMP: nuclear matrix protein; RT-PCR: real-time polymerase chain reaction.

[a] FISH is a molecular cytogenetic technology that can be used with either DNA or RNA probes to detect chromosomal abnormalities. DNA FISH probe technology involves the creation of short sequences of fluorescently labeled, single-strand DNA probes that match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted.

FDA-approved or cleared Urinary Tumor Marker Tests: BTA stat, BTA TRAK, Alere NMP22, BladderChek and UroVysion.

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, FDA has chosen not to require any regulatory review of these tests. Laboratory-developed tests include:

- Cxbladder Monitor (Pacific Edge) measures the expression of 5 genes (*MDK*, *HOXA13*, *CDC2*, *IGFBP5*, *CXCR2*). Pacific Edge also has Cxbladder Detect and Cxbladder Triage tests and Cxbladder Detect+.
- Xpert® Bladder Cancer Monitor (Cepheid) measures mRNA (*ABL1, CRH, IGF2, UPK1B, ANXA10*) in voided urine by reverse transcription-polymerase chain reaction (RT-PCR).
- EarlyTect® Bladder Cancer Detection (EarlyTect® BCD)
- UriFind® Urothelial Carcinoma Assay, DiaCarta, Inc, AnchorDx

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Medical Policy Statement

The safety and effectiveness of FDA-approved urinary tumor marker tests for bladder cancer have been established. An FDA-approved urinary tumor marker test may be considered a useful diagnostic option when used as an adjunct to cytology and cystoscopy.

Inclusionary and Exclusionary Guidelines

Inclusions:
The assessment of FDA-approved urinary tumor markers for bladder cancer, as an adjunct to cytology and cystoscopy, is considered established in:

- The diagnosis of urinary bladder malignancy in individuals at very high risk.
- The follow-up of individuals with a history of urinary bladder malignancy when the measurements of these markers is deemed essential in making management decisions.

Exclusions:

All other indications for bladder cancer not specified under the inclusions

The peer reviewed medical literature has not demonstrated the analytical validity and clinical utility outcomes of Cxbladder™ therefore, Cxbladder tests are considered experimental/ investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

86294	86386	88120	88121

Other codes (investigational, not medically necessary, etc.):

0012M	0013M	0420U	0363U	0452U	0465U

Rationale

URINARY TUMOR MARKER TESTING OF INDIVIDUALS WITH SYMPTOMS OF BLADDER CANCER

Clinical Context and Test Purpose

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

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with signs and/or symptoms of bladder cancer. This includes individuals with no prior diagnosis who present with urinary symptoms suggestive of bladder cancer (most commonly unexplained microscopic hematuria).

Interventions

The test being considered is urinary tumor marker tests in addition to cystoscopy.

Comparators

The following practices are currently being used to assess individuals with signs and/or symptoms of bladder cancer: cystoscopy along and cytology. Individuals with microscopic hematuria with no etiology identified after an evaluation for glomerular disease or infection would typically be recommended for cystoscopy and biopsy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. Beneficial outcomes are primarily related to detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

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

Study Selection Criteria

For the evaluation of the clinical validity of the urinary biomarkers for the indications within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews
Studies have evaluated the diagnostic performance of individual markers compared with urine cytology, the standard urine-based test for bladder tumor diagnosis and surveillance. Cystoscopy and biopsy are generally used as the criterion standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared with combinations of markers.

Several systematic reviews of diagnostic accuracy studies were identified. 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 part of an Agency for Healthcare Research and Quality Comparative Effectiveness Review on the diagnosis and treatment of non-muscle-invasive bladder cancer.[1] Two studies were rated as having low risk of bias, 3 studies at high risk of bias, and the remainder considered to have a moderate risk of bias. Only studies that used cystoscopy or histopathology as the reference standard were analyzed. Results of pooled analyses of diagnostic accuracy in patients with symptoms of bladder cancer are displayed in Table 2.

