Policy Statement

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.

Policy Guidelines

For the purpose of this policy, standard diagnostic procedures for bladder cancer consist of urine cytology and cystoscopy, with or without biopsy.

Coding

The BTA (bladder tumor antigen) stat® and nuclear matrix protein 22 (NMP22) are immunoassay tests.

When performed qualitatively in the physician’s office, the following CPT codes may be used to describe the corresponding tests:

- **BTA stat Test**
  - 86294: Immunoassay for tumor antigen, qualitative and semiquantitative (e.g., bladder tumor antigen)

- **NMP22 Test**
  - 86386: Nuclear Matrix Protein 22 (NMP22), qualitative

For clinical laboratories performing a quantitative version of these tests, the following CPT code may be used to describe the test:

- **86316**: Immunoassay for tumor antigen; other antigen, quantitative (e.g., CA 50, 72-4, 549), each

There are specific CPT codes for urinary fluorescence in situ hybridization (FISH) testing:

- **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

The CertNDx™ test is likely to be reported with the following CPT code:

- **81479**: Unlisted molecular pathology procedure

Effective April 1, 2018, the following are specific MAA codes for Cxbladder:

- **0012M**: Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), 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

The following is a code for the PolypDx test:

- **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
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.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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 or surveillance of bladder cancer patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Detection</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat®</td>
<td>Polymedco</td>
<td>Point of care immunoassay</td>
<td>Human complement factor H-related protein</td>
<td>Qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer</td>
</tr>
<tr>
<td>BTA TRAK®</td>
<td>Polymedco</td>
<td>Reference laboratory immunoassay</td>
<td>Human complement factor H-related protein</td>
<td>Quantitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer</td>
</tr>
<tr>
<td>Alere NMP22®</td>
<td>Alere</td>
<td>Immunoassay</td>
<td>NMP22 protein</td>
<td>in vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy</td>
</tr>
<tr>
<td>BladderChek®</td>
<td>Alere</td>
<td>Point of care immunoassay</td>
<td>NMP22 protein</td>
<td>Adjunct to cystoscopy in patients at risk for bladder cancer</td>
</tr>
<tr>
<td>uCyt+/ImmunoCyt™</td>
<td>Scimedx</td>
<td>IHC</td>
<td>Cell-based mucin glycoprotein and an antigen</td>
<td>Monitoring as an adjunct to cystoscopy</td>
</tr>
<tr>
<td>UroVysion®</td>
<td>Abbott</td>
<td>FISHa</td>
<td>Cell-based chromosomal abnormalities</td>
<td>Aid in the initial diagnosis of bladder cancer (P030052) and monitoring patients with previously diagnosed bladder cancer (K033982)</td>
</tr>
</tbody>
</table>
FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NMP: nuclear matrix protein

* 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 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. Urine-based tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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.
- **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 United States, results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma), typically presents as a tumor confined to the superficial mucosa of the bladder. The most frequent symptom of early bladder cancer is hematuria; however, urinary tract symptoms (i.e., urinary frequency, urgency, dysuria) may also occur. Cigarette smoking is an important risk factor for urothelial carcinoma.

**Diagnosis**

The criterion standard for a confirmatory diagnosis of bladder cancer is cystoscopic examination with biopsy. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. 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. 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.

**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 patients who have signs and/or symptoms of bladder cancer is to inform a decision whether to proceed to cystoscopy and biopsy.

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

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

**Patients**

The relevant populations of interest are patients with signs and/or symptoms of bladder cancer. This includes patients with no prior diagnosis, who present with urinary symptoms suggestive of bladder cancer, most commonly unexplained microscopic hematuria.

**Interventions**

The interventions of interest are urinary tumor marker tests, examples of which are described in the Regulatory Status section.

**Comparators**

Patients with microscopic hematuria with no etiology identified after an evaluation for glomerular disease or infection would typically be recommended for cystoscopy and biopsy.

