Urinary Tumor Markers for Bladder Cancer

Policy Number: AHS – G2125 – Urinary Tumor Markers for Bladder Cancer	Prior Policy Name and Number, as applicable:
Effective Date: 02/01/2023	

POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

I. Policy Description

Bladder cancer is defined as a malignancy that develops from the tissues of the bladder. It is the most common cancer of the urinary system. The cancer typically arises from the urothelium, although it may originate in other locations such as the ureter or urethra (Lerner, 2020).

Tumor biomarkers are proteins detected in the blood, urine, or other body fluids that are produced by the tumor itself or in response to it. Urinary tumor markers may be used to help detect, diagnose, and manage some types of cancer including bladder cancer (Hottinger & Hormigo, 2011).

II. Related Policies

Policy Number	Policy Title
AHS-G2124	Serum Tumor Markers for Malignancies

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website https://www.cms.gov/medicare-coverage-database/search.aspx or the manual website.

1) Urinary biomarkers (bladder tumor antigen (BTA) test, nuclear matrix protein (NMP22) test, or fluorescence in situ hybridization (FISH) UroVysion Bladder Cancer test) **MEET COVERAGE CRITERIA**:

   a) As an adjunct in the diagnostic exclusion of bladder cancer for patients who have an atypical or equivocal cytology

   b) As an adjunct in the monitoring of high-risk, non-muscle invasive bladder cancer

2) The use of fluorescence immunocytology (ImmunoCyt/uCyt) **MEETS COVERAGE CRITERIA** as an adjunct to cystoscopy or cytology in the monitoring of persons with bladder cancer.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

3) Urinary biomarkers (bladder tumor antigen (BTA) test, nuclear matrix protein (NMP22) test, or fluorescence in situ hybridization (FISH) UroVysion Bladder Cancer test) **DO NOT MEET COVERAGE CRITERIA** for screening of bladder cancer, evaluation of hematuria, diagnosing bladder cancer in symptomatic individuals, and all other indications.

4) The use of fluorescence immunocytology (ImmunoCyt/uCyt) **DOES NOT MEET COVERAGE CRITERIA** in the evaluation of hematuria, diagnosing bladder cancer, or for screening for bladder cancer in asymptomatic persons and all other indications.

5) Any other urinary tumor markers for bladder cancer not mentioned above **DO NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
AACC	American Association for Clinical Chemistry
AMH	Asymptomatic microhematuria
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AUC	Area under the curve
BC	Bladder cancer
BCG	Bacillus calmette-guerin
BLCA-1	Bacillus collagen-like protein of anthracis
BLCA-4	Bacillus collagen-like protein of anthracis
BTA	Bladder tumor antigen
CFHrp	Complement factor h-related protein
CIS	Carcinoma in situ
CK	Cytokeratins
CLIA '88	Clinical laboratory improvement amendments of 1988

CMS	Centers for Medicare and Medicaid
CXCR2	C-X-C motif chemokine receptor 2
DNA	Deoxyribonucleic acid
EAU	European Association of Urology
EIA	Enzyme immunoassay
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridization
hCFHrp	Complement factor h-related protein
ICUD-SIU	International Consultation on Urological Diseases & Société Internationale d'Urologie
LDTs	Laboratory-developed tests
MRI	Magnetic resonance imaging
NACB	National Academy of Clinical Biochemistry Laboratory Medicine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NED	Non-evidence of disease
NID2	Nidogen 2
NMIBC	Non-muscle invasive bladder cancer
NMP22	Nuclear matrix protein 22
NMP52	Nuclear matrix protein 52
PCR	Polymerase chain reaction
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
SUO	Society of Urologic Oncology
TWIST1	Twist-related protein 1
uCyt+	*ImmunoCyt* test
USPSTF	U.S. Preventive Services Task Force
UT	Urine derived tumor
utDNA	Urine derived tumor deoxyribonucleic acid

V. Scientific Background

In 2020 in the United States, there were more than 81,000 cases and 17,900 deaths due to bladder cancer (NCCN, 2019; R. L. Siegel, Miller, & Jemal, 2017; Rebecca L. Siegel, Miller, & Jemal, 2020). According to the American Cancer Society, an estimated 83,730 new cases of bladder cancer will be diagnosed in the United States in 2021 with 17,200 deaths from bladder cancer (ACA, 2021). Bladder cancer is the sixth most common cancer in the United States, affects men four times more frequently than women, and is typically diagnosed in individuals above the age of 40, with 73 the median age at diagnosis (DeGeorge, Holt, & Hodges, 2017; NCCN, 2019). Bladder cancer risk factors include smoking, a family history of the disease, pelvic radiation, obesity, diabetes, and chronic infection of the urinary tract.

Bladder cancer commonly presents as painless hematuria (blood in urine) and may be gross (visible) or microscopic. Gross hematuria tends to increase the likelihood of bladder cancer, but hematuria as a whole may be transient or due to non-cancer related causes (Perazalla, 2020). Other common symptoms of bladder cancer include pain or irritative and obstructive voiding symptoms such as urge incontinence, dysuria, straining, or nocturia. These symptoms are often mistaken for another condition such as kidney stones, can be temporary, and are not necessarily specific for bladder cancer (Y. Lotan, Choueiri, Toni, 2020). In fact, hematuria is the most common symptom of bladder cancer, but a study reported a 13% prevalence rate of bladder cancer out of 6728 patients with hematuria (DeGeorge et al., 2017; Sutton et al., 2018). Approximately 70%-75% of patients present with superficial tumors (50 – 70% of which can recur but are usually not life threatening), and 25%-30% present as invasive tumors with a high risk of metastasis (Chou & Dana, 2010; Kaufman, Shipley, & Feldman, 2009).

Cystoscopy (white light) is the gold standard for a diagnosis of bladder cancer. This procedure involves a bladder examination and urine sample for cytology. Any lesions are observed and recorded. Cystoscopy does not detect all malignancies or visualize the upper urinary tract. Furthermore, although cystoscopy is minimally invasive, it may be uncomfortable and promote anxiety, which can lead to suboptimal compliance with management recommendations. Fluorescent cystoscopy is somewhat more efficient at detecting tumors than white light cystoscopy; although, it comes with its own set of issues such as higher false-positive rates and costs (Y. Lotan, Choueiri, Toni, 2017, 2020; Mitra, Birkman, Penson, & Cote, 2019). Cytology, or the analysis of cells in urine, is often completed in addition to cystoscopy analysis.