Table 2. Diagnostic Accuracy of Urinary Biomarkers in Patients With Symptoms of Bladder Cancer

Test	TP/n	Pooled Sensitivity (95% CI), %	Studies, n	Pooled Specificity (95% CI), %	Studies, n
BTA *stat*					
Quantitative test	37/49	76 (61 to 87)	1	53 (38 to 68)	1
Qualitative test	275/372	76 (67 to 83)	8	78 (66 to 87)	6
NMP22 BladderChek					
Quantitative test	235/368	67 (55 to 77)	9	84 (75 to 90)	7
Qualitative test	69/145	47 (33 to 61)	2	93 (81 to 97)	2
FISH (eg, UroVysion)	82/144	73 (50 to 88)	2	95 (87 to 98)	1
Cxbladder	54/66	82 (70 to 90)	1	85 (81 to 88)	1

Adapted from Chou et al (2015).[1],
CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives.

Clinical Validity of FDA-Approved or Cleared Urinary Tumor Marker Tests (eg, BTA stat, BTA TRAK, Alere NMP22, BladderChek and UroVysion)
Numerous studies have evaluated the accuracy of the urinary tumor markers BTA stat, NMP22 and UroVysion 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No direct evidence was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Urinary Tumor Marker Testing of Individuals with Symptoms of Bladder Cancer
Numerous studies have evaluated the accuracy of the urinary tumor markers for diagnosing and/or monitoring bladder cancer. Systematic reviews of these studies have been published. In studies on the initial diagnosis of bladder cancer, urinary tumor marker tests have pooled sensitivity ranging from 47% to 82% and pooled specificity ranging from 53% to 95% when compared with cystoscopy and biopsy. There is no evidence of the clinical utility of urinary biomarker testing in this population.

URINARY TUMOR MARKER TESTING FOR INDIVIDUALS WITH A HISTORY OF BLADDER CANCER

Clinical Context and Test Purpose
The purpose of urinary tumor marker testing in individuals who have a history of bladder cancer is to monitor for recurrence and inform a decision as to whether to proceed to cystoscopy and biopsy. A potential benefit of urinary tumor markers would be a reduction of testing using routine cystoscopy s or earlier detection of recurrence. Individuals with a history of bladder cancer have a higher pretest probability of cancer than those with no history.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with a history of bladder cancer**.**

Interventions
The test being considered is urinary tumor marker tests in addition to cystoscopy.

Comparators
The following practices are currently being used to assess individuals with a history of bladder cancer: cystoscopy alone and cytology.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. Beneficial outcomes are primarily related to detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

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

Study Selection Criteria
See information under the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews
Pooled analysis on the diagnostic accuracy of urinary biomarkers by Chou et al (2015) is provided in Table 3.[2] The reference standard was cystoscopy or histopathology.

Table 3. Diagnostic Accuracy of Urinary Biomarkers in Patients With a History of Bladder Cancer

Test	TP/n	Pooled Sensitivity (95% CI), %	Studies, n	Pooled Specificity (95% CI), %	Studies, n
BTA *stat*					
Quantitative test	39/67	58 (46 to 69)	2	79 (72 to 85)	2
Qualitative test	325/544	60 (55 to 65)	11	76 (69 to 83)	8
NMP22 BladderChek					
Quantitative test	235/368	61 (49 to 71)	10	71 (60 to 81)	8
Qualitative test	99/159	70 (40 to 89)	2	83 (75 to 89)	2
FISH (eg, UroVysion)	189/299	55 (36 to 72)	7	80 (66 to 89)	6

Adapted from Chou et al (2015).[2]
CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives.

Observational Studies - Fibroblast Growth Factor Receptor 3
The Fibroblast growth factor receptor 3 (*FGFR3*) variants may be associated with lower grade bladder tumors that have a good prognosis. Several studies have evaluated urine-based assays for identifying *FGFR3* variants.

A study was published by Fernandez et al (2012); several coauthors were employees of Predictive Biosciences, the manufacturer of the CertNDx test.[3] The study included 323 individuals who had been treated for bladder cancer; 48 of these had recurrent bladder cancer, and the remaining 275 had no current evidence of disease. Seven patients without disease did not have sufficient DNA for *FGFR3* variant testing and were excluded from further analysis. *FGFR3* variants were detected in 15 samples, 5 from patients with cancer recurrence and 10

from patients without evidence of disease. This resulted in a sensitivity of 5 (10%) of 48 and a specificity of 258 (96%) of 268.

