Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance

Policy # 00129
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of any of the following bladder tumor markers to be **eligible for coverage**** when used in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA-Stat®‡, BTA-TRAK®‡;
- ImmunoCyt™‡;
- NMP22®‡, NMP22 BladderChek®‡;
- UroVysion®‡

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of urinary bladder tumor markers for screening for bladder cancer to be **investigational.***

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Based on review of available data, the Company considers the use of urinary bladder tumor markers for evaluation of hematuria or microhematuria to be **investigational.***

Based on review of available data, the Company considers the use of urinary tumor markers in the screening for precancerous colonic polyps to be **investigational.***

Background/Overview

Urinary Bladder Cancer

Urinary bladder cancer, a relatively common form of cancer in the U.S., 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 (ie, 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. 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. Therefore, interest has been reported in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

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

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 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)

FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein.
[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 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 rtPCR.
- 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/Source

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.

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 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 that the technology results in an improvement in the net health outcomes.

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

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 outcomes.

Additional Information
In 2012, clinical input revealed a unanimous agreement that urinary tumor markers approved by the U.S. Food and Drug Administration (FDA) 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.

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, 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

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (v.6.2020) bladder cancer guidelines include consideration for urinary urothelial tumor markers every 3 months along with urine cytology for the first 2 years of follow-up for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation). The guidelines include the following statement: "Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumors may be considered during surveillance of high-risk non-muscle-invasive bladder cancer. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors."

American Urological Association and Society of Urologic Oncology
The guidelines from the American Urological Association and Society of Urologic Oncology (2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review completed by the Agency for Health Care Research and Quality and through additional supplementation that further addressed key questions and more recently published literature. Table 2 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

Table 2. Guidelines for Urine Tumor Markers After the Diagnosis of Bladder Cancer

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

"In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance."		Expert opinion
"In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion®‡ FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)‡."		Expert opinion

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

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

In 2020, the American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a guideline on the diagnosis, evaluation, and follow-up of microhematuria. 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 (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). In April 2019, a literature surveillance report was published that scanned for relevant literature in PubMed and PubMed databases and the Cochrane library from 2009 to present. The researchers found "no relevant systematic reviews 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 randomized, controlled trials or controlled observational studies compared the benefits or harms of treatment of screen-detected bladder cancer with no treatment."

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 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03413982	Bladder Cancer Longitudinal Biorepository for Development of Novel Therapeutics/Biomarkers	1000	Jan 2035
NCT04100733	Surveillance of High-grade Non-muscle Invasive Bladder Tumors Using the Expert Bladder Cancer Monitor	392	Sep 2029
NCT03973307	Evaluation of UroX™‡ Biomarker Screening Test in the Investigation of Bladder Cancer From Urine Samples - a Single Site Pilot Study	100	Jul 2025

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	1100	Sep 2021
Completed			
NCT03125460[a]	Clinical Evaluation of Xpert Bladder Cancer Monitor for Monitoring the Recurrence of Bladder Cancer	424	May 2019
NCT02745301[a]	Urinary Biomarkers in the Detection of Urothelial Carcinoma of the Bladder	50	Jan 2018
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	380	Jul 2018

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

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Policy History

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09/18/2002	Managed Care Advisory Council approval
12/07/2004	Medical Director review
12/14/2004	Medical Policy Committee Review. Format revision - Rationale and source added to policy.

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01/31/2005	Policy archived. Managed Care Advisory Council approval. Archived.
03/05/2010	Medical Policy Committee approval
03/19/2010	Medical Policy Implementation Committee approval. Returned to active status.
03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. Archived policy.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Retired policy.
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. This policy has been reactivated with multiple revisions to the coverage section. Title changed from "Urinary Tumor Markers for Bladder Cancer" to "Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance".
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0002U, 0012M, 0013M, 0154U, 81479, 88120, 88121
HCPCS	No codes
ICD-10 Diagnosis	R31.0-R31.9, Z12.6

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

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For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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