2.04.07	Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance		
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Section:	2.0 Medicine	**Page:**	Page 1 of 22

Policy Statement

I. The use of urinary tumor markers is considered **investigational** in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

See the Codes table for details.

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 biomarkers that might be used to supplement or supplant these tests have been actively investigated. Urinary biomarkers have also been suggested to have utility in identifying colonic polyps.

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 a sensitivity ranging from 47% to 82% 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. The evidence is insufficient 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 and 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 52% to 84% and pooled specificity ranging from 71% to 91%. The decision analysis found only a small clinical benefit for use of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies using the preferred trial design to evaluate clinical utility were identified; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without the use of urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers. The

evidence is insufficient 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 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 low diagnostic yield. The evidence is insufficient 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 colon cancer who receive urinary tests for precancerous polyps, the evidence includes a validation study. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. The clinical data supporting a urine metabolite assay for adenomatous polyps includes a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 535
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care

plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

FDA Approved or Cleared Urinary Tumor Marker Tests

Table 1 lists urinary tumor marker tests approved or cleared for marketing by the 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, or identification of colonic polyps.

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

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.
[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.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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 (CLIA). Urine-based tests are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the 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.
- 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.

Rationale

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

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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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 evaluation of individuals who have signs and/or symptoms of bladder cancer is to inform a decision whether to proceed to cytology 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 alone 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 the 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 have been published. Chou et al (2015) reported on a systematic review and meta-analysis of studies of the diagnostic accuracy of urinary biomarkers for the diagnosis or follow-up of non-muscle-invasive bladder cancer, which was done as part of an Agency for Healthcare Research and Quality Comparative Effectiveness Review on the diagnosis and treatment of non-muscle-invasive bladder cancer.[2,] Two studies were rated as having a 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 (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).[2]
CI: confidence interval; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein; TP: true positives.

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% CI, 0.27 to 0.61). Additionally, CxbT demonstrated a sensitivity of 90%, specificity of 56%, and a negative predictive value of 99%.

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 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 urinary biomarker testing has not been established, the conclusion of testing using these markers to diagnose individuals with signs and/or symptoms of bladder cancer cannot be drawn.

Section Summary: Urinary Tumor Marker Testing of Individuals With Symptoms of Bladder Cancer

Numerous studies have evaluated the accuracy of 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% 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.

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

Clinical Context and Test Purpose

The purpose of using urinary tumor markers in the evaluation of individuals who have a history of bladder cancer is to monitor for recurrence and inform a decision whether to proceed to cytology and biopsy.

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 OS, disease-specific survival, test accuracy and validity, and resource utilization. Beneficial outcomes are primarily related to the 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

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

Test	TP/n	Pooled Sensitivity (95% CI), %	Studies, n	Pooled Specificity (95% CI), %	Studies, n
FISH (e.g., 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; NMP: nuclear matrix protein; TP: true positives.

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.[4,] The study included 323 individuals who had been treated for bladder cancer; 48 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.[5,] The research team, based in the Netherlands, developed an assay to identify common *FGFR3* variants in urine samples. This team 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<.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).[6,] 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 a 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.[7,] 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.[8,] 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.

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.[9,] 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). 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.[10,]

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.

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.[11,] 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; the authors concluded that the marker did not aid clinical decision making in most cases.[12,] 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.[13,] 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)[12,]	4. All patients had negative cytology		2. No control group	1. Management decisions	
Kim et al (2014)[13,]	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 gaps 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)[12,]	1.No allocation	1,2.No blinding				1. Decision curve analysis
Kim et al (2014)[13,]	1.No allocation	1,2.No blinding				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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 differences.
[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 a 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 tests 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 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 OS, disease-specific survival, test accuracy, and test validity. Beneficial outcomes are primarily related to the 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

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 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.[14,] 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.[15,] 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. The investigators determined that 2 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 were 25% (95% CI, 0.63% to 80.6%) and 96.6% (95% CI, 94.2% to 98.2%), respectively. 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.[16,]

Section Summary: Urinary Marker Tests to Screen Asymptomatic Individuals for Bladder Cancer

We found no RCTs evaluating the impact of screening for 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.

Urinary Marker Tests to Screen Asymptomatic Individuals for Precancerous Colonic Polyps

Clinical Context and Test Purpose

The purpose of screening tests for urinary markers 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.[17,] 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.

Populations

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

Interventions
The test being considered is urinary tests for precancerous polyps (PolypDx). PolypDx is a urine metabolite assay that uses an algorithm to compare urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.