Zuiverloon et al (2010) applied *FGFR3* variant analysis to the detection and prediction of bladder cancer recurrence.[4] The research team, based in the Netherlands, developed an assay to identify common *FGFR3* variants in urine samples. They identified tumor *FGFR3* variant status in 200 patients with low-grade non-muscle-invasive bladder cancer. *FGFR3* variants were identified in 134 (67%) patients. The sensitivity of the assay to detect concomitant recurrences was 26 (58%) of 45. After at least 12 months of follow-up from the last urine sample, an additional 34 recurrences were identified. Overall, 85 (81%) of 105 *FGFR3*-positive urine samples were associated with a bladder cancer recurrence compared with 41 (11%) of 358 *FGFR3*-negative urine samples. Using a Cox time-to-event analysis, an *FGFR3*-positive urine test was associated with a 3.8-fold higher risk of recurrence ($p<0.001$).

Another study by Zuiverloon et al (2013) assessed a total of 716 urine samples collected from 136 patients with non-muscle-invasive bladder cancer (at least 3 samples per patient were required for study entry).[5] During a median of 3 years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity and specificity of *FGFR3* for detecting a recurrence were 201 (49%) of 408 and 124 (66%) of 187, respectively. In comparison, the sensitivity of cytology was 211 (56%) of 377 and the specificity was 106 (57%) of 185. Combining *FGFR3* and cytology increased sensitivity to 76% but lowered specificity to 42%.

Two studies prospectively evaluated the use of Xpert Bladder Cancer Monitor in follow-up of patients with a history of non-muscle invasive bladder cancer. D'Elia et al (2021) followed 416 patients, of whom 168 patients had a new recurrence of non-muscle invasive bladder cancer. In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 52.4% and specificity of 78.4%; cytology demonstrated an overall sensitivity of 17.9% and specificity of 98.5%.[6] Pichler et al (2018) followed 140 patients, of whom 43 patients had a new recurrence of non-muscle invasive bladder cancer. In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 84% and specificity of 91%; cytology demonstrated an overall sensitivity of 33% and specificity of 94%. Blinding was not discussed for either study; studies were further limited by a short follow-up period.[7]

The Bladder EpiCheck DNA methylation biomarker test was evaluated in 2 prospective clinical trials which have only been described in the FDA review of data for the 510(k) premarket submission.[8.] One clinical trial enrolled 674 adults urothelial carcinoma who had undergone resection within 12 months prior and were undergoing cystoscopy surveillance. Patients provided voided urine specimens at up to 3 study visits (baseline and 2 surveillance visits). Valid Bladder EpiCheck and gold standard (cytology or combined cystoscopy/pathology) results were obtained for 449 patients. Bladder EpiCheck was found to have an accuracy of 78.8%, sensitivity of 66.7%, and specificity of 84.2%, with positive and negative predictive values of 65.3% and 85.1%, respectively. In the second study, Bladder EpiCheck was compared to the predicate approval device, UroVysion in 352 matched patients (specific patient characteristics and matching criteria not described) using the same gold standard reference. Bladder EpiCheck was found to be similar to UroVysion, with numerically higher sensitivity (difference, 4.82%; 95% CI, -5.7 to 15.3) and numerically lower specificity (difference, -2.97%; 95% CI, -7.8 to 1.9).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the standard timing of cystoscopies would be altered unless the sensitivity of urinary marker(s) approaches 100%. Some have suggested that consideration should 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 initiated.[9] No published studies were identified comparing different cystoscopy protocols, used in conjunction with urinary markers, to monitor recurrence.

