Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Category: Laboratory
***Current Policy Effective Date: 5/1/12**

Title: Urinary Tumor Markers for Bladder Cancer

****Procedure Code(s): 86294, 88120**

Description / Background

Urinary bladder carcinoma, the fourth most common cancer in men and the ninth most common cancer in women, results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma) typically presents as a tumor confined to the superficial mucosa of the bladder. The most common symptom of early bladder cancer is hematuria, although other urinary tract symptoms, such as urinary frequency, urgency and dysuria, may also occur. Most urologists follow the American Urological Association (AUA) guidelines for hematuria, which recommend cystoscopic evaluation of all adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with risk factors for developing bladder cancer. A diagnosis of bladder cancer is made cystoscopic examination and biopsy, which is considered the gold standard. In approximately 70 percent of patients diagnosed with bladder cancer, the cancer is confined to the epithelium or the subepithelial connective tissue. Depending on depth of tissue invasion and tumor grade, non-muscle invasive disease is usually treated with transurethral resection, with or without intravesical therapy. There is a 75 percent incidence of recurrence in these patients, with a 10 to 15 percent incidence of progression to muscle invasion over a five-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every three months for one to three years, every six months for an additional two to three years, and then annually thereafter, assuming no recurrence. While urine cytology is a specific test (from 90–100 percent), its sensitivity is lower, ranging from 50–60 percent overall and is considered even lower for low-grade tumors. Therefore, interest has been reported in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

Commercially Available Bladder Tumor Markers
The BTA (bladder tumor antigen) *stat*® test, (Polymedco Inc., Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that was shown to be produced by several human bladder cell lines but not by other epithelial cell lines.

The BTA *stat*® test is an in vitro immunoassay intended for the qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer. The BTA TRAK® test (Polymedco Inc., Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both tests have sensitivities comparable to that of cytology for high-grade tumors and better than cytology for low-grade tumors.

Nuclear matrix protein 22 (NMP-22) is a protein associated with the nuclear mitotic apparatus. It is thought that this protein is released from the nuclei of tumor cells during apoptosis. Normally, only very low levels of NMP-22 can be detected in the urine, and elevated levels may be associated with bladder cancer. NMP-22 may be detected in the urine using an immunoassay.

Fluorescence in situ hybridization (FISH) DNA probe technology has also been used to detect chromosomal abnormalities in voided urine to assist not only in bladder cancer surveillance but also in the initial identification of bladder cancer. FISH DNA probe technology is a technique to visualize nucleic acid sequences within cells by creating short sequences of fluorescently labeled, single-strand DNA, called probes, which match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. UroVysion® (Vysis Inc., Downers Grove, IL) is a commercially available FISH test.

The ImmunoCyt™ test (DiagnoCure Inc., Quebec) uses fluorescence immunohistochemistry with antibodies to a mucin glycoprotein and a carcinoembryonic antigen (CEA). These antigens are found on bladder tumor cells. The test is used for monitoring bladder cancer in conjunction with cytology and cystoscopy.

With the exception of the ImmunoCyt test, which is only cleared for monitoring bladder cancer recurrence, all tests are FDA-cleared as adjunctive tests for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients, in conjunction with standard procedures.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

86294 86386 88120 88121

Other codes (investigational, not medically necessary, etc.):

88299

Diagnoses / Medical Conditions

Bladder cancer

Medical Policy Statement

The safety and effectiveness of urinary tumor markers have been established. They may be considered a useful diagnostic and monitoring option when used as an adjunct in the diagnosis of bladder cancer or when used as an adjunct in the monitoring of bladder cancer.

Rationale

Studies have evaluated the diagnostic performance of individual markers compared to urine cytology, the standard urine-based test for bladder tumor diagnosis and surveillance. Cystoscopy and biopsy are generally used as the gold standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared to combinations of markers.

The U.K. Health Technology Assessment Program published a systematic review in 2010 of studies on the diagnostic performance of the urine biomarkers Fluorescence in Situ Hybridization (FISH, e.g., UroVysion test), ImmunoCyt, and NMP22. The review combined studies that evaluated the tests for initial diagnosis of bladder cancer and those evaluating tests to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard.

