Subject:	Urinary Tumor Markers for Bladder Cancer		
Policy Number:	PO-RE-037v3		
Effective Date:	08/01/2024	**Last Approval Date:**	06/25/2024

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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, 2023).

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).

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" of this policy document.

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** in any of the following situations:
    a. As an adjunct in the diagnostic exclusion of bladder cancer for individuals who have an atypical or equivocal cytology
    b. As an adjunct in the monitoring of high-risk, non-muscle invasive bladder cancer

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

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 an individual's illness.

3. For the evaluation of hematuria, to screen for bladder cancer in asymptomatic individuals, to diagnose bladder cancer in symptomatic individuals, or for any other indication not discussed above, the following tests **DO NOT MEET COVERAGE CRITERIA**:
    a. Urinary biomarkers (bladder tumor antigen (BTA) test, nuclear matrix protein (NMP22) test, or fluorescence in situ hybridization (FISH) UroVysion Bladder Cancer test).
    b. Fluorescence immunocytology (ImmunoCyt/uCyt).

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

Scientific Background

Each year in the United States, the American Cancer Society estimates there are about 82,290 new cases of bladder cancer and about 16,710 deaths from bladder cancer (ACS, 2023). 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 et al., 2017; NCCN, 2023a). 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, 2021). 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 (Lotan, 2022). 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 et al., 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 (Lotan & Choueiri, 2022; Mitra et al., 2023). 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 et al., 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 (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 et al., 2016). All 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., 2023).

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., 2023).

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., 2023).

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., 2023).

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., 2023).

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., 2023).

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., 2023).

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 et al., 2023). The BTA stat® test and the BTA TRAK® test are available from Polymedco and measure qualitative and quantitative detection of bladder tumor-associated antigen, respectively. 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 et al., 2005; Mitra et al., 2023; Zuiverloon et al., 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, 2023; 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., 2023).

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, 2020). 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, 2020). 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, 2019).

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. UBC® Rapid is the only quantitative point of care test platform for urine-based detection of bladder cancer. (AroCell, 2023). 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, 2023). 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, 2022).

The Xpert® Bladder Cancer Monitor can be used as a diagnostic in a population of patients with a history of non-muscle invasive bladder cancer (NMIBC). The test was designed for use in follow-up of patients undergoing routine surveillance. Pichler et al. (2018) enrolled 140 patients with a history

of NMIBC and the patients underwent urine cytology using the Paris classification system. Urinary specimens were also analyzed with PCR using the Xpert® BC monitor, which measures five target mRNAs (ABL1, CRH, IGF2, UPK1B, and ANXA10). The overall sensitivity of the Xpert® BC Monitor was 0.84 with an NPV of 0.93. The authors write that this was “significantly superior” to the sensitivity of bladder washing cytology (0.33 and 0.76; P < 0.001). Another subgroup analysis confirmed the sensitivity as compared to barbotage cytology (Pichler et al., 2018).

D'Elia et al. (2021) also performed a study tracking follow-up and diagnostic utility of the Xpert® BC for patients with a history of NMIBC. This prospective study was done using 1015 samples from a group of 416 patients. Patients had a urinary cytology, the Xpert® Bladder Cancer monitor test, and cystoscopy. If the cystoscopy was positive, a transurethral resection of the bladder was completed. The Xpert® BC test identified 168 recurrent tumors: 126 were low-grade and 42 were high-grade; the overall sensitivity was 17.9% for cytology, 52.4% for the Xpert® BC test and 54.2% for the two tests combined. Overall specificity was 98.5% for cytology, 78.4% for the Xpert® BC test, and 78.2% for the two tests combined (D'Elia et al., 2021).

Analytical Validity

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 (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 et al. (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 (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 et al., 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).

An in-depth health technology assessment (HTA) of Cxbladder test was performed by Landaas et al. (2020) integrating clinical data and real-world usage scenarios to highlight the test’s sensitivity and specificity. Data from a vendor-funded study showed sensitivity of 91% and specificity of 60% for Cxbladder; another study indicated a sensitivity of 0.82 and specificity of .85. The authors also noted an Agency for Healthcare Research and Quality (AHRQ)-funded systematic review by Chou et al. (2015) highlighting the high false-positive rate and poor accuracy of Cxbladder for low-stage and low-grade tumors. The AHRQ concluded that urinary biomarkers like Cxbladder would miss a substantial portion of bladder cancer cases and tests were subject to false positive results (Chou et al., 2015).