Shariat et al (2011) used a decision curve analysis to assess the impact of urinary marker testing using the nuclear matrix protein 22 (NMP22) assay on the decision to refer for cystoscopy; they concluded that the marker did not aid clinical decision making in most cases.[10] The study included 2222 patients with non-muscle-invasive bladder cancer and negative cytology, at various stages of surveillance. All patients underwent cystoscopy, and 581 (26%) were found to have disease recurrence. The NMP22 level was found to be significantly associated with both disease recurrence and progression ($p<.001$ for both). The investigators found only a small clinical net benefit for the NMP22 test over the strategy of "cystoscopy for all patients." For patients with at least a 15% risk of recurrence, using a model containing age, sex, and NMP22, 229 (23%) cystoscopies could be avoided, 236 (90%) recurrences would be identified, and 25 (15%) recurrences would be missed. Thus, for clinicians or patients who would opt for cystoscopy even if patients had a low risk of recurrence (eg, 5%), NMP22 would not add clinical benefit and the optimal strategy would be to offer cystoscopy to all at-risk patients.

Kim et al (2014) examined data on the fluorescence in situ hybridization (FISH) testing 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.[11] The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every 3 to 6 months. A total of 243 patients who met the previous criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy 2 to 6 months after reflex FISH. The FISH results were not

significantly associated with the results of the next cystoscopy (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.26 to 2.74; p=1.0). Because of this lack of short-term association between FISH results and cystoscopy, the results suggest that FISH has limited ability to modify the surveillance schedule in non-muscle-invasive bladder cancer.

The purpose of the limitations tables (Tables 4 and 5) is to display notable limitations identified in each study.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Shariat et al (2011)[10]	4. All patients had negative cytology		2. No control group	1. Management decisions	
Kim et al (2014)[11]	4. All patients had negative cystoscopy		2. No control group		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Shariat et al (2011)[8.]	1.No allocation	No blinding				1. Decision curve analysis
Kim et al (2014)[9.]	1.No allocation	No blinding				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Urinary Tumor Marker Testing for Individuals With a History of Bladder Cancer

Diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 52% to 84% and pooled specificity ranging from 71% to 91%. There are several diagnostic performance studies on *FGFR3* for monitoring bladder cancer. These

studies generally showed that the markers had higher sensitivity than cytology. Direct evidence that outcomes are improved or not worsened with an altered schedule would be useful. However, no controlled studies were identified that prospectively evaluated health outcomes in patients managed with and without the use of urinary tumor marker tests. There is a lack of direct evidence that health outcomes improve in patients managed with urinary tumor marker tests compared with those managed without tumor marker tests. Furthermore, there is a lack of direct evidence that cystoscopy protocols would be changed when urinary tumor marker tests are used. The available studies have found low potential clinical benefit of urinary tumor marker testing for patients with non-muscle-invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

Urinary Tumor Marker Tests To Screen 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 bladder cancer at an earlier stage than it would present otherwise at a stage when treatment would permit improved outcomes.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are asymptomatic and are at a population-level risk of bladder cancer.

Interventions
The test being considered is urinary tumor marker tests.

Comparators
The following practices are currently being used to assess asymptomatic individuals at population-level risk of bladder cancer: standard surveillance without urinary tumor marker testing. 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 (OS), disease-specific survival, test accuracy, and tests validity. Beneficial outcomes are primarily related to detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

If indicated, screening for non-muscle-invasive bladder cancer would typically occur periodically over the course of years.

Study Selection Criteria
See information under the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Review

The ideal study for evaluating the effectiveness of a screening program is an RCT comparing outcomes in patients who did and did not participate in a screening program. Chou et al (2010) updated a U.S. Preventive Services Task Force evidence review on screening adults for bladder cancer.[12] The quality of evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only 1 prospective study rated as poor quality. The systematic review did not identify any studies evaluating the sensitivity or specificity of diagnostic tests for bladder patients in asymptomatic average-risk patients. Moreover, reviewers did not identify any suitable studies assessing whether the treatment of screen-detected bladder cancer reduces disease-specific morbidity and mortality or evaluating potential harms of screening for bladder cancer. Reviewers concluded: "major gaps in evidence make it impossible to reach any reliable conclusions about screening."