Results of pooled patient-level analyses are:

	FISH	ImmunoCyt	NMP22
No. studies	12	8	28
No. patients	3101	3041	10,565
Sensitivity percent (95 percent CI)	76 (65-84)	84 (77-91)	68 (62-74)
Specificity percent (95 percent CI)	85 (78-92)	75 (68-83)	79 (74-84)

The BTA *stat*® test was evaluated in a prospective multicenter study conducted by the FinnBladder Group at 18 medical institutions in Finland and compared to cytology. Consecutive patients (n=501; men = 397; mean age, 69 years, range 28–92) with a history of transitional cell carcinoma who were under follow-up, were recruited. The primary tumor classification for the recruited patients was Ta (n=215), 48 percent; T1 (n=171), 38 percent; T2-3 (n=7), 1.6 percent; carcinoma in situ (CIS; n=15), 3.4 percent; and classification unknown (n=37), 8.3 percent. A majority of patients (n=327, 67 percent) had no prior history of intravesical instillation treatments; 97 patients (20 percent) had past (at least three months from the last) instillation (Group B); 66 patients (14 percent) had present instillations. Patients with missing instillation information (n=nine) and patients with urine infection (n=six) were excluded. Freshly voided urine samples were obtained from all participants before cystoscopy and split for culture, cytology, and BTA testing. Cytology specimens were not

available for central review in all patients; only patients with available cytology (n=445) were included in the analysis comparing BTA and cytology. The overall sensitivity and specificity were calculated based on cystoscopy findings, including those for which further examination was performed.

The key results were as follows:

- 133 patients had recurrence of bladder cancer at cystoscopy; BTA detected 71 (53.4 percent)
- In the remaining 368 patients, 96 (26.1 percent) had a positive BTA test result
- An additional nine (16.4 percent) recurrences were detected at further examinations
- The overall sensitivities were 56.0 percent and 19.2 percent, and specificities were 85.7 percent and 98.3 percent for BTA and cytology, respectively
- Urine infection, past bacillus Calmette-Guerin (BCG) instillations, and present instillations of any type caused false positive test results.

Limitations of this study include lack of both cytology and BTA test results on approximately 10 percent of patients and lack of follow-up on all patients with negative cystoscopic and positive BTA test and/or cytology findings.

Sarosdy and colleagues compared FISH to the BTA test and voided cytology. In a multicenter trial, each of the three tests was performed on urine samples from 176 patients with known transitional cell carcinoma to determine sensitivities. The authors reported finding overall sensitivities of 71 percent, 50 percent, and 26 percent for FISH, BTA test, and cytology, respectively.

A cross-sectional study from Germany, published by Horstmann and colleagues in 2009, compared the performance of UroVysion, ImmunoCyt and NMP22 used to detect bladder cancer recurrence in a sample of 221 patients diagnosed with non-muscle-invasive transitional cell carcinoma. Patients subsequently underwent cystoscopy as part of regular follow-up (n=49) or transurethral reception of the bladder (TURB) for suspicion of recurrent disease (n=172). Findings from cystoscopy or TURB were considered the gold standard diagnosis. The investigators evaluated the diagnostic performance of individual markers, urinary cytology, and all possible combinations of markers. When combinations of markers were used, the test was considered positive if at least one marker was positive.

