
Medical Policy



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***Current Policy Effective Date: 11/1/26**
(See policy history boxes for previous effective dates)

Title: Urine-Based Tests for Bladder Cancer and Pre-Cancerous Colon Adenomas

Description

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

Additionally, urine metabolite testing has been proposed for the detection of adenomatous polyps, which may be precursors to colorectal cancer. PolypDx™ is a urine metabolite assay that uses liquid chromatography with tandem mass spectrometry to measure selected urine metabolites and applies an algorithm to estimate the likelihood of colonic adenomatous polyps. This testing is intended as a noninvasive screening adjunct for individuals at average risk for colorectal cancer; however, colonoscopy remains the criterion standard for detection and removal of adenomatous polyps.

Medical Policy Statement

FDA-approved or FDA-cleared urinary tumor marker tests for bladder cancer are **established** when criteria are met.

Urine metabolite testing for the detection of adenomatous polyps (e.g., PolypDx™) is **experimental/investigational**. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:

When all of the following are met:

- FDA-approved or FDA-cleared
- Urinary tumor markers for bladder cancer, as an adjunct to cytology and cystoscopy, are **established** in any of the following:
 - when used as a diagnostic exclusion of bladder cancer for individuals who have an atypical or equivocal cytology.
 - In the monitoring of high-risk, non-muscle invasive bladder cancer.

Exclusions:

- All non-FDA approved and non FDA-cleared urinary tumor marker tests (e.g. Cxbladder) for bladder cancer
 - All other indications for bladder cancer not specified under the inclusions.
 - All urine metabolite testing for the detection of adenomatous polyps
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CPT/HCPCS Level II Codes

Established codes:

86294	86386	88120	88121	86316
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Other codes (investigational, not medically necessary, etc.):

0013M	0002U	0420U	0363U	0452U	0465U
0365U	0366U	0367U	0549U	0613U	

Notes:

- *Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*
 - *Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*
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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 (i.e., 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 (e.g., 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.

Adenomatous Polyps

Adenomatous polyps, also referred to as adenomas, are neoplastic lesions of the colon and rectum that may serve as precursors to colorectal cancer. Most colorectal cancers are believed to arise from the adenoma-carcinoma sequence, a gradual process in which benign adenomatous tissue may acquire dysplastic changes and progress to invasive malignancy over time. The risk of progression varies based on polyp features, including size, histology, number of polyps, and degree of dysplasia. Advanced adenomas are generally defined by features such as larger size, villous histology, high-grade dysplasia, or multiplicity. Screening for colorectal cancer is intended to detect cancer at an earlier and more treatable stage and to identify and remove precancerous adenomatous polyps before malignant transformation occurs. Colonoscopy remains the criterion standard for detection and removal of adenomatous polyps because it allows direct visualization, biopsy, and polypectomy during the same procedure. Other accepted screening options include stool-based testing and structural examinations, depending on patient risk factors, age, and screening history. Urine-based metabolomic testing has been proposed as a noninvasive method to estimate the likelihood of adenomatous polyps in asymptomatic individuals at average risk for colorectal cancer.

PolypDx™ is a non-invasive urine-based diagnostic test for the detection of adenomatous polyps, which can be the precursor to colorectal cancer. The assay uses liquid chromatography with tandem mass spectrometry to measure levels of three metabolites in an individual's urine: ascorbic acid, succinic acid, and carnitine. An algorithm compares urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps. PolypDx™ is intended for use in average-risk individuals who should be receiving regular colorectal cancer screening.

PolypDx™ is the flagship product of Metabolomic Technologies Inc. (MTI), a privately held Canadian company based in Edmonton, Alberta. Metabolomic Technologies Inc. signed an agreement with Atlantic Diagnostic Laboratories (ADL), based in Philadelphia, PA, giving ADL exclusive licensing and distribution rights in the U.S.³⁵

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 95% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. In a randomized trial, a sensitivity of 90%, specificity of 56%, and a negative predictive value of 99% were demonstrated among low-risk patients. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 91% and pooled specificity ranging from 65% to 91%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 one 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 outcome.