Although cystoscopy has long been the gold standard for a diagnosis of bladder cancer, its high cost and unpleasant burden has led to the search for a non-invasive test that can match the high specificities and sensitivities set by cystoscopy. Urinary biomarkers including "Cell-free proteins and peptides, exosomes, cell-free DNA, methylated DNA and DNA mutations, circulating tumor cells, miRNA, lncRNA, rtRNA and mRNAs" have now been identified for bladder cancer diagnostic purposes (Lopez-Beltran et al., 2019). Urine is exposed to urothelial tissue in many different locations, and therefore has the potential to contain several biomarkers associated with cancer. Validation of these biomarkers could lessen the use of cystoscopy as well as increase the overall sensitivity for bladder cancer identification (D'Costa, Goldsmith, Wilson, Bryan, & Ward, 2016). However, because of the lower disease prevalence in a screening population, even in those at increased risk, the use of biomarkers for screening is not cost effective or recommended (Y. Lotan et al., 2009). Despite the promise of urine biomarkers, cystoscopy remains the procedure of choice both for initial diagnosis and for surveillance in previously treated patients.

Epigenetic changes may also play an important role in bladder cancer tumorigenesis. These changes are becoming more prevalent as identification rates increase due to improvements in high-throughput DNA sequencing technologies. Epigenetic changes can "regulate [the] gene expression outcome without changing the underlying DNA sequence" with alterations based on DNA methylation, nucleosome positioning, microRNA regulation and histone medications (Li, Duymich, Weisenberger, & Liang, 2016). All of these epigenetic-based changes are distorted in each human cancer type. "A substantial portion (76%) of all primary bladder tumors displays mutations in at least one chromatin regulatory gene. These mutations cause epigenetic dysregulation in bladder cancers (Li et al., 2016)."

Numerous other urinary biomarkers have been proposed as contributors to management of bladder cancer.

Other nuclear matrix proteins aside from NMP22 have been investigated. NMP52, BLCA-4, and BLCA-1 have all been studied as potential markers. Initial data for these markers appears promising, but most likely requires further evaluation (Mitra et al., 2019).

Cytokeratins, protein components of the cell structure, have also been identified as possible markers. Cytokeratins ("CK"), -8, -18, -19, and -20 have been considered for use in bladder cancer evaluation. However, further data is needed (Mitra et al., 2019).

Other markers that have been considered as potential indicators of bladder cancer include the following:

Telomerase is an enzyme that adds telomeres to the ends of chromosomes. This enzyme is only expressed in proliferating cells such as cancer cells, thereby lending credence to its use as a cancer marker. Despite its high sensitivity, its clinical application is limited, as the current assay used to detect telomerase is "significantly" affected by sample collection and processing (Mitra et al., 2019).

Hyaluronic acid is a polysaccharide that promotes tumor progression and metastasis. It is cleaved by *hyaluronidase*, which creates smaller fragments of the polysaccharide that further promote tumor angiogenesis. This pair of markers has been found to detect low-grade and low-stage disease with higher sensitivities than other markers, but requires further data for evaluation (Mitra et al., 2019).

Fibrin degradation products may also be useful in detection of cancer. High levels of vascular endothelial growth factor can increase the permeability of surrounding cellular structures, which cause serum proteins to "leak". These proteins are eventually degraded to fibrin, and then to fibrin degradation products (Mitra et al., 2019).

Survivin is an apoptosis inhibitor. Survivin is frequently elevated in cancers, but virtually undetectable in normal tissues. However, no commercial assays for survivin exist as of time of writing (Mitra et al., 2019).

Finally, *miRNA* markers have been considered for use in bladder cancer management. These markers are small sequences of non-coding RNA that contribute to gene expression regulation. MiRNAs-126, -200c, -143, and -222 have all been considered to have "promising" results (Mitra et al., 2019).

Proprietary Testing

The two most studied urinary biomarkers are bladder tumor antigen (BTA) and nuclear matrix protein 22 (NMP22). The BTA test is designed to detect complement factor H-related protein (hCFHrp) which is elevated in cancer cells. This test is available in both a quantitative and qualitive version, and its manufacturer-recommended cut-off is 14U/mL (Mahnert et al., 1999; Mitra, Birkman, & Penson, 2017). Similarly, the NMP22 test is designed to detect a protein that is more highly available in cancer cells than normal cells. In this case, cancer cells release more NMP22 into the urine following apoptosis than normal cells do. The NMP22 tests are also available in a quantitative and qualitative version, and its FDA-approved cut-off is 10U/mL (Grossman, Messing, Soloway, & et al., 2005; Mitra et al., 2017; Mitra et al., 2019; Zuiverloon, de Jong, & Theodorescu, 2017). A number of proprietary tests exist revolving around one of these two biomarkers; these tests include Abbott's "Alere NMP22 BladderCheck" and Quest's Bladder Tumor Antigen DetectR (Abbott, 2020; Quest, 2020).

The FDA has approved two additional tests for urinary biomarkers. One is *UroVysion*, which is designed to detect chromosomal alterations that are distinctive of bladder cancer. This test is a fluorescent in situ hybridization (FISH) assay that uses DNA probes to detect alterations (such as aneuploidies) on chromosomes 3, 7, and 17 or loss of the 9p21 locus. The second test is known as *ImmunoCyt* (or uCyt+)

that uses a similar fluorescent technique to detect certain glycoproteins that are expressed solely on cancerous cells (Mitra et al., 2017; Mitra et al., 2019).

Recently, Pangea Laboratory has created a laboratory developed test termed Bladder *CARE*™ which measures the methylation status of specific DNA biomarkers in urine for the detection of bladder cancer via an at-home collection kit. This non-invasive test has not been approved by the FDA, is purported to be more cost-effective, and uses an epigenetic-based detection approach. Specifically, the methylation of bladder cancer DNA biomarkers are measured (Pangea, 2019a). As little as 5 ng of urine DNA from a 100 mL urine sample is required, and it has a limit detection of 0.1% leading to the identification of a single cancerous cell in a sample of 1,000 normal cells (Pangea, 2019a). The authors claim that Bladder *CARE*™ has a sensitivity of 94% and specificity of 86%, allowing for the identification of 88% of low-grade bladder cancer cases; these results are based on a study completed by Pangea Laboratory and Zymo Research which analyzes urine samples from 182 patients (97 with bladder cancer and 85 healthy controls) (Pangea, 2019b).

Another test, termed the Bladder EpiCheck test, has been developed by the Israeli company Nucleix. This non-invasive epigenetic urine test helps to detect bladder cancer with a panel of 15 DNA methylation biomarkers. Nucleix reports a sensitivity of 92%, a specificity of 88% and a negative predictive value of 99% for the Bladder EpiCheck test; these results are based on a multi-center clinical study with 353 bladder cancer patients (Nucleix, 2015). Similar results have been reported by D'Andrea et al. (2019). However, this test is not available in the United States (Nucleix, 2015).