The main findings are as follows:

	Sensitivity (percent)	Specificity (percent)
Single tests		
Cytology	84	62
NMP22	68	49
UroVysion	76	63
ImmunoCyt	73	72
Combination of 2 tests		
Cytology + NMP22	94	34
Cytology + UroVysion	87	54

Cytology + ImmunoCyt	93	56
NMP22 + UroVysion	91	31
NMP22 + ImmunoCyt	91	38
UroVysion + ImmunoCyt	93	53
Combination of 3 tests		
Cytology, NMP22 and UroVysion	96	28
Cytology, NMP22 and ImmunoCyt	98	31
Cytology, UroVysion and ImmunoCyt	93	49
UroVysion, ImmunoCyt and NMP22	98	32
Combination of all 4 tests	98	31

Cytology was the most sensitive single marker (84 percent) but was less specific than ImmunoCyt (62 percent and 72 percent, respectively). The authors commented that the performance of cytology was better than in previous similar studies and the performance of other single markers were similar to previous studies. All combinations of two tests increased the sensitivity. Sensitivities varied from 94 percent, with a combination of cytology and NMP22, to 87 percent for the combination of cytology and UroVysion. Combining two tests generally lowered the specificity. In monitoring patients for bladder cancer recurrence, sensitivity is the more important test characteristic. Still, the combination with the best tradeoff of sensitivity and specificity was cytology and ImmunoCyt, which had a sensitivity of 93 percent and a specificity of 56 percent. Combining three tests increased the sensitivity even further. Two combinations attained a sensitivity of 98 percent, NMP22 and ImmunoCyt combined with either cytology or UroVysion. Specificity of these combinations was low, 31 percent-32 percent. The best tradeoff with three markers was the combination of cytology, ImmunoCyt, and UroVysion, which had a sensitivity of 93 percent and a specificity of 49 percent. Combining all four tests did not substantially improve the diagnostic performance.

Sullivan and colleagues also recently published a cross-sectional study that compared urinary tumor markers. A single voided sample was obtained from 100 patients with a history of bladder cancer. Immediately after urine collection, patients underwent cystoscopy to identify cancer recurrence. Cystoscopy with biopsy was the gold standard; only biopsy-proven cases were considered positive. The urine sample was divided and used to evaluate cytology, ImmunoCyt and UroVysion; each type of analysis was conducted blindly in a different laboratory. Of the 100 samples, two were considered inadequate for cytology, two were inadequate for ImmunoCyt analysis, and 12 had cell counts too low for UroVysion analysis. Thus, sample size was 98 for cytology and ImmunoCyt and 88 for UroVysion. Sensitivities were 21 percent for cytology, 76 percent for ImmunoCyt, and 13 percent for UroVysion. Specificities were 97 percent for cytology, 63 percent for ImmunoCyt, and 90 percent for UroVysion. Diagnostic performance of the combination of cytology and ImmunoCyt, but not cytology and UroVysion, was reported. In the analysis of two tests, sensitivity was calculated with either test positive and specificity with both tests negative. For the combination of cytology and ImmunoCyt, the sensitivity was 75 percent and specificity was 63 percent. The specificity of this combination of tests was similar to that found by Horstmann and colleagues, described above, 56 percent. The combined sensitivity was

lower than in the Horstmann study (93 percent), likely due to the higher sensitivity of urinary cytology found by Horstmann et al. The Sullivan study was limited by a small sample size. Moreover, the study was supported by DiagnoCure, the manufacturer of ImmunoCyt; the Horstmann study did not receive industry funding.

3. Impact on patient care
Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the schedule of cystoscopies will be altered unless the sensitivity of a urinary marker/markers approaches 100 percent. However, Grocela and McDougal have suggested that consideration be given to lengthening the intervals of cystoscopy in patients with low levels of an accurate marker and low-grade bladder cancer. In addition, while urinary tumor markers might not alter the schedule of cystoscopies, if their results suggest a high likelihood of tumor recurrence, the resulting cystoscopy might be performed more thoroughly, or investigation of the upper urinary tract might be instigated. Horstmann comments that tests could be performed in a stepwise approach, with a positive test triggering a cystoscopy and a negative test leading to an additional tumor marker test. No studies were identified that prospectively evaluated patients who were managed with and without the use of urinary tumor marker tests.