Studies found for the urine-based metabolomic diagnostic test PolypDx™ were proof-of-concept studies, with no true comparator. Randomized, controlled clinical trials are needed to confirm this test's sensitivity and specificity. Currently, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

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.

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 have been published. Woldu et al (2021) conducted a systematic review of urinary biomarkers to detect bladder cancer.² Eleven studies were included in the meta-analysis. The pooled sensitivity of urinary biomarker tests was 58% to 95% compared to 68% sensitivity of cytology. The post-test probability of bladder cancer among individuals with a negative urine biomarker test was 0% to 0.2% for low-risk patients, 0.2% to 0.5% for intermediate-risk patients, and 0.4% to 1.1% for high-risk patients. For individuals with a positive urine biomarker test, the post-test probability of bladder cancer was 1.1% to 3.7% among low-risk patients, 2.1% to 7.8% among intermediate-risk patients, and 4.2% to 19.2% among high-risk patients.

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.³ 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 1.

Table 1. 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 (e.g., 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).³

CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives.

Clinical Validity of FDA-Approved or Cleared Urinary Tumor Marker Tests (e.g., 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.

Randomized Trial

Lotan et al (2024) conducted a multicenter prospective randomized controlled trial (RCT) to compare the use of Cxbladder Triage (CxbT) to traditional cystoscopy (control) in patients with microhematuria.³ The study included 390 patients, categorized into 2 groups: 135 lower risk (LR) patients, defined as having 3 to 29 red blood cells per high-power field and minimal smoking history (<10 pack-years), and 255 not lower risk (NLR) patients. The LR patients were randomized into either the CxbT group or the control group. Results showed that CxbT significantly reduced the need for cystoscopy in LR patients, with only 27% of those in the CxbT group undergoing the procedure compared to 67% in the control group (relative risk, 0.41; 95% confidence interval [CI], 0.27 to 0.61). Additionally, CxbT demonstrated a sensitivity of 90%, specificity of 56%, and a negative predictive value of 99%.

While these findings may demonstrate the diagnostic performance of Cxbladder Triage and a reduction in cystoscopy utilization in selected low-risk patients with microhematuria, the study did not evaluate cost-effectiveness, and evidence that use of the test improves clinically

meaningful outcomes, such as earlier detection, reduced morbidity, reduced mortality, or improved overall survival, was not demonstrated.

Observational Study

Pagano et al (2025) conducted a prospective evaluation of the diagnostic performance of the Oncuria assay in 931 patients with hematuria.⁵ An additional 69 patients with other cancer types (kidney and prostate) served as a control group. The overall prevalence of bladder cancer (as determined by biopsy) was 20%. Oncuria detected bladder cancer in 105 of 121 cases, with a sensitivity of 85%, specificity of 72%, negative predictive value of 95%, and positive predictive value of 42%.

Sordelli et al (2024) conducted a prospective cohort study of the Xpert Bladder Cancer Detection assay in patients presenting to the emergency department with hematuria.⁶ Urine samples were obtained and tested in the emergency department. Cytoscopy identified 24 cases of suspected bladder cancer, and 16 patients had pathology-diagnosed bladder cancer. Of the 76 patients with an evaluable Xpert test, the sensitivity was 93.8% (95% CI, 69.8% to 99.8%), specificity was 51.7% (95% CI, 38.4% to 64.8%), positive predictive value was 34.1% (95% CI, 20.5% to 49.9%), and negative predictive value was 96.9% (95% CI, 83.8% to 99.9%). In comparison, the sensitivity, specificity, positive predictive value, and negative predictive value for cytосcopy were 25%, 100%, 100%, and 83.3%.