Another test, termed "UBC® Rapid" has been developed by the Swedish company ODL Biotech. This point-of-care test measures soluble fragments of cytokeratins 8 and 18 in urine samples. The test can produce results within 10 minutes and may be tested with hematuria-containing samples (IDL_Biotech, 2020). Ecke et al. (2018) performed a validation of this test, which encompassed 242 patients with bladder cancer (134 non-muscle-invasive low-grade tumors, 48 non-muscle-invasive high-grade tumors, 60 muscle-invasive high-grade tumors), 62 patients with non-evidence of disease [NED], and 226 healthy controls. The authors found a sensitivity of 38.8% for non-muscle-invasive low-grade bladder cancer, 75% for non-muscle-invasive high-grade bladder cancer and 68.3% for muscle-invasive high-grade bladder cancer. Specificity over the entire cohort was 93.8% (Ecke et al., 2018).

The URO17 assay by Protean Biodiagnostics, an immunohistochemistry-based test that detects the presence of the oncoprotein keratin 17 in bladder cancer and urogenital cancer. Unlike other urine-based test URO17 can detect patients with visible or invisible hematuria, which allows for early diagnosis. URO17 can also detect recurrent bladder cancer in patients under surveillance for relapse (NICE, 2021). The test has 100% sensitivity and 96% specificity for detecting bladder cancer from urine samples (Protean_Biodiagnostics, 2021).

Nonagen Bioscience released Oncuria, an in-vitro multiplex immunoassay, which detects protein biomarkers associated with bladder cancer in the urine. This non-invasive test detects ten proteins from a single urine sample in patients with hematuria with suspicion of bladder cancer. Biomarker levels are combined in a weighted algorithm to aid in the prediction of responding to Bacillus Calmette-Guerin (BCG) therapy in patients with intermediate to high-risk, early-stage bladder cancer (Nonagen_Bioscience, 2021).

Analytical Validity

Recently, Piao et al. (2019) have developed a way to differentiate patients with bladder cancer from patients with a nonmalignant hematuria without bladder cancer by measuring urinary cell-free microRNA expression. This study shows that the non-invasive measurement of urinary microRNA-6124 and microRNA-4511 can be used as a diagnostic tool with a sensitivity of >90% (Piao et al., 2019). This testing method will help to reduce the number of unnecessary cystoscopies in patients with hematuria that are being evaluated for bladder cancer.

The performance of an epigenetic-based bladder cancer detection tool has been evaluated by Fantony et al. (2017); the urine-based TWIST1/NID2 methylation assay has been analyzed for the detection of urothelial carcinoma via the addition of urine cytology. This multi-institutional study analyzed data from 172 patients. The authors note that "The AUC [area under the curve] for cytology alone with equivocal cytologies positive was 0.704, and improved to 0.773 with the addition of the DNA methylation assay (p < 0.001) (Fantony et al., 2017)." The authors conclude by stating that this TWIST1/NID2 methylation assay is a sensitive diagnostic tool that adds value to urine cytology for the detection of urothelial carcinoma, which is the most common type of bladder cancer.

Soubra and Risk (2015) found the sensitivity of fluorescent cystoscopy to be 0.92 and the sensitivity of white light cystoscopy to be 0.71; the specificity of fluorescent cystoscopy was lower at 0.57, and the specificity of white light cystoscopy was identified at 0.72. Furthermore, fluorescent cystoscopy's sensitivity for carcinoma *in situ* (which is difficult to visualize) was measured at 0.924, while white light cystoscopy's sensitivity for carcinoma *in situ* was much lower at 0.605, but these differences tended to decrease on higher grade lesions (Soubra & Risk, 2015). Cytology is also a common analytic technique in addition to cystoscopy. Its overall sensitivity is low at 0.34 and its sensitivity for grade 1 and 2 tumors is even lower at 0.12 and 0.26, respectively (Yair Lotan & Roehrborn, 2003).

Breen et al. (2015) compared the sensitivity and specificity values of four diagnostic tests (cytology, NMP22, UroVysion, and CxBladder); CxBladder was found to have the highest sensitivity at 74% and cytology was identified with the highest specificity at 95%. The authors report comparable sensitivity values for cytology, NMP22, and UroVysion at 46%, 45.9% and 47.7% respectively (Breen et al., 2015). It is important to note that even though CxBladder is reported to have the highest sensitivity, the specificity (81.7%) is the lowest; the other tests were reported to have superior specificities with NMP22 at 88%, and UroVysion at 87.7% (Breen et al., 2015).

Sathianathen, Butaney, Weight, Kumar, and Konety (2018) published a study focusing on biomarkers in patients presenting with hematuria. This study encompassed BTA, NMP22, FISH, and uCyt+, as well as a fifth biomarker known as AssureMDx. Sensitivities ranged from 0.67 (BTA) to 0.95 (AssureMDx, second highest was uCyt+ at 0.83) while specificities ranged from 0.68 (BTA) to 0.93 (quantitative NMP22). However, this data is consistent with the previously published meta-analysis that covered all settings, not just hematuria (Chou et al., 2015). Cytology was also found to have superior specificity to all studied biomarkers; although, biomarkers tended to have better sensitivity. The authors concluded that, due to the high heterogeneity and small sample size, more studies were needed to validate biomarkers to replace diagnostic evaluation of hematuria (Sathianathen et al., 2018).

Although many studies emphasize the high validity of biomarkers such as NMP22 and BTA, these studies often have a large proportion of high-grade tumors which inflate the specificity and sensitivity; hence, the problem of identifying low-grade cancers remains. There may be changes at the genetic level in a low-grade cancer, but the proteins tested in the urine may still be relatively normal (D'Costa et al., 2016). Another issue is the conflicting results for the validity of the biomarkers. For example, the sensitivity of the quantitative NMP22 test has been found to range from as low as 0.26 to 1.00 with its specificity

ranging from 0.49 to 0.98. Similarly, the *BTA STAT* test's sensitivity and specificity have been found to range from 0.29 to 0.91 and from 0.54 to 0.86 respectively (Zuiverloon et al., 2017). For comparison, a study found the sensitivity and specificity of flexible cystoscopy (out of 778 hematuria patients) to be 0.98 and 0.938, respectively (Sutton et al., 2018).

Dudley et al. (2019) have developed a novel high-throughput sequencing method that uses urine derived tumor DNA (utDNA) known as utDNA CAPP-Seq (uCAPP-Seq) to detect bladder cancer. This technique was used to analyze samples from 118 patients with early-stage bladder cancer and 67 healthy adults. "We detected utDNA pretreatment in 93% of cases using a tumor mutation-informed approach and in 84% when blinded to tumor mutation status, with 96% to 100% specificity (Dudley et al., 2019)." These results show that utDNA can be used to diagnose early-stage bladder cancer with high sensitivity and specificity.