Observational Studies

Several uncontrolled studies have reported on screening studies. Bangma et al (2013) reported on a population-based program with men in The Netherlands.[13] The study evaluated the feasibility of screening using urine-based markers and examined performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least 1 positive home hematuria test underwent screening for 4 urine-based molecular markers. Men with at least 1 positive urine-based test were recommended to undergo cystoscopy. Of 6500 men invited to participate in screening, 1984 (30.5%) agreed and 1747 (88.1%) underwent hematuria testing. Of these, 409 (23.4%) tested positive for hematuria and 385 (94%) underwent urine-based marker testing. Cancer was diagnosed in 4 (0.002%) of 1747 men who underwent screening (3 bladder cancers, 1 kidney cancer). Although men in the study who tested negative on screening tests did not receive further testing, the investigators were able to link participants' data to a Dutch cancer registry. They determined that two cancers (1 bladder cancer, 1 kidney cancer) had been diagnosed in men who completed the protocol; these were considered false-negatives. The sensitivity and specificity of the U.S. Food and Drug Administration-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 a low diagnostic yield.

Lotan et al (2009) published a prospective study that screened 1502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure.[14] Individuals with positive BladderChek tests received cystoscopy and cytology. Eighty-five (5.7%) of the 1502 participants had a positive BladderChek test. Two of the 85 patients were found to have bladder cancer (noninvasive), yielding a positive predictive value of 2.4%. There was also 1 case of atypia. Follow-up at a mean of 12 months was obtained for 1309 (87%) of 1502 screened patients. No additional cancers were diagnosed in the group that had positive BladderChek tests. Two participants with a negative BladderChek screen had been diagnosed with bladder cancer; both tumors were less than 1 cm. Because no follow-up tests were done on participants who initially tested negative, it is unclear whether these were false-negative findings or new cancers. Study limitations included lack of follow-up testing on approximately 20% of participants who tested positive and lack of early cystoscopy and incomplete 1-

year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (eg, sensitivity) cannot be calculated.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of screening using urinary biomarkers in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Urinary Marker Tests to Screen 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.

Laukhtina et al (2021)[15] conducted a systematic review and network meta-analysis (NMA) on the diagnostic accuracy of novel urinary biomarker tests UBTs in non-muscle-invasive bladder cancer (NMIBC). PubMed, Web of Science, and Scopus were searched up to April 2021 to identify studies addressing the diagnostic values of UBTs: Xpert bladder cancer, Adxbladder, Bladder EpiCheck, Uromonitor and Cxbladder Monitor, and Triage and Detect. The primary endpoint was to assess the pooled diagnostic values for disease recurrence in NMIBC patients using a DTA meta-analysis and to compare them with cytology using an NMA. The secondary endpoints were the diagnostic values for high-grade (HG) recurrence as well as for the initial detection of bladder cancer. Twenty-one studies, comprising 7330 patients, were included in the quantitative synthesis. In most of the studies, there was an unclear risk of bias. For NMIBC surveillance, novel UBTs demonstrated promising pooled diagnostic values with sensitivities up to 93%, specificities up to 84%, positive predictive values up to 67%, and negative predictive value up to 99%. Pooled estimates for the diagnosis of HG recurrence were similar to those for the diagnosis of any-grade recurrence. The analysis of the number of cystoscopies potentially avoided during the follow-up of 1000 patients showed that UBTs might be efficient in reducing the number of avoidable interventions with up to 740 cystoscopies. The NMA revealed that diagnostic values (except specificity) of the novel UBTs were significantly higher than those of cytology for the detection of NMIBC recurrence. There was too little data on UBTs in the primary diagnosis setting to allow a statistical analysis. The authors concluded that their analyses support high diagnostic accuracy of the studied novel

UBTs, supporting their utility in the NMIBC surveillance setting. This might potentially help prevent unnecessary cystoscopies safely. There is not enough data to reliably assess their use in the primary diagnostic setting.

SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have sensitivity ranging from 47% to 85% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy.

For individuals who have a history of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies, meta-analyses, as well as a decision curve analysis and a retrospective study examining the clinical utility of urinary tumor marker tests. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. The diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 46% to 84% and pooled specificity ranging from 71% to 91%.