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 95% and pooled specificity ranging from 53% to 95% when compared with cystoscopy and biopsy. In a randomized trial, a sensitivity of 90%, specificity of 56%, and a negative predictive value of 99% were demonstrated among low-risk

patients. There is no evidence of the clinical utility of urinary biomarker testing in this population for broad diagnostic use; however, the evidence supports the clinical validity of selected FDA-approved or FDA-cleared urinary tumor marker tests when used as adjuncts to cytology and cystoscopy in specified situations.

Following a review of the American Urological Association's (AUA) guidelines on microhematuria, a conditional recommendation was made for incorporating Cxbladder Triage into the diagnostic process for individuals with hematuria, although the supporting evidence was not compelling. Similarly, the Centers for Medicare and Medicaid Services (CMS) reviewed the available data and determined that the test was not medically necessary. This is consistent with BCBSM's noncoverage position for Cxbladder Triage.

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 cystoscopies or earlier detection of recurrence. Individuals with a history of bladder cancer have a higher pretest probability of cancer than those with no history.

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

Chiang et al (2024) conducted a systematic review and meta-analysis of Bladder EpiCheck for detecting recurrence in patients with non-muscle invasive bladder cancer.⁷ A total of 6 studies (n=1588) compared Bladder EpiCheck to cytology. Results showed that the pooled sensitivity was 81% (95% CI, 63% to 91%; I2 = 43%) and specificity was 87% (95% CI, 83% to 91%; I2 = 20%). Cytology in the included studies had a sensitivity of 63% (95% CI, 29% to 87%; I2 = 61%) and specificity was 97% (95% CI, 78% to 100%; I2 = 79%). The positive predictive value and negative predictive value of Bladder EpiCheck were 62% and 94%, respectively, compared to 87% and 84%, respectively for cytology. For high-grade tumors Bladder EpiCheck had a sensitivity of 90% compared to 72% for cytology.

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

Table 2. 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 (e.g., UroVysion)	189/299	55 (36 to 72)	7	80 (66 to 89)	6

Adapted from Chou et al (2015).³

CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives.

Randomized Trials

Dryer et al (2025) conducted a randomized trial of patients with high-grade non-muscle invasive bladder cancer who underwent urinary biomarker testing using the Xpert Bladder Cancer Monitor assay.⁸ The Xpert Bladder Cancer Monitor test was used in an alternating manner with cystoscopy every 4 months for 2 years, or patients received cystoscopy at all follow-up time points. Recurrence occurred in 43 patients (22 in the Xpert arm, 21 in the cystoscopy arm). A total of 2 high-grade recurrences were missed by the Xpert assay. For the Xpert Bladder Cancer Monitor assay, sensitivity, specificity, positive predictive value, and negative predictive value were 91%, 65%, 16%, and 99%, respectively. For cytology, sensitivity, specificity, positive predictive value, and negative predictive value were 9%, 97%, 22%, and 91%, respectively. The authors stated that a limitation of the study was a lower than expected rate of recurrence in the study overall.

Schmitz-Drager et al (2025) conducted a randomized trial of 392 patients with low- or intermediate-risk bladder cancer who underwent surveillance using urinary markers (n=105) or cystoscopy (n=109).⁹ Surveillance using urinary markers (UroVysion or Alere NMP22) plus ultrasound every 6 months was compared to cystoscopy. After 2.4 years of follow-up, cancer recurrence was identified in 29 patients in the urinary marker group and 30 patients in the cystoscopy group (risk difference, 0.08%; 95% CI, -7.3% to 7.4%). Sensitivity was 81.5% (95% CI, 61.9% to 93.7%) for urinary marker surveillance and 96.5% (95% CI, 82.2% to 99.9%) for cystoscopy surveillance. One low-grade tumor was overlooked with cytology surveillance, and 5 low-grade tumors were overlooked with urinary marker surveillance.

Observational Studies

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.¹⁰ 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.¹¹ 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).¹² 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.¹³ 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%. 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.¹⁴

Fleshner et al (2025) enrolled 674 adults with urothelial carcinoma who had undergone resection within 12 months prior and were undergoing cystoscopy surveillance.¹⁵ 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 a sensitivity of 67% (95% CI, 58% to 74%) and specificity of 84% (95% CI, 80% to 88%), with positive and negative predictive values of 65% (95% CI, 57% to 73%) and 85% (95% CI, 81% to 89%), respectively.