Other Markers
Studies have been published with other potential tumor markers in bladder cancer. These potential new markers include the following: telomerase, soluble fats, tumor-associated trypsin inhibitor (TATI), soluble e-cadherin, bladder cancer specific biomarkers BLCA-1 and BLCA-4, cytokeratins 8 18 19 and 20, survivin, microsatellite markers, hyaluronic acid/hyaluronidase (HYAL1), DD23 monoclonal antibody, fibronectin, and protein and mRNA human chorionic gonadotropin (HCG). There are no FDA-approved tests using any of the above markers. A 2009 review article by Shirodkar et al., commented on potential new tumor markers, they noted that bladder cancer tumor markers is a rapidly evolving field in which new markers are constantly identified. The review concludes: “one) there exists a dizzying number of markers identified using newer expertise and two) much more work will need to be done to delineate which markers may be clinically applicable and which will be discarded.”

Published studies that evaluate these markers have generally included small numbers of patients and were preliminary investigations (e.g., eight to ten). Recently, a larger prospective study was published by Eissa and colleagues in Egypt evaluating HYAL1 and survivin. This study included a total of 278 patients who underwent urine analysis and cystoscopy; 166 were found to have bladder cancer, and 112 had benign bladder lesions. One hundred healthy volunteers served as controls and did not undergo cystoscopy. The authors aimed to determine the ability of the two urinary tumor markers to identify malignant cases. Using qualitative RT-PCR analysis, HYLA1 was identified in 153 (92 percent) malignant samples and 12 (11 percent) of benign samples, and survivin in 126 (76 percent) of malignant samples and 12 (11 percent) of benign samples. HYAL1 and survivin were not identified in any of the control samples. Using the best cutoffs for discriminating the malignant and non-malignant groups, the sensitivity of HYAL1 was 92.2 percent at 94.3 percent specificity. This was higher than a comparable analysis of survivin which had a 75.9 percent sensitivity and 94.3 percent specificity. Using semi-quantitative RT-PCR analysis,

the sensitivity of HYAL1 was 91 percent and of survivin was 95.9 percent; specificity in both cases was 100 percent. The sensitivity and specificity of the two markers would need to be confirmed in additional studies.

Urinary Markers to Screen Asymptomatic Individuals for Bladder Cancer

In 2004, the U.S. Preventive Services Task Force updated their recommendation on screening for bladder cancer in asymptomatic adults. They found fair evidence that available screening tests can detect bladder cancer; however, they concluded that the potential benefit would be small, at best, for the following reasons: "there is fair evidence that many of the cancers detected by screening, have a low tendency to progress to invasive disease; there is a relatively low overall prevalence of asymptomatic bladder cancer that would eventually lead to important clinical consequences; and there is limited evidence that early treatment of bladder cancer detected through screening improves long-term health outcomes." Moreover, the Task Force concluded that the potential harms of screening are at least small because, since screening tests have a low positive predictive value, there would be many false-positive findings which would lead to unnecessary invasive procedures. In their recommendation statement, they commented that smoking increases the risk of bladder cancer, and that current smokers should be counseled on quitting smoking. Working in certain occupations such as the dye or rubber industries may also increase the risk of bladder cancer; they did not review evidence on targeted screening of individuals who may be at risk due to occupational exposure.

A modeling study, by Svatek et al., published in 2006 reported that screening the general population for bladder cancer using tumor markers would not be beneficial but that screening an asymptomatic high-risk population would yield a benefit similar to other cancer screening programs (e.g., prostate, colon, and breast cancer). In 2009, Lotan and colleagues published a prospective study in which 1502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure were screened. Approximately 60 percent of the sample was recruited from a Veterans Administration hospital and 1175 (78 percent) of the study population was male. Participants were all at least 50 years old (mean age was 62.5 years). A total of 1298 individuals had a ten-year or greater smoking history, and 513 had a greater than 15-year occupational exposure. Approximately 73 percent of participants had undergone urinalysis within three years of screening. Individuals with a history of urological malignancy or gross malignancy and those with current urinary problems that might increase the false positive rate were excluded. The study used the NMP22 BladderChek test and was supported by Matritech, the test manufacturer. Individuals with positive BladderChek tests underwent additional testing, beginning with urinalysis. Those found to have infection on urinalysis were treated and their urine was re-tested; others who tested positive received cystoscopy and cytology. Individuals with a negative BladderChek test did not have to undergo additional testing. However, all participants were contacted after 12 months to determine whether they had been diagnosed with bladder cancer or were experiencing gross hematuria. Eighty-five (5.7 percent) of the 1502 participants had a positive BladderChek test. Of these, 69 (81 percent) underwent cystoscopy; 14 refused, and two patients with urethral strictures were unable to be examined. Two of the 85 patients were found to have bladder cancer (non-invasive), yielding a positive predictive value of 2.4 percent. There was also one case of atypia. Follow-up at a mean of 12 months was obtained for 1309 of 1502 (87 percent) screened individuals. No additional cancers were