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 OS, disease-specific survival, and test accuracy and validity. A 2010 systematic review (conducted for the U.S. Preventive Services Task Force) 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 the Task Force rated as poor quality. A more recent retrospective study, assessing a population-based screening program in the Netherlands, reported a low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN;v.4.2024) 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).[16]

American Urological Association and Society of Urologic Oncology

The guidelines from the American Urological Association and Society of Urologic Oncology (2016; amended 2020) 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 and through additional supplementation that further addressed key questions and more recently published literature.[17] Table 6 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

Table 6. Guidelines for Urine Tumor Markers After the Diagnosis of Bladder Cancer

Guidance Statement	SOR	LOE
"In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation."	Strong	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

BCG: bacillus Calmette-Guérin; LOE: level of evidence; NMIBC: non-muscle-invasive bladder cancer; SOR: strength of recommendation.

American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction

In 2020, the American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a guideline on the diagnosis, evaluation, and follow-up of microhematuria.[18] This guideline recommended the following with regard to urinary markers:

- Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria [Strong recommendation; Evidence level: Grade C]
- Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ [Expert opinion]

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF;2011) concluded that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults.[19]The recommendation was based on insufficient evidence (grade I).

In November 2021, a literature surveillance report was published that scanned for relevant literature in PubMed and PubMed databases and the Cochrane library from 2009 to present.[20] The researchers found "no relevant studies on the impact of screening for bladder cancer on morbidity and mortality, outcomes of treatment of screen-detected bladder cancer, or harms of screening for or treatment of screen-detected bladder cancer." Additionally, "no studies compared the benefits or harms of treatment of screen-detected bladder cancer with no treatment."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04100733	Surveillance of High-grade Non-muscle Invasive Bladder Tumors Using the Xpert Bladder Cancer Monitor	392	Sep 2029
NCT03973307	Evaluation of UroX™ Biomarker Screening Test in the Investigation of Bladder Cancer From Urine Samples - a Single Site Pilot Study	100	Jul 2025
NCT05080998	An Observational Study of Cxbladder Monitoring for Recurrence of Urothelial Carcinoma in Intermediate and High-Risk Patients	450	Dec 2025
NCT03664258[a]	Evaluation of the Xpert® Bladder Cancer Monitor Assay Compared to Cystoscopy for the Follow-up of Patients With History of Low or Intermediate Risk Non-muscle-invasive Bladder Cancer (NMIBC): an Observational Prospective Interventional Multicenter Study	852	Sep 2022
Unpublished			
NCT03125460[a]	Clinical Evaluation of Xpert Bladder Cancer Monitor for Monitoring the Recurrence of Bladder Cancer	424	May 2019 (Completed)
NCT02969109[a]	Clinical Validation of a Urine-based Assay With Genomic and Epigenomic Markers for Predicting Recurrence During Surveillance for Non-muscle Invasive Bladder Cancer	417	Sep 2018 (Completed)

NCT: national clinical trial

[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no National Coverage Determination that addresses urinary tumor markers for bladder cancer.

Local:

Wisconsin Physicians Insurance Corporation (WPS)
Local Coverage Article: Billing and Coding: Lab: Bladder/Urothelial Tumor Markers (A56332)
Original Effective Date: 04/15/2019
Revision Effective Date: 12/26/2019 – Retirement Date: 02/25/2021

WPS GHA will only cover bladder tumor marker FISH testing services when performed using validated assays. To date, UroVysion Bladder Cancer Kit is the only FDA approved assay that is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus via FISH. The assay is performed on urine specimens from persons with hematuria suspected of having bladder cancer as an aid for initial diagnosis of bladder carcinoma and subsequent monitoring for tumor recurrence in patient previously diagnosed with bladder cancer. UroVysion Bladder Kit services may only be billed by a CLIA certified lab.

The 2024 CMS Laboratory Fee Schedule lists fees for procedure codes 86294, 86386, 0012M, 0013M, 0363U and 0420U. Codes 88120 and 88121 are not found on the fee schedule. An assigned fee is not a guarantee of coverage.