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.¹⁶ In the unpublished 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). A systematic review of observational studies found the following sensitivity, specificity, and positive and negative predictive values for Bladder EpiCheck test: 71.6%, 84.5%, 56.4%, and 92.8%, respectively.¹⁷

Lee et al (2025) conducted a prospective study to evaluate the diagnostic accuracy of the Earlytect BCD assay in patients with 13 cancer types.¹⁸ Of the 183 patients enrolled, 8 had bladder cancer, 9 had upper tract urothelial carcinoma, and 166 had other types of cancer. When non-bladder cancers were used as the control group, the sensitivity and specificity of the Earlytect BCD assay were 94.1% (95% CI, 71.5% to 99.9%) and 95.8% (95% CI, 91.5% to 98.4%), respectively. The assay sensitivity for bladder cancer was 87.5% and for upper tract urothelial carcinoma was 100%. Seven patients with other cancer types had a positive result with the Earlytect BCD test.

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.¹⁹ 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.²⁰ 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 (e.g., 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.²¹ 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 3 and 4) is to display notable limitations identified in each study.

Table 3. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Shariat et al (2011) ²⁰	4. All patients had negative cytology		2. No control group	1. Management decisions	
Kim et al (2014) ²¹	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 4. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Shariat et al (2011) ²⁰	1.No allocation	No blinding				1. Decision curve analysis
Kim et al (2014) ²¹	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 91% and pooled specificity ranging from 65% 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, the available studies have found some 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.

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.²² The quality of evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only one 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.²³ 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.²⁴ 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 (e.g., 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)³³ 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.

Urinary Metabolite Testing to Screen Asymptomatic Individuals for Precancerous Colonic Polyps

Clinical Context and Test Purpose

The purpose of screening tests for urinary metabolites in asymptomatic individuals is to detect disease at an earlier stage than it would present otherwise when treatment would permit improved outcomes. Screening for polyps is currently conducted by colonoscopy, with a U.S. Preventive Services Task Force recommendation of screening every 10 years beginning at 45 years of age.³⁵ Colonoscopy is invasive and uncomfortable and results in poor compliance with screening recommendations. The availability of a noninvasive test for precancerous polyps could improve referral for colonoscopy and early detection of colon cancer. The following PICO was used to select literature to inform this review.

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

Validation Study

Deng et al (2017) reported on the development and validation of PolypDx. Urine and stool samples were prospectively collected from 695 individuals participating in a colorectal cancer screening program to undergo colonoscopy.³⁴ Metabolites in urine that were associated with adenomatous polyps were determined from 67% of the samples using nuclear magnetic resonance spectroscopy. Blinded testing on the validation set was performed in 33% of the samples using mass spectrometry, with a resulting area under the curve of 0.692.

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, more effective therapy, or avoid unnecessary therapy or 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.

No direct evidence on clinical utility 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.

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

Section Summary: Urinary Metabolite Testing to Screen Asymptomatic Individuals for Precancerous Colon Polyps

The clinical data supporting a urine metabolite assay for adenomatous polyps involves a report of a training and validation set. There is insufficient evidence on the diagnostic accuracy of urinary metabolite testing to draw conclusions about its use to screen asymptomatic individuals for precancerous colon polyps.

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.2.2026) 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). The guidelines include the following statement: "Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumors may be considered during surveillance of high-risk non-muscle-invasive bladder cancer. However, it remains unclear whether these tests offer additional useful information for detection and management of non-muscle-invasive bladder tumors."²⁵

Biomarkers have the greatest clinical value in the further evaluation of patients with subjective findings at the time of office cystoscopy (e.g., focal or diffuse redness raising concern most notably in a patient with previous intravesical treatment that could explain such findings) or in the context of abnormal voided cytology (most notably when the upper tract diagnostic imaging evaluation is negative). However, we leave this to the discretion and clinical judgment of board-certified practicing urologists to determine if and when such biomarkers may be clinically used in their practice.