Comparators
The following practices are currently being used to assess asymptomatic individuals at population-level risk of colon cancer: colonoscopy and fecal testing. The U.S. Preventive Services Task Force has recommended screening for colon cancer starting at age 45 and continuing until age 75.[17,] The criterion standard for screening for adenomatous polyps is a colonoscopy. Alternative methods for screening include computed tomography colonography and fecal tests.

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

Follow-up for precancerous polyps 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
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.[18,] 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 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 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 tumor markers to draw conclusions about its use to screen asymptomatic individuals for precancerous colon polyps.

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 a sensitivity ranging from 47% to 82% 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. The evidence is insufficient 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 and 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 52% to 84% and pooled specificity ranging from 71% to 91%. The decision analysis found only a small clinical benefit for use of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies using the preferred trial design to evaluate clinical utility were identified; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without the use of urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers. The evidence is insufficient 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 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 low diagnostic yield. The evidence is insufficient 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 colon cancer who receive urinary tests for precancerous polyps, the evidence includes a validation study. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. The clinical data supporting a urine

metabolite assay for adenomatous polyps includes a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received through 2 physician specialty societies and 5 academic medical centers while this policy was under review in 2012. There was a unanimous agreement that urinary tumor markers approved by the U.S. Food and Drug Administration may be considered medically necessary as an adjunctive test in the diagnosis and monitoring of bladder cancer in conjunction with standard diagnostic procedures. In contrast, there was mixed support, but no consensus on the incremental value of urinary tumor markers compared with urinary cytology alone and for whether urinary tumor markers lead to changes in patient management. There was a unanimous agreement that the use of urinary tumor markers is investigational to screen for bladder cancer in asymptomatic subjects.

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; v4.2024) 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).[19,] 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."

The NCCN colorectal cancer screening guidelines (v1.2024) do not mention use of urinary tumor markers for detection of colon cancer in asymptomatic individuals at population-level risk of colon cancer.[19,] Colonoscopy or fecal testing are recommended for screening purposes in these individuals.

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.[20,] 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; FISH: fluorescence in situ hybridization; 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.[21,] 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.[22,] The recommendation was based on insufficient evidence (grade I). In August 2024 , a literature surveillance report was published that scanned for relevant literature in PubMed and PubMed databases and the Cochrane library from 2009 to present.[23,] 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.

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."[24,]

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04100733[a]	Surveillance of High-grade Non-muscle Invasive Bladder Tumors Using the Xpert Bladder Cancer Monitor	392	Apr 2027

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03973307[a]	Evaluation of UroX™ Biomarker Screening Test in the Investigation of Bladder Cancer From Urine Samples - a Single Site Pilot Study	100	Jul 2025
NCT05080998[a]	An Observational Study of Cxbladder Monitoring for Recurrence of Urothelial Carcinoma in Intermediate and High-Risk Patients	450	Dec 2025
NCT05864599	External Validation of Uromonitor as a Biomarker for Optimization of NMIBC Management by the CUETO Group	600	Jun2024
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
Unpublished			
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 (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.

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps
	0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
	0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
	0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
	0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma
	0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative
	0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
	0549U	Oncology (urothelial), DNA, quantitative methylated real-time PCR of TRNA-Cys, SIM2, and NKX1-1, using urine, diagnostic algorithm reported as a probability index for bladder cancer and/or upper tract urothelial carcinoma (UTUC)
	86294	Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)
	86316	Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each
	86386	Nuclear Matrix Protein 22 (NMP22), qualitative
	88120	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
	88121	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/07/2006	Policy Adopted - BCBSA MPP
01/07/2011	Policy title change from Urinary Tumor Markers for Bladder Cancer Policy revision with position change
01/21/2011	Coding Update
03/13/2012	Coding Update
10/05/2012	Policy revision with position change
12/14/2012	Policy revision with position change
06/30/2015	Policy title change from Urinary Tumor Markers Policy revision without position change
02/01/2017	Coding update
03/01/2017	Policy revision without position change
08/01/2017	Policy revision without position change
09/01/2018	Policy title change from Urinary Tumor Markers for Bladder Cancer Policy revision without position change
03/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated Coding update
07/01/2020	Coding update
02/01/2021	Annual review. No change to policy statement. Literature review updated.
02/01/2022	Annual review. No change to policy statement. Policy guidelines and literature updated.
10/01/2025	Policy reactivated. Previously archived from 02/01/2023 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug

Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
- Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
- The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
- The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
- The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
- The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
- The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
- When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance 2.04.07** **Policy Statement:** I. The use of urinary tumor markers is considered **investigational** in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.