Palmetto GBA
Billing and Coding: Lab: Bladder/Urothelial Tumor Markers
(A53095)
Original Effective Date:10/01/2015
Revision Effective Date: 08/03/2023

The information in this article contains billing, coding or other guidelines that complement the Local Coverage Determination (LCD) for Lab: Bladder/Urothelial Tumor Markers (L33420). Palmetto GBA will only cover bladder tumor marker fluorescence in situ hybridization (FISH) testing services when performed using validated assays. To date, UroVysion™ Bladder Cancer Kit is the only Federal Drug Administration (FDA) approved assay that is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus via FISH. The assay is performed on urine specimens from persons with hematuria suspected of having bladder cancer as an aid for initial diagnosis of bladder carcinoma and subsequent monitoring for tumor recurrence in patient previously diagnosed with bladder cancer. UroVysion™ Bladder Kit services may only be billed by a CLIA certified lab.

To bill UroVysion™ Bladder Kit services, submit the following claim information:

- Select CPT® code 88120 or 88121 as appropriate

Laboratories reporting only the technical component for a UroVysion™ service should append the appropriate code 88120 or 88121 with the TC modifier.

All other services that meet the code 88120 or 88121 definition performed by any provider type MUST bill the following claim information.

- Select CPT® code 88120 or 88121 as appropriate

Note: Physicians may NOT submit claims for a code 88120 and 88121 professional component when the interpretive information is provided by a lab technician or scientist. Per Chapter 10 in the NCCI Policy Manual for Medicare Services, Version 16.3, the physician work component requires a physician to read, quantitate and interpret the tissues/cells stained with the probes(s). Physicians who knowingly report and interpretation based on the documented results of another professional may be subject to additional corrective action including Recovery Audit Contractor (RAC) or fraud referrals.
To report a Bladder/Urothelial Tumor Marker service, please submit the following claim information:

- Select the appropriate CPT® code
- Enter 1 unit of service (UOS)

- Select the appropriate ICD-10 code

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Polymetabolite Urine Testing for Adenomatous Polyps

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/13/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/11	4/19/11	5/3/11	Joint policy established
5/1/12	2/21/12	2/21/12	Routine maintenance, CPT code 86386 added to policy
8/1/15	4/21/15	5/18/15	• Routine maintenance • Deleted NOC code 88299 • Added NOC code 81479 • Added Inclusionary Guidelines • Added Divergent Statement
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance; added Cxbladder E/I
1/1/19	10/16/18	10/16/18	Routine maintenance; code update for Cxbladder (0012M and 0013M); edits to rationale
1/1/20	10/15/19		Routine maintenance; title change to reflect policy expansion of urinary biomarkers to screen for colonic polyps CMS: WPS article
1/1/21	10/20/20		Routine maintenance Title change: Urinary Biomarkers for Bladder Cancer. References in rationale re: colon polyps removed.
7/1/21	4/20/21		Routine maintenance. Ref 15 added
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Reference added 14,18 Vendor Managed: Avalon Removed all references to the colon cancer testing that still remained in the policy removed references 13, and 16 from policy.

3/1/24	12/19/23		2024 CPT Code Update -Add 0420U as E/I (jf) Policy updated to EST per the written MPS.
7/1/24	4/16/24		Routine maintenance (jf) Vendor Managed: Avalon • Added Bladder EpiCheck® under the regulatory section. No CPT code available in the U.S. (only available in Europe). • Added 0363U as E/I to the policy. It represents Cxbladder Triage. Reference added:1,8,15
11/1/24	8/20/24		2024 PLA Code Update effective 7/1/24 (jf) Vendor Managed: Avalon • Add 0452U EarlyTect® Bladder Cancer Detection (EarlyTect® BCD) by Promis Diagnostics as E/I • Add 0465U UriFind® Blood Cancer Assay by DiaCarta, AnchorDx as E/I. PLA Code update Effective revision effective 10/1/24 0465U Revision to proprietary name New name: UriFind® Urothelial Carcinoma Assay, DiaCarta, Inc, AnchorDx

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: URINARY BIOMARKERS FOR BLADDER CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered if criteria is met
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.