**Outcomes**

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

**Timing**

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

**Setting**

Testing for urinary tumor markers would typically be requested by a primary care physician or urologist.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).
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. Two studies were rated as having low risk of bias, 3 studies at high risk of bias, and the remainder considered to have a moderate risk of bias. Only studies that used cystoscopy or histopathology as the reference standard were analyzed. Results of pooled analyses of diagnostic accuracy in patients with symptoms of bladder cancer are displayed in Table 2.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>TP/n</th>
<th>Pooled Sensitivity (95% CI), %</th>
<th>Studies, n</th>
<th>Pooled Specificity (95% CI), %</th>
<th>Studies, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test</td>
<td>37/49</td>
<td>76 (61 to 87)</td>
<td>1</td>
<td>53 (38 to 68)</td>
<td>1</td>
</tr>
<tr>
<td>Qualitative test</td>
<td>275/372</td>
<td>76 (67 to 83)</td>
<td>8</td>
<td>78 (66 to 87)</td>
<td>6</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test</td>
<td>235/368</td>
<td>67 (55 to 77)</td>
<td>9</td>
<td>84 (75 to 90)</td>
<td>7</td>
</tr>
<tr>
<td>Qualitative test</td>
<td>69/145</td>
<td>47 (33 to 61)</td>
<td>2</td>
<td>93 (81 to 97)</td>
<td>2</td>
</tr>
<tr>
<td>FISH (e.g., UroVysion)</td>
<td>82/144</td>
<td>73 (50 to 88)</td>
<td>2</td>
<td>95 (87 to 98)</td>
<td>1</td>
</tr>
<tr>
<td>uCyt+ (ImmunoCyt)</td>
<td>334/401</td>
<td>85 (78 to 90)</td>
<td>6</td>
<td>83 (77 to 87)</td>
<td>7</td>
</tr>
<tr>
<td>Cxbladder</td>
<td>54/66</td>
<td>82 (70 to 90)</td>
<td>1</td>
<td>81 (81 to 88)</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from Chou et al (2015).1

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

### 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.

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 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 85% and pooled specificity ranging from 53% to 95% compared...
Urinary biomarkers for cancer screening, diagnosis, and surveillance

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with cystoscopy and biopsy. There is no evidence of the clinical utility of urinary biomarker testing in this population.

**Urinary Tumor Marker Testing for Individuals with a History of Bladder Cancer**

**Clinical Context and Test Purpose**

The purpose of urinary tumor marker testing in patients who have a history of bladder cancer is to monitor for recurrence and inform a decision as to whether or not cystoscopy is warranted beyond the routine cystoscopy surveillance routine. Cystoscopy can be uncomfortable, which may result in poor compliance with surveillance recommendations. Repeated use of sedation may also be required. A potential benefit of urinary tumor markers would be a reduction in cystoscopies or earlier detection of recurrence.

The question addressed in this evidence review is: Does the use of urinary tumor markers, in addition to routine cystoscopy, improve the net health outcome for patients with a history of bladder cancer?

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

**Patients**

The relevant population of interest is patients with a history of bladder cancer.

**Interventions**

The interventions of interest are urinary tumor marker tests, examples of which are described in the Regulatory Status section.

**Comparators**

The following tests are currently being used: cystoscopy or biopsy.

**Outcomes**

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

**Timing**

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

**Setting**

Testing for urinary tumor markers would typically be by a primary care physician or urologist.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