A follow-up pilot study by Landaas et al. (2020) was initiated at UW Medicine to analyze the best use-case scenario for Cxbladder. The pilot study involved patients with a history of urothelial carcinoma, comparing those tests with Cxbladder (group 1) to a control group (group 2). Group 1 patients underwent various follow-up tests including urine cytologies, cystoscopies, and biopsies, with recurrence detected in two out of six patients within the study period. Group 2, without

Cxbladder testing, had three out of six patients with detected recurrence. The study essentially found no significant differences in follow-up tests between the two groups. These findings underscore the complexities of adopting new molecular diagnostic tests like Cxbladder on a system-wide basis. However, the study did find that Cxbladder testing *was* beneficial for a specific patient profile: those with normal cystoscopy results and atypical cytology. In such cases. Cxbladder testing led to fewer follow-up procedures (cystoscopies, cytologies, and biopsies) while still detecting a similar proportion of bladder cancer recurrences as standard procedures within the year. In conclusion, Cxbladder appears most suitable for those undergoing surveillance for bladder cancer recurrence, particularly those with normal cystoscopy and atypical cytology (Landaas et al., 2020).

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).

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

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, 2023b)

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.” Overall, the guideline states that “the panel does not recommend using urine cytology or urine-based tumor markers in the initial evaluation of MH [microhematuria] because, to date, markers have not demonstrated incrementally additive information to cystoscopy in the MH population, not have they been found to be of sufficient predictive value to obviate cystoscopy” (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., 2020). 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, 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 (NCI)

In the 2022 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, 2022) .

European Association of Urology (EAU)

The EAU has published guidelines on non-muscle-invasive bladder cancer (NIBC).

In 2022, the EAU concluded that "Cystoscopy is necessary for the diagnosis of bladder cancer" and that "Urinary cytology has high sensitivity in high-grade tumors 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., 2022).

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" (Babjuk et al., 2022).

An update to the EAU guidelines was published in 2023. In it, the EAU commented on urinary molecular marker tests, "None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up." However, they remarked that "promising urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies. Four of the promising and commercially available urine biomarkers, Cxbladder, ADX-Bladder, Xpert Bladder and EpiCheck, although not tested in RCTs, have such high sensitivities and negative predictive values in the referenced studies for high grade disease that these biomarkers may approach the sensitivity of cystoscopy. These 4 tests might be used to replace and/or postpone cystoscopy as they may identify the rare HG recurrences occurring in low/intermediate NMIBC" (EAU, 2023).

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 et al., 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

II. Applicable Codes

Code	Description	Comment
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	
0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma Proprietary test: Cxbladder™ Triage Lab/Manufacturer: Pacific Edge Diagnostics USA, Ltd	
0365U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of bladder cancer Proprietary test: Oncuria® Detect Lab/Manufacturer: DiaCarta Clinical Lab	
0366U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer	

0367U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection Proprietary test: Oncuria® Predict Lab/Manufacturer: DiaCarta Clinical Lab	
0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma.	

III. Definitions

Term	Meaning
N/A	N/A

IV. Related Policies

Policy Number	Policy Description
PO-RE-041	Serum Tumor Markers for Malignancies

Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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VI. Revision History

Revision Date	Summary of Changes
03/06/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
12/06/2023	Off-cycle coding modification: Added CPT code 0420U (new code effective 1/1/2024)
03/01/2023	N/A – see PRISM portal and redlined Avalon Base Policy for clarity and consistency edits.

	Added PLA codes 0363U, 0365U, 0366U, 0367U (new PLA codes 0365U, 0366U, 0367U are effective 4/1/23)

Disclaimer

Healthfirst's claim edits follow national industry standards aligned with CMS standards that include, but are not limited to, the National Correct Coding Initiative (NCCI), the National and Local Coverage Determination (NCD/LCD) policies, appropriate modifier usage, global surgery and multiple procedure reduction rules, medically unlikely edits, duplicates, etc. In addition, Healthfirst's coding edits incorporate industry-accepted AMA and CMS CPT, HCPCS and ICD-10 coding principles, National Uniform Billing Editor's revenue coding guidelines, CPT Assistant guidelines, New York State-specific coding, billing, and payment policies, as well as national physician specialty academy guidelines (coding and clinical). Failure to follow proper coding, billing, and/or reimbursement policy guidelines could result in the denial and/or recoupment of the claim payment.

This policy is intended to serve as a resource for providers to use in understanding reimbursement guidelines for professional and institutional claims. This information is accurate and current as of the date of publication. It provides information from industry sources about proper coding practice. However, this document does not represent or guarantee that Healthfirst will cover and/or pay for services outlined. Reimbursement decisions are based on the terms of the applicable evidence of coverage, state and federal requirements or mandates, and the provider's participation agreement. This includes the determination of any amounts that Healthfirst or the member owes the provider.