Hirasawa et al. (2021) studied the diagnostic performance of Oncuria™, a multiplex immunoassay urinalysis test for bladder cancer. Urine samples from 362 subjects with suspicion of bladder cancer were measured using Oncuria™ for ten biomarkers (A1AT, APOE, ANG, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA). Results of the test were confirmed by cystoscopy and tissue biopsy. "The Oncuria™ test achieved a strong overall diagnostic performance, achieving an overall AUC of 0.95, sensitivity and specificity values of 93% and 93%, respectively, and a negative predictive value (NPV) and positive predictive value (PPV) of 99% and 65%, respectively. The Oncuria™ test shows promise for clinical application in the non-invasive diagnosis and surveillance bladder cancer, and potentially for screening at-risk, asymptomatic individuals (Hirasawa et al., 2021)."

Clinical Utility and Validity

A meta-analysis of 57 studies detailed the accuracy of several biomarkers for the diagnosis and surveillance of bladder cancer. These included the six FDA-approved tests (quantitative and qualitive NMP22, quantitative and qualitative BTA, FISH, and uCyt+) as well as a laboratory developed test that does not require FDA approval termed CxBladder. Sensitivities ranged from 0.57 (qualitative NMP22) to 0.82 (CxBladder); however, the CxBladder cohort was only comprised of one study. The specificities ranged from 0.74 (quantitative BTA) to 0.88 (qualitative NMP22). Sensitivity increased as a tumor progressed (higher grade or stage) with low accuracy for lower stage or grade tumors. A cytologic evaluation performed with a biomarker assessment increased sensitivity as well but missed about 10% of cases. Ultimately, the authors concluded that urinary biomarkers reported many false-positive results and failed to identify a large percentage of patients with bladder cancer (Chou et al., 2015). The authors also noted that this was the first study which focused on the measurement of clinical outcomes based on urinary biomarkers.

The ideal marker will be "easier, better, faster, and cheaper" (Schmitz-Dräger et al., 2015). Overall, although there have been numerous promising studies for the clinical utility of these urinary biomarkers, the biomarkers do not yet measure up to the standards set by cystoscopy as the primary method of diagnosis. Most of the biomarkers are yet to be well-validated and the ones that are, such as NMP22 and BTA, fall short of cystoscopy's standards (D'Costa et al., 2016). Furthermore, because of the lower disease prevalence in a screening population, even in those at increased risk, the use of biomarkers for screening is not cost effective or recommended (Y. Lotan et al., 2009). Although the cost of tests is non-clinical, it is still a crucial issue; the *BTA* and *NMP22* tests are relatively inexpensive at $25 but ImmunoCyt costs around $80 and the CxBladder and UroVysion cost $325 and $800, respectively (Zuiverloon et al., 2017). For comparison, a cystoscopy cost around $210 in 2016, and a cystoscopy with a biopsy cost about $370 (Halpern, Chughtai, & Ghomrawi, 2017). These biomarkers to date have not

been highly recommended within any clinical guidelines. Therefore, the authors concluded that biomarkers have not had significant effect on clinical decision-making (Schmitz-Dräger et al., 2015). The majority of studies performed on these biomarkers did not focus on their ability to predict the course of cancer (D'Costa et al., 2016) but some biomarkers may play a role in the diagnosis or surveillance of bladder cancer in the future (Schmitz-Dräger et al., 2015). Even this may be a difficult barrier to cross; Meleth et al. (2014) prepared an assessment for the Agency for Healthcare Research and Quality that stated "although UroVysion is marketed as a diagnostic rather than a prognostic test, limited evidence from two small studies (total n=168) supported associations between test result and prognosis for risk of recurrence (Meleth et al., 2014)." The authors went on to note that no studies that established clinical utility were found.

D'Andrea et al. (2019) analyzed 357 urine samples from patients at five different centers under surveillance for non-muscle-invasive bladder cancer to investigate the clinical utility of the Bladder EpiCheck™ non-invasive urine test. A specificity of 88% was identified with this test, a negative predictive value of 94.4% for the detection of any cancer, and a negative predictive value of 99.3% for the detection of high grade cancer; the use of the Bladder EpiCheck™ test helped to improve the cancer recurrence predictive value by a difference of 16-22% (D'Andrea et al., 2019). This high-performing diagnostic test may help in the surveillance of non-muscle-invasive bladder cancer.

Tan et al. (2018) completed a systematic review to identify the diagnostic sensitivity and specificity of urinary biomarkers for the diagnosis of bladder cancer. The authors report that multi-target biomarker panels were more accurate than single biomarker targets, and that both the sensitivity and specificity of urinary biomarkers were higher in primary diagnostic scenarios compared to patients under surveillance (Tan et al., 2018). The authors note that "few biomarkers achieve a high sensitivity and negative predictive value," with single biomarkers reporting a sensitivity of 2-94% and specificity of 46-100%, and multi-target biomarkers reporting a sensitivity of 24-100% and specificity of 48-100% (Tan et al., 2018).

Mossanen et al. (2019) performed a cost analysis to characterize the costs of managing non-muscle-invasive bladder cancer (NMIBC). The authors created a Markov model with four health states: no evidence of disease, recurrence, progression and cystectomy, and death. Patients were stratified into three risk categories of low, intermediate, and high. The authors found that "cumulative costs of care over a 5-year period were $52,125 for low-risk, $146,250 for intermediate-risk, and $366,143 for high-risk NMIBC". The authors identified that the primary driver of cost was "progression to muscle-invasive disease requiring definitive therapy", which was found to contribute 81% and 92% to overall cost for intermediate and high-risk disease, respectively. Progression of disease was found to contribute 71% to overall cost for low-risk disease. The authors concluded that although protracted surveillance cystoscopy does contribute to management cost, progression of disease was the dominant factor in increasing cost of care (Mossanen et al., 2019).

Vasdev et al. (2021) studied the role of URO17™ biomarker in the diagnosis of bladder or urothelial cancer in new hematuria patients. Urine samples from 71 subjects were stained using the URO17™ immunobiomarker and results were compared to the biopsy and histology. URO17™ was shown to have an overall sensitivity of 100%, specificity of 92.6%, positive predictive value of 0.957, and negative predictive value of 1. URO17™ investigation was positive in every case of urothelial malignancy. According to the authors, URO17™ test can help improve "diagnostic capabilities in primary care, reduce the number of referrals to Urology department, and reduce the number of unnecessary invasive procedures for new patients with a suspected urinary bladder cancer" (Vasdev et al., 2021).

VI. Guidelines and Recommendations

National Comprehensive Cancer Network

The NCCN has stated that "Urine molecular tests for urothelial tumor markers are now available. 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 tumor markers 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. Therefore, the panel considers this to be a category 2B recommendation (NCCN, 2018, 2019, 2020, 2021)."