Pooled analysis on the diagnostic accuracy of urinary biomarkers by Chou et al (2015) is provided in Table 3. The reference standard was cystoscopy or histopathology.
Table 3. Diagnostic Accuracy of Urinary Biomarkers in Patients with a History of Bladder Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>TP/n</th>
<th>Pooled Sensitivity (95% CI), %</th>
<th>Studies, n</th>
<th>Pooled Specificity (95% CI), %</th>
<th>Studies, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test</td>
<td>39/67</td>
<td>58 (46 to 69)</td>
<td>2</td>
<td>79 (72 to 85)</td>
<td>2</td>
</tr>
<tr>
<td>Qualitative test</td>
<td>325/544</td>
<td>60 (55 to 65)</td>
<td>11</td>
<td>76 (69 to 83)</td>
<td>8</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative test</td>
<td>235/368</td>
<td>61 (49 to 71)</td>
<td>10</td>
<td>71 (60 to 81)</td>
<td>8</td>
</tr>
<tr>
<td>Qualitative test</td>
<td>99/159</td>
<td>70 (40 to 89)</td>
<td>2</td>
<td>83 (75 to 89)</td>
<td>2</td>
</tr>
<tr>
<td>FISH (e.g., Urovysion)</td>
<td>189/299</td>
<td>55 (36 to 72)</td>
<td>7</td>
<td>80 (66 to 89)</td>
<td>2</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>302/406</td>
<td>75 (64 to 83)</td>
<td>7</td>
<td>76 (70 to 81)</td>
<td>8</td>
</tr>
</tbody>
</table>

Adapted from Chou et al (2015).1

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

Fibroblast Growth Factor Receptor 3

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.2 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.3 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).4 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%.

Subsection Summary: Clinically Valid

The diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 55% to 75% and pooled specificity ranging from 71% to 83%. There are several diagnostic performance studies on FGFR3 for monitoring bladder cancer. These studies generally showed that the markers had higher sensitivity than cytology.

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.

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. 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. 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<0.001 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. 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. FISH results were not significantly associated with the results of the next cystoscopy (odds ratio, 0.84; 95% CI, 0.26 to 2.74; p=1.0). Because of this lack of short-term association between FISH results and cystoscopy, the results would suggest that FISH has limited ability to modify the surveillance schedule in non-muscle-invasive bladder cancer.

The purpose of the gaps tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

**Table 4. Relevance Gaps**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shariat et al (2011)</td>
<td>4. All patients had negative cytology</td>
<td>2. No control group</td>
<td>1. Management decisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al (2014)</td>
<td>4. All patients had negative cystoscopy</td>
<td>2. No control group</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- 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).
- Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- 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.

### Table 5. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shariat et al</td>
<td>1. No allocation</td>
<td>No blinding</td>
<td></td>
<td></td>
<td></td>
<td>1. Decision curve analysis</td>
</tr>
<tr>
<td>(2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al</td>
<td>1. No allocation</td>
<td>No blinding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

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

Diagnostic accuracy studies report that urinary tumor marker tests have pooled sensitivity ranging from 55% to 75% and pooled specificity ranging from 71% to 83%. 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. And there is a lack of direct evidence that cystoscopy protocols would be changed when urinary tumor marker tests are used. The available studies have found low potential clinical benefit of urinary tumor marker testing for patients with non-muscle-invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

### Urinary Tumor Marker Tests to Screen Asymptomatic Individuals for Bladder Cancer

**Clinical Context and Test Purpose**

The purpose of screening 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 question addressed in this evidence review is: Does population-level screening with urinary markers improve outcomes in asymptomatic individuals?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals without signs and/or symptoms of bladder cancer.

**Interventions**
The interventions of interest are urinary tumor marker tests, examples of which are described in the Regulatory Status section.

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

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

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

**Setting**
Testing for urinary tumor markers would typically be by a primary care physician or urologist.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

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. 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 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.”

Several uncontrolled studies have reported on screening studies. Bangma et al (2013) reported on a population-based program with men in the Netherlands. 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 data. They determined that 2 cancers (1 bladder cancer, 1 kidney cancer) had been diagnosed in men who completed the protocol; they were considered false-negatives. The sensitivity and specificity of the FDA-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 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. 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 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.

No evidence was identified addressing the impact of screening using urinary biomarker testing to diagnose precancerous colonic polyps.

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
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 50
years of age. 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 question addressed in this evidence review is: Does population-level screening for urinary markers improve outcomes in asymptomatic individuals?

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

**Patients**
The relevant population of interest is individuals without signs and/or symptoms of colon cancer.

**Interventions**
The test being considered is 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 U.S. Preventive Services Task Force has recommended screening for colon cancer starting at age 50 and continuing until age 75. 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 overall survival and disease-specific survival. Beneficial outcomes are primarily related to 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.