NCCN Clinical Practice Guidelines in Oncology, Colorectal Cancer Screening, V.2.2026 does not discuss urine-based testing.³⁵

American Urological Association and Society of Urologic Oncology

The guidelines from the American Urological Association and Society of Urologic Oncology (2016; amended 2020 and 2024) 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.^{27,28} Table 5 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

Table 5. 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.

Microhematuria: AUA/SUFU Guideline (2025)²⁸

Clinicians should not routinely use urine cytology or urine-based tumor markers to decide whether to perform cystoscopy in the initial evaluation of low/negligible- or high-risk patients with microhematuria. (*Strong Recommendation; Evidence Level: Grade C*).

In 2025, 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.²⁸ This guideline recommended the following with regard to urinary markers:

- In appropriately counseled intermediate-risk patients who want to avoid cystoscopy and accept the risk of forgoing direct visual inspection of the bladder urothelium, clinicians may offer urine cytology or validated urine-based tumor markers to facilitate the decision regarding utility of cystoscopy. Renal and bladder ultrasound should still be performed in these cases. [Conditional recommendation; Evidence level: Grade C]
- Clinicians should not routinely use urine cytology or urine-based tumor markers to decide whether to perform cystoscopy in the initial evaluation of low/negligible- or high-risk patients with microhematuria. [Strong recommendation; Evidence level: Grade C]
- Clinicians should not routinely use cytology or urine-based tumor markers as adjunctive tests in the setting of a normal cystoscopy. [Strong recommendation; Evidence level: Grade C]
- Clinicians may obtain urine cytology for high-risk patients with equivocal findings on cystoscopic evaluation or those with persistent microhematuria and irritative voiding symptoms or risk factors for carcinoma in situ after a negative workup. [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.²⁹ The recommendation was based on insufficient evidence (grade I).

The USPSTF concludes the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults. Literature scans conducted in July 2024 in the MEDLINE and PubMed databases and the Cochrane Library showed a lack of new evidence to support an updated systematic review on the topic at this time. See the Literature Surveillance Report under the Supporting Evidence section of this webpage.³⁰

The USPSTF (2021) recommendation for screening for colorectal cancer "does not include serum tests, urine tests, or capsule endoscopy for colorectal cancer screening because of the limited available evidence on these tests and because other effective tests are available."³¹

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT06751667	Xpert Bladder Monitor: a Non-Invasive Follow-Up Tool for Detecting Relapse in High Grade or High Risk Bladder Cancer	50	Jan 2032

NCT06818136 ^a	Evaluation of the Efficacy of Bladder EpiCheck® for the Primary Detection of Urothelial Carcinoma in Subjects Presenting With Haematuria	600	Apr 2026
NCT06878027	Analysis of Urinary Methylation Patterns Via Liquid Biopsy as a Tool for Early Diagnosis, Non-invasive Monitoring and Prediction of Recurrence Risk in Bladder Cancer	100	Feb 2026
NCT03973307	Evaluation of UroX™ Biomarker Screening Test in the Investigation of Bladder Cancer From Urine Samples - a Single Site Pilot Study	100	Jul 2025 (unknown status)
NCT05080998 ^a	An Observational Study of Cxbladder Monitoring for Recurrence of Urothelial Carcinoma in Intermediate and High-Risk Patients	450	Aug 2026
NCT05864599	External Validation of Uromonitor as a Biomarker for Optimization of NMIBC Management by the CUETO Group	600	Jun 2024
NCT06026189	Safely Reduce Cystoscopic Evaluations for Hematuria Patients	1100	May 2027
NCT05646485	Optimal Screening Strategy for Bladder Cancer in at Risk Patients	1000	April 2028
<i>Unpublished</i>			
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	Jan 2022 (Completed)
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.