The NCCN previously stated that an FDA-approved urinary biomarker test such as fluorescence *in situ* hybridization (FISH) or nuclear matrix protein 22 may be considered in monitoring for recurrence (NCCN, 2018). However, updated NCCN (2019, 2020); (NCCN, 2021) guidelines no longer address these biomarker tests.

National Academy of Clinical Biochemistry Laboratory Medicine

The NACB Laboratory Medicine Practice Guidelines do not recommend use of any FDA–approved urinary tumor marker tests for the diagnosis of bladder tumors or for monitoring bladder cancer patients. The guideline states that "There are no prospective clinical trial data that establish the utility of any of the FDA cleared markers or the proposed markers for increasing survival time, decreasing the cost of treatment or improving the quality of life of bladder cancer patients (NACB, 2010)." The NACB is now known as the AACC, or American Association for Clinical Chemistry, and have not since released any further updates on this topic (NACB, 2010).

American Urological Association (AUA)

The AUA's guidelines on the diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults do not recommend use of urine markers (NMP22, BTA-stat, UroVysion) as part of routine evaluation (Davis et al., 2012).

The AUA and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) published a guideline on microhematuria in 2020. In it, they remark that "Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria", stating that "insufficient evidence exists that routine use would improve detection of bladder cancer." However, the guideline states that "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." (Barocas et al., 2020)

The AUA and Society of Urologic Oncology (SUO) joint guidelines on Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer (NMIBC) do not recommend using urinary biomarkers to replace cystoscopy when monitoring NMIBC (grade B), although a clinician can use biomarkers to evaluate a patient's response to Bacillus Calmette-Guerin (BCG) therapy or a separate cytology such as FISH or ImmunoCyt. However, a urinary biomarker should not be used for monitoring a patient with a normal cystoscopy and a history of low-risk cancer (Chang et al., 2016). This 2016 guideline was amended in 2020, but no relevant changes were identified.

The 2021 American Urologic Association (AUA) annual meeting included a guideline amendment update for non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) to the 2020 guidelines. According to the update, a clinical should not use urinary biomarkers in place of cystoscopy. "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. 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™)" (AUA/SUO, 2020). The panel does acknowledge the uptake of Cxbladder in clinical practice; however, there is a lack of high quality evidence in the potential replacement of cystoscopy with Cxbladder (AUA, 2021).

Similarly, the joint guidelines between the AUA, the SUO, the American Society of Clinical Oncology (ASCO), and the American Society for Radiation Oncology (ASTRO) regarding non-metastatic muscle-invasive bladder cancer note that molecular biomarkers may be important for staging cancer and deciding a course of treatment soon. Nevertheless, at this time the biomarkers have not been properly validated (Chang et al., 2017).

U.S. Preventive Services Task Force (USPSTF)

The USPSTF concluded in 2011 that there was insufficient evidence to evaluate screening for bladder cancer in asymptomatic adults, assigning a grade I to this recommendation. Since then, there have been no further guidelines published on this topic by the USPSTF (Moyer, 2011).

In 2021, the USPSTF published the following statement regarding bladder cancer screening in adults: "Literature scans conducted in November 2021 in the MEDLINE and PubMed databases and the Cochrane Library showed a lack of new evidence to support an updated systematic review on the topic at this time (USPSTF, 2019, 2021)."

3rd International Consultation on Urological Diseases & Société Internationale d'Urologie (ICUD-SIU)

With a level of evidence of 3 and a grade of "B", the ICUD-SIU recommends, "examination of urine cytology must be a part of the expectant management or active surveillance protocol." Concerning the surveillance strategies for NMIBC, "Surveillance strategies following a negative 3 months surveillance cystoscopy should be: (1) for low risk disease, cystoscopy 6–9 months later and annually thereafter; consider cessation following five recurrence-free years. No upper tract imaging necessary unless hematuria present; (2) for intermediate risk, cystoscopy with cytology every 3–6 months for 2 years; then every 6–12 months during years 3 and 4; then annually for lifetime. Upper tract imaging every 1–2 years; (3) for high risk, cystoscopy with cytology every 3 months for 2 years; then every 6 months during years 3 and 4; then annually for lifetime [Level of evidence: 3; Grade C] (Monteiro et al., 2018)."

National Cancer Institute

In the 2020 update to the NCI's *Bladder and Other Urothelial Cancers Screening (PDQ®)—Health Professional Version*, the NCI states that "There is inadequate evidence to determine whether screening for bladder and other urothelial cancers has an impact on mortality… Based on fair evidence, screening for bladder and other urothelial cancers would result in unnecessary diagnostic procedures with attendant morbidity (NCI, 2018, 2020, 2021)."

European Association of Urology (EAU)

The EAU has published guidelines on non-muscle-invasive bladder cancer (NIBC). Regarding urinary molecular marker tests, the EAU has stated that "Driven by the low sensitivity and low negative predictive value of urine cytology, numerous urinary tests have been developed. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines (M. Babjuk et al., 2017)." Further, as an exploratory measure after hematuria or after other bladder cancer symptoms have been identified, the EAU states that "It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS [carcinoma *in situ*]. In this setting, sensitivity for high-grade tumours and specificity are particularly important (M. Babjuk et al., 2017)." Finally, the EAU states that currently, there is no urinary marker with the ability to replace cystoscopy.

An update to these guidelines was published in 2020. In it, the EAU concluded that "Cystoscopy is necessary for the diagnosis of bladder cancer" and that "Urinary cytology has high sensitivity in high-grade tumours including carcinoma in situ." The EAU remarks that "There is no known urinary marker specific for the diagnosis of invasive BC [bladder cancer]" (Witjes et al., 2020).

An update to guidelines on non-muscle-invasive bladder cancer (NIBC) was published in 2022. The EAU concluded that urinary molecular marker tests cannot replace cystoscopy in routine practice, "but the knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy." Diagnosis ultimately depends on "cystoscopy examination of the bladder and histological evaluation of sampled tissue" (Marko Babjuk et al., 2022).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

On April 16, 1997, the FDA approved the *Bard BTA stat™ Test*, created by Bard Diagnostic Sciences Inc. From the FDA site: "the BTA stat test is an *in vitro* diagnostic immunoassay indicated for the qualitative detection of bladder tumor associated antigen in urine of persons diagnosed with bladder cancer. This test is indicated for use as an aid in the management of bladder cancer patients in conjunction with cystoscopy."

On April 15, 1998, the FDA approved the *BTA TRAK™ Test*, created by Bard Diagnostic Sciences Inc. From the FDA site: "the BTA TRAK test is an *in vitro* diagnostic immunoassay indicated for the quantitative detection of bladder tumor associated antigen in human urine. This test is indicated for use as an aid in the management of bladder cancer patients in conjunction with cystoscopy."