**Timing**
Follow-up for precancerous polyps would typically occur periodically over the course of years.

**Setting**
Testing for urinary tumor markers would typically be by a primary care physician or gastroenterologist.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

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. 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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**

A urine metabolite assay for adenomatous polyps is at a very early stage of development, with 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 cytology, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have sensitivity ranging from 47% to 85% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a history of bladder cancer who receive urinary tumor marker tests in addition to cytology, 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 overall survival, 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 55% to 75% and pooled specificity ranging from 71% to 83%. 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 the effects of the technology on health outcomes.

For individuals who are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A 2010 systematic review (conducted for the U.S. Preventive Services Task Force) did not identify any RCTs, 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 the effects of the technology on health outcomes.
For individuals who are asymptomatic and at a population-level risk of colon cancer who receive urinary tests for precancerous polyps, evidence includes a validation study. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A urine metabolite assay for adenomatous polyps is at a very early stage of development, with 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 the effects of the technology on health outcomes.

Supplemental Information

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.

In response to requests from Blue Cross Blue Shield Association, input was received through 2 physician specialty societies and 5 academic medical centers in 2012. There was unanimous agreement that urinary tumor markers approved by the 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 unanimous agreement that use of urinary tumor markers is investigational to screen for bladder cancer in asymptomatic subjects.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v.4.2018) 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).13

American Urological Association et al

The 2016 guidelines from the American Urological Association and Society of Urologic Oncology 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. 14 Table 6 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

<table>
<thead>
<tr>
<th>Guidance Statement</th>
<th>SOR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation.”</td>
<td>Strong</td>
<td>B</td>
</tr>
<tr>
<td>“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.”</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>“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™).”</td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>


The 2012 guidelines from the American Urological Association (reviewed and affirmed in 2016) on the evaluation of microscopic hematuria recommended cystoscopic evaluation for the following individuals15:

- Older than age 40 with microscopic hematuria; and
- Younger than age 40 with microscopic hematuria and risk factors for developing bladder cancer.
U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (2011) concluded that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was based on insufficient evidence (grade I).

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 unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
<td>Clinical Validation of a Urine-based Assay with Genomic and Epigenomic Markers for Predicting Recurrence During Surveillance for Non-muscle Invasive Bladder Cancer</td>
<td>380</td>
<td>Jul 2018</td>
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<tr>
<td>NCT02745301a</td>
<td>Urinary Biomarkers in the Detection of Urothelial Carcinoma of the Bladder</td>
<td>50</td>
<td>Sep 2020</td>
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<tr>
<td>NCT03413982</td>
<td>Bladder Cancer Longitudinal Biorepository for Development of Novel Therapeutics/Biomarkers</td>
<td>1000</td>
<td>Jan 2035</td>
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</tbody>
</table>

*a Denotes industry-sponsored or cosponsored trial.

References


### Documentation for Clinical Review

- No records required

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

#### IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0012M</td>
<td>Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCIR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma</td>
</tr>
<tr>
<td>CPT®</td>
<td>0013M</td>
<td>Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCIR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma</td>
</tr>
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<td></td>
<td>0002U</td>
<td>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</td>
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<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td></td>
<td>86294</td>
<td>Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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</tr>
<tr>
<td></td>
<td>86316</td>
<td>Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each</td>
</tr>
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<td></td>
<td>86386</td>
<td>Nuclear Matrix Protein 22 (NMP22), qualitative</td>
</tr>
<tr>
<td></td>
<td>88120</td>
<td>Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual</td>
</tr>
<tr>
<td></td>
<td>88121</td>
<td>Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology</td>
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**Policy History**

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

<table>
<thead>
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<td>12/07/2006</td>
<td>Policy Adopted - BCBSA MPP</td>
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</tr>
<tr>
<td>01/21/2011</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<td>10/05/2012</td>
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<td>12/14/2012</td>
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**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions,
but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.