diagnosed in the group that had had positive BladderChek tests. Two participants with negative BladderChek screen had been diagnosed with bladder cancer; both tumors were less than one cm. Since no follow-up tests were done on participants who initially tested negative, it cannot be known whether these were false negative findings or new cancers. The authors report that there was a lower cancer prevalence in this population than expected, which could be due in part to the large proportion that had previously undergone urinalysis. Study limitations include lack of follow-up testing on approximately 20 percent of participants who tested positive, and lack of early cystoscopy and incomplete one-year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Summary

Numerous well-designed studies have evaluated the diagnostic performance of the FDA-approved urinary tumor markers. Overall, studies have found reasonable sensitivities and specificities, and a recent study found that that one or two of these urinary tumor markers can enhance the sensitivity of urinary cytology. Studies describing other, non-FDA approved markers generally involve limited numbers of patients, and they have not been compared to urinary cytology or the commercially available tests. Based on the available evidence, the FDA-approved urinary markers are considered medically necessary for their approved indications when used in conjunction with standard diagnostic procedures, and other markers are considered investigational.

The existing evidence does not support the use of urinary tumor markers to screen for bladder cancer due to the low prevalence of asymptomatic disease in the general population and the lack of evidence that early treatment of screen-detected bladder cancer improves health outcomes. A recent prospective study also found a low yield when the BladderChek test was used in an industry-sponsored trial to screen high-risk asymptomatic individuals. Thus, urinary tumor markers to screen asymptomatic individuals is considered investigational.

Technology Assessments, Guidelines, and Position Statements

The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend use of any of the FDA-approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients. The guideline states, “In selected patients, and when used in combination with cystoscopy, their measurement may provide additional information, but there is no evidence that this improves outcome.” The tests are also not recommended for bladder cancer screening.

National Comprehensive Cancer Network (NCCN) 2009 Practice Guidelines in Oncology Bladder Cancer include the following statements regarding urothelial tumor markers: “Urine molecular tests for urothelial tumor markers are now available. Most of these tests have a better sensitivity for detecting bladder cancer than urine cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information which is useful for detection and management of non-muscle invasive bladder tumors. Therefore, The NCCN Bladder Cancer panel members consider this a category 2B recommendation.”

National Cancer Institute (NCI) Bladder and Other Urothelial Cancers Physician Data Query (PDQ®) provides comprehensive, peer-reviewed information about general population screening for bladder and other urothelial cancers. The summary, updated in 2008, includes the following statements regarding screening for bladder and other urothelial cancers: "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."

The American Urological Association's 2007 guideline on management of bladder cancer (18) includes the following statement regarding urine-based markers for bladder cancer: "Despite their present and future potential, the critical evaluation and comparison of urine-based markers is beyond the scope of the current guideline involving the management of nonmuscle invasive bladder cancer."

The U.S. Preventive Services Task Force recommends against routine screening for bladder cancer in adults (D recommendation). The recommendation was last updated in 2004.

Medical Policy Position Summary (Non-clinical summary statement for customer use)

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. As bladder cancer has a high recurrence rate, follow-up cystoscopies and urine cytology help to identify recurrence. Urinary Tumor markers are used to detect higher-than-normal levels of specific proteins that may indicate the presence of a certain types of cancer. Urinary tumor