On July 2, 1996, the FDA approved the *MATRITECH NMP22™ TEST KIT*, created by Alere Scarborough Inc. From the FDA site: "The Matritech NMP22 Test Kit is an enzyme immunoassay (EIA) for the in vitro quantitative determination of nuclear matrix protein NMP22 in stabilized voided urine."

On July 30, 2002, the FDA approved the *NMP22 BladderChek*, created by Matritech Inc. From the FDA site: "The Matritech NMP22 BladderChek Test is indicated for professional and prescription home use as an aid in monitoring bladder cancer patients, in conjunction with standard diagnostic procedures." This assay is qualitative.

On January 24, 2005, the FDA approved the *UROVYSION BLADDER CANCER KIT*. From the FDA site: "The UroVysion Bladder Cancer Kit (UroVysion Kit) is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via fluorescence in situ hybridization (FISH) in urine specimens from persons with hematuria suspected of having bladder cancer."

On February 23, 2000, the FDA approved the *ImmunoCyt,* created by Diagnocure Inc. From the FDA site: "ImmunoCyt is a qualitative direct immunofluorescence assay intended for use in conjunction with cytology to increase overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer. ImmunoCyt is indicated for use as an aid in the management of bladder cancer in conjunction with urinary cytology and cystoscopy (FDA, 2018)."

All of the FDA-approved tests apart from ImmunoCyt are approved for both diagnosis and surveillance of bladder cancer whereas ImmunoCyt is only approved for surveillance (Darwiche, Parekh, & Gonzalgo, 2015).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
86294	Immunoassay for tumor antigen, qualitative or semiquantitative (eg, bladder tumor antigen)
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each
86386	Nuclear Matrix Protein 22 (NMP22), qualitative
88120	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
88346	Immunofluorescence, per specimen; initial single antibody stain procedure

88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
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 Proprietary test: Cxbladder™ Detect Lab/manufacturer: Pacific Edge Diagnostics USA, Ltd
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 Proprietary test: Cxbladder™ Monitor Lab/manufacturer: Pacific Edge Diagnostics USA, Ltd

Current Procedural Terminology© American Medical Association. All Rights reserved.

IX. Evidence-based Scientific References

Abbott. (2020). ALERE NMP22® BLADDERCHEK®. Retrieved from https://www.globalpointofcare.abbott/en/product-details/nmp22-bladderchek.html

ACA. (2021). Retrieved from https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html

AUA. (2021). AUA Guideline Amendment: Non-Muscle Invasive Bladder Cancer/Muscle Invasive Bladder Cancer. Retrieved from https://www.urotoday.com/conference-highlights/aua-2021-program/aua-2021-bladder-cancer/131965-aua-2021-aua-guideline-amendment-non-muscle-invasive-bladder-cancer-muscle-invasive-bladder-cancer.html

AUA/SUO. (2020). Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Joint Guideline (2020). Retrieved from https://www.auanet.org/guidelines/guidelines/bladder-cancer-non-muscle-invasive-guideline

Babjuk, M., Bohle, A., Burger, M., Capoun, O., Cohen, D., Comperat, E. M., . . . Zigeuner, R. (2017). EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol, 71*(3), 447-461. doi:10.1016/j.eururo.2016.05.041

Babjuk, M., Burger, M., Capoun, O., Cohen, D., Compérat, E. M., Dominguez Escrig, J. L., . . . Sylvester, R. J. (2022). European Association of Urology Guidelines on Non–muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *European Urology, 81*(1), 75-94. doi:https://doi.org/10.1016/j.eururo.2021.08.010

Barocas, D. A., Boorjian, S. A., Alvarez, R. D., Downs, T. M., Gross, C. P., Hamilton, B. D., . . . Souter, L. H. (2020). Microhematuria: AUA/SUFU Guideline. *J Urol, 204*(4), 778-786. doi:10.1097/ju.0000000000001297

Breen, V., Kasabov, N., Kamat, A. M., Jacobson, E., Suttie, J. M., O'Sullivan, P. J., . . . Darling, D. G. (2015). A holistic comparative analysis of diagnostic tests for urothelial carcinoma: a study of Cxbladder Detect, UroVysion® FISH, NMP22® and cytology based on imputation of multiple datasets. *BMC medical research methodology, 15*, 45-45. doi:10.1186/s12874-015-0036-8

Chang, S. S., Bochner, B. H., Chou, R., Dreicer, R., Kamat, A. M., Lerner, S. P., . . . Holzbeierlein, J. M. (2017). Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. *J Urol, 198*(3), 552-559. doi:10.1016/j.juro.2017.04.086

Chang, S. S., Boorjian, S. A., Chou, R., Clark, P. E., Daneshmand, S., Konety, B. R., . . . McKiernan, J. M. (2016). Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol, 196*(4), 1021-1029. doi:10.1016/j.juro.2016.06.049

Chou, R., & Dana, T. (2010). Screening adults for bladder cancer: A review of the evidence for the u.s. preventive services task force. *Annals of Internal Medicine, 153*(7), 461-468. doi:10.7326/0003-4819-153-7-201010050-00009

Chou, R., Gore, J. L., Buckley, D., Fu, R., Gustafson, K., Griffin, J. C., . . . Selph, S. (2015). Urinary Biomarkers for Diagnosis of Bladder Cancer: A Systematic Review and Meta-analysis. *Ann Intern Med, 163*(12), 922-931. doi:10.7326/m15-0997

D'Andrea, D., Soria, F., Zehetmayer, S., Gust, K. M., Korn, S., Witjes, J. A., & Shariat, S. F. (2019). Diagnostic accuracy, clinical utility and influence on decision-making of a methylation urine biomarker test in the surveillance of non-muscle-invasive bladder cancer. *BJU Int, 123*(6), 959-967. doi:10.1111/bju.14673

D'Costa, J. J., Goldsmith, J. C., Wilson, J. S., Bryan, R. T., & Ward, D. G. (2016). A Systematic Review of the Diagnostic and Prognostic Value of Urinary Protein Biomarkers in Urothelial Bladder Cancer. *Bladder Cancer, 2*(3), 301-317. doi:10.3233/blc-160054

Darwiche, F., Parekh, D. J., & Gonzalgo, M. L. (2015). Biomarkers for non-muscle invasive bladder cancer: Current tests and future promise. *Indian J Urol, 31*(4), 273-282. doi:10.4103/0970-1591.166448

Davis, R., Jones, J. S., Barocas, D. A., Castle, E. P., Lang, E. K., Leveillee, R. J., . . . Weitzel, W. (2012). Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol, 188*(6 Suppl), 2473-2481. doi:10.1016/j.juro.2012.09.078

DeGeorge, K. C., Holt, H. R., & Hodges, S. C. (2017). Bladder Cancer: Diagnosis and Treatment. (1532-0650 (Electronic)).