Regulatory Status

Table 7 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 7. 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

Reviewed 4/27/26

FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; NMIBC: non-muscle invasive bladder cancer; NMP: nuclear matrix protein; RT-PCR: real-time polymerase chain reaction.

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 Diagnostic Tests

FDA-approved diagnostic tests include:

- Tests which are billed with CPT* codes (most laboratories are able to process these)
- Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in "U".

*CPT® is a registered trademark of the American Medical Association

Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments.

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 Triage tests and Cxbladder Triage Plus. (*Cxbladder Detect test is no longer offered in the U.S. effective 2026*)
- Xpert® Bladder Cancer Monitor (Cepheid) measures mRNA (*ABL1, CRH, IGF2, UPK1B, ANXA10*) in voided urine by reverse transcription-polymerase chain reaction (RT-PCR).
- PolypDx™ (Metabolomic Technologies) is a urine metabolite assay that uses liquid chromatography-mass spectrometry. An algorithm compares urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.
- EarlyTect® BCD (Promis Diagnostics) measures urinary levels of PENK, a methylated DNA biomarker.
- UriFind® Urothelial Carcinoma Assay, DiaCarta, Inc, AnchorDx
- AssureMDx (Vesica Health) measures the methylation of urinary DNA (*TWIST1, OTX1, ONECUT2* genes) and DNA mutations (*FGFR3, TERT, HRAS* genes).
- Oncuria® (Nonagen Bioscience Corp.) immunoassay that detects 10 biomarker proteins (*MMP9, IL8, VEGF, CA9, A1AT, ANG, APOE, PAI1, SDC1, MMP10*).

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 2026 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: 10/1/24

Article Text

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.

This A/B MAC 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 patients 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 provide 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 & Medicaid 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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July, 2026, 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
7/1/25	4/15/25		Routine maintenance (jf) Vendor Managed: Avalon - Added 0365U, 0366U and 0367U as E/I to the policy - Added 86316 as EST - Code 0365U revised EFD 1/1/25 - Added 0549U PLA code as E/I effective 4/1/25 Edited MPS-safety and effectiveness removed Added Ref: 3,10, 20
9/1/25	6/17/25		Routine maintenance (jf) Vendor Managed: Avalon

			Literature Review (jf) Cxbladder Triage 0363U to remain E/I Add Ref: 25,26 • PLA Code Update Revision 0420U: "Cxbladder Detect+ was rebranded as Cxbladder Triage Plus" • Updated Cxbladder Triage Plus in the nomenclature and body of the policy. • Edits to the inclusions, exclusions, MPS and summary of evidence • Added description to policy • Added information to clarify the difference between CLIA and FDA test in regulatory section
9/1/26	6/16/26		• Routine Maintenance (jf/fr) • 2026 CPT Annual code Update • Add 0613U as E/I effective 1/1/26 • Delete/Remove 0012M from policy. Based on review of the laboratory website, the Cxbladder Detect test is no longer offered in the U.S. • Ref added: 2,5,6,7,8,9,15,18,28 • Formatting changes made: • Sections rearranged for better flow • MPS edited • Notes edited in code section
11/1/26	8/18/26		• Off Cycle Review (jf/fr) • Vendor Managed: Avalon • Policy was expanded to include urine-based testing for adenomatous polyps due to retirement of the separate Polymetabolite Urine Testing policy. • Added 0002U as E/I • Edits to the Title, description, Background, MPS, Rationale,

			exclusions, Regulatory, Supplemental, Summary of Evidence • Policy changed to Mixed status • Added Ref: 35, 36,37,38 • Original Title: Urinary Tumor Markers for Bladder Cancer New Title Change: Urine-Based Tests for Bladder Cancer and Pre-Cancerous Colon Adenomas
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Next Review Date: 2nd Qtr, 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: URINE BASED TESTS FOR BLADDER CANCER AND PRE-CANCEROUS COLON
ADENOMAS

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.