Dudley, J. C., Schroers-Martin, J., Lazzareschi, D. V., Shi, W. Y., Chen, S. B., Esfahani, M. S., . . . Diehn, M. (2019). Detection and Surveillance of Bladder Cancer Using Urine Tumor DNA. *Cancer Discov, 9*(4), 500-509. doi:10.1158/2159-8290.Cd-18-0825

Ecke, T. H., Weiß, S., Stephan, C., Hallmann, S., Arndt, C., Barski, D., . . . Gerullis, H. (2018). UBC(®) Rapid Test-A Urinary Point-of-Care (POC) Assay for Diagnosis of Bladder Cancer with a focus on Non-Muscle Invasive High-Grade Tumors: Results of a Multicenter-Study. *Int J Mol Sci, 19*(12). doi:10.3390/ijms19123841

Fantony, J. J., Longo, T. A., Gopalakrishna, A., Owusu, R., Lance, R. S., Foo, W. C., . . . Abern, M. R. (2017). Urinary NID2 and TWIST1 methylation to augment conventional urine cytology for the detection of bladder cancer. *Cancer Biomark, 18*(4), 381-387. doi:10.3233/cbm-160261

FDA. (2018). Devices@FDA.

FDA. (2021). Devices@FDA.

Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H., . . . Naghavi, M. (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol, 3*(4), 524-548. doi:10.1001/jamaoncol.2016.5688

Grossman, H., Messing, E., Soloway, M., & et al. (2005). Detection of bladder cancer using a point-of-care proteomic assay. *JAMA, 293*(7), 810-816. doi:10.1001/jama.293.7.810

Halpern, J. A., Chughtai, B., & Ghomrawi, H. (2017). Cost-effectiveness of Common Diagnostic Approaches for Evaluation of Asymptomatic Microscopic Hematuria. *JAMA Intern Med, 177*(6), 800-807. doi:10.1001/jamainternmed.2017.0739

Hirasawa, Y., Pagano, I., Chen, R., Sun, Y., Dai, Y., Gupta, A., . . . Furuya, H. (2021). Diagnostic performance of Oncuria™, a urinalysis test for bladder cancer. *Journal of Translational Medicine, 19*(1), 141. doi:10.1186/s12967-021-02796-4

Hottinger, A. F., & Hormigo, A. (2011). Serum Biomarkers. In M. Schwab (Ed.), *Encyclopedia of Cancer* (pp. 3390-3394). Berlin, Heidelberg: Springer Berlin Heidelberg.

IDL_Biotech. (2020). UBC® Rapid. Retrieved from https://idlbiotech.com/products/ubc-rapid/

Kaufman, D. S., Shipley, W. U., & Feldman, A. S. (2009). Bladder cancer. *Lancet, 374*(9685), 239-249. doi:10.1016/s0140-6736(09)60491-8

Lerner, S. P., Raghavan, Derek. (2020). Overview of the initial approach and management of urothelial bladder cancer. Retrieved from https://www.uptodate.com/contents/overview-of-the-initial-approach-and-management-of-urothelial-bladder-cancer

Li, H. T., Duymich, C. E., Weisenberger, D. J., & Liang, G. (2016). Genetic and Epigenetic Alterations in Bladder Cancer. *Int Neurourol J, 20*(Suppl 2), S84-94. doi:10.5213/inj.1632752.376

Lopez-Beltran, A., Cheng, L., Gevaert, T., Blanca, A., Cimadamore, A., Santoni, M., . . . Montironi, R. (2019). Current and emerging bladder cancer biomarkers with an emphasis on urine biomarkers. *Expert Rev Mol Diagn*, 1-13. doi:10.1080/14737159.2020.1699791

Lotan, Y., Choueiri, Toni. (2017). Clinical presentation, diagnosis, and staging of bladder cancer. Retrieved from https://www.uptodate.com/contents/clinical-presentation-diagnosis-and-staging-of-bladder-cancer?search=bladder%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H14

Lotan, Y., Choueiri, Toni. (2020). Clinical presentation, diagnosis, and staging of bladder cancer. Retrieved from https://www.uptodate.com/contents/clinical-presentation-diagnosis-and-staging-of-bladder-cancer?search=bladder%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H14

Lotan, Y., Elias, K., Svatek, R. S., Bagrodia, A., Nuss, G., Moran, B., & Sagalowsky, A. I. (2009). Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. *J Urol, 182*(1), 52-57; discussion 58. doi:10.1016/j.juro.2009.02.142

Lotan, Y., & Roehrborn, C. G. (2003). Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. *Urology, 61*(1), 109-118. doi:10.1016/S0090-4295(02)02136-2

Mahnert, B., Tauber, S., Kriegmair, M., Schmitt, U. M., Hasholzner, U., Reiter, W., . . . Stieber, P. (1999). BTA-TRAK--a useful diagnostic tool in urinary bladder cancer? *Anticancer Res, 19*(4a), 2615-2619.

Meleth, S., Reeder-Hayes, K., Ashok, M., Clark, R., Funkhouser, W., Wines, R., . . . Jonas, D. E. (2014). AHRQ Technology Assessments. In *Technology Assessment of Molecular Pathology Testing for the Estimation of Prognosis for Common Cancers*. Rockville (MD): Agency for Healthcare Research and Quality (US).

Mitra, A., Birkman, M., & Penson, D. (2017). Urine biomarkers for the detection of urothelial (transitional cell) carcinoma of the bladder - UpToDate. In M. Ross (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/urine-biomarkers-for-the-detection-of-urothelial-transitional-cell-carcinoma-of-the-bladder?source=see_link

Mitra, A., Birkman, M., Penson, D., & Cote, R. (2019). Urine biomarkers for the detection of urothelial (transitional cell) carcinoma of the bladder - UpToDate. *UpToDate.* Retrieved from https://www.uptodate.com/contents/urine-biomarkers-for-the-detection-of-urothelial-transitional-cell-carcinoma-of-the-bladder?source=see_link

Monteiro, L. L., Witjes, J. A., Agarwal, P. K., Anderson, C. B., Bivalacqua, T. J., Bochner, B. H., . . . McKiernan, J. M. J. W. j. o. u. (2018). ICUD-SIU International Consultation on Bladder Cancer 2017: management of non-muscle invasive bladder cancer. 1-10. Retrieved from http://urology.stanford.edu/content/dam/sm/urology/JJimages/publications/ICUD-SIU-International-Consultation-on-Bladder-Cancer-2017-management-of-non-muscle-invasive-bladder-cancer.pdf

Mossanen, M., Wang, Y., Szymaniak, J., Tan, W. S., Huynh, M. J., Preston, M. A., . . . Chang, S. L. (2019). Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories. *World J Urol, 37*(10), 2059-2065. doi:10.1007/s00345-018-2550-x

Moyer, V. A. (2011). Screening for bladder cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med, 155*(4), 246-251. doi:10.7326/0003-4819-155-4-201108160-00008

NACB. (2010). Use of Tumor Markers in Liver, Bladder, Cervical, and Gastric Cancers. Retrieved from https://www.aacc.org/science-and-practice/practice-guidelines/liver-tumor-markers

NCCN. (2018). NCCN Clinical Practice Guidelines in Oncology; Bladder Cancer version 5.2018. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

NCCN. (2019). Bladder Cancer - Version 1.2020 - November 27, 2019. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

NCCN. (2020). Bladder Cancer Version 3.2020 - January 17, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

NCCN. (2021). NCCN Pratice Guidelines: Bladder Cancer. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

NCI. (2018, 03/02/2018). Bladder and Other Urothelial Cancers Screening (PDQ®)–Health Professional Version. *PDQ®.* Retrieved from https://www.cancer.gov/types/bladder/hp/bladder-screening-pdq

NCI. (2020). Bladder and Other Urothelial Cancers Screening (PDQ®)–Health Professional Version. *PDQ®.* Retrieved from https://www.cancer.gov/types/bladder/hp/bladder-screening-pdq

NCI. (2021). NCI's Bladder and Other Urothelial Cancers Screening (PDQ®)—Health Professional Version. Retrieved from https://www.cancer.gov/types/bladder/hp/bladder-screening-pdq#_60

NICE. (2021). URO17 for detecting bladder cancer. Retrieved from https://www.nice.org.uk/advice/mib250/chapter/The-technology

Nonagen_Bioscience. (2021). Bladder Cancer. Retrieved from https://www.nonagen.com/products

Nucleix. (2015). BLADDER EPICHECK Retrieved from https://www.nucleix.com/bladder-epicheck/

Pangea. (2019a). Features of Bladder CARE™. Retrieved from https://www.pangealab.com/bladdercare/

Pangea. (2019b). Pangea® Laboratory to License Bladder CARE™ Technology from Zymo Research. Retrieved from https://www.prnewswire.com/news-releases/pangea-laboratory-to-license-bladder-care-technology-from-zymo-research-300800622.html

Perazalla, M. (2020). Etiology and evaluation of hematuria in adults. Retrieved from https://www.uptodate.com/contents/etiology-and-evaluation-of-hematuria-in-adults?topicRef=2989&source=see_link

Piao, X. M., Jeong, P., Kim, Y. H., Byun, Y. J., Xu, Y., Kang, H. W., . . . Kim, W. J. (2019). Urinary cell-free microRNA biomarker could discriminate bladder cancer from benign hematuria. *Int J Cancer, 144*(2), 380-388. doi:10.1002/ijc.31849

Protean_Biodiagnostics. (2021). URO17 is the Most Sensitive and Specific Urine Test for Bladder Cancer. Retrieved from https://www.proteanbiodx.com/uro17

Quest. (2020). Bladder Tumor Antigen DetectR™. Retrieved from https://testdirectory.questdiagnostics.com/test/test-detail/34055/bladder-tumor-antigen-detectr?cc=MASTER

Sathianathen, N. J., Butaney, M., Weight, C. J., Kumar, R., & Konety, B. R. (2018). Urinary Biomarkers in the Evaluation of Primary Hematuria: A Systematic Review and Meta-Analysis. *Bladder Cancer, 4*(4), 353-363. doi:10.3233/blc-180179

Schmitz-Dräger, B. J., Droller, M., Lokeshwar, V. B., Lotan, Y., Hudson, M. A., van Rhijn, B. W., . . . Shariat, S. F. (2015). Molecular Markers for Bladder Cancer Screening, Early Diagnosis, and Surveillance: The WHO/ICUD Consensus. *Urologia Internationalis, 94*(1), 1-24. doi:10.1159/000369357

Siegel, R. L., Miller, K. D., & Jemal, A. (2017). Cancer Statistics, 2017. *CA Cancer J Clin, 67*(1), 7-30. doi:10.3322/caac.21387

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians, 70*(1), 7-30. doi:https://doi.org/10.3322/caac.21590

Soubra, A., & Risk, M. C. (2015). Diagnostics techniques in nonmuscle invasive bladder cancer. *Indian J Urol, 31*(4), 283-288. doi:10.4103/0970-1591.166449

Sutton, A. J., Lamont, J. V., Evans, R. M., Williamson, K., O'Rourke, D., Duggan, B., . . . Ruddock, M. W. (2018). An early analysis of the cost-effectiveness of a diagnostic classifier for risk stratification of haematuria patients (DCRSHP) compared to flexible cystoscopy in the diagnosis of bladder cancer. *PLoS One, 13*(8), e0202796. doi:10.1371/journal.pone.0202796

Tan, W. S., Tan, W. P., Tan, M. Y., Khetrapal, P., Dong, L., deWinter, P., . . . Kelly, J. D. (2018). Novel urinary biomarkers for the detection of bladder cancer: A systematic review. *Cancer Treat Rev, 69*, 39-52. doi:10.1016/j.ctrv.2018.05.012

USPSTF. (2019). Bladder Cancer in Adults: Screening. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/bladder-cancer-in-adults-screening?ds=1&s=bladder%20cancer

USPSTF. (2021). Bladder Cancer in Adults: Screening. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/bladder-cancer-in-adults-screening?ds=1&s=bladder%20cancer

Vasdev, N., Hampson, A., Agarwal, S., Swamy, R., Chilvers, M., Hampson, A., . . . Kim, N. (2021). The role of URO17™ biomarker to enhance diagnosis of urothelial cancer in new hematuria patients—First European Data. *BJUI Compass, 2*(1), 46-52. doi:https://doi.org/10.1002/bco2.50

Witjes, J. A., Bruins, H. M., Cathomas, R., Compérat, E. M., Cowan, N. C., Gakis, G., . . . van der Heijden, A. G. (2020). Muscle-invasive and Metastatic Bladder Cancer. Retrieved from https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/

Zuiverloon, T. C. M., de Jong, F. C., & Theodorescu, D. (2017). Clinical Decision Making in Surveillance of Non-Muscle-Invasive Bladder Cancer: The Evolving Roles of Urinary Cytology and Molecular Markers. *Oncology (Williston Park), 31*(12), 855-862.

X. Revision History

Revision Date	Summary of Changes
07/01/2021	Initial Effective Date
07/19/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria. Added the word "as" to the following CC for clarity: As an adjunct in the diagnostic exclusion of bladder cancer for patients who have an atypical or equivocal cytology. Revised code disclaimer statement
10/02/2022	Added CPT codes 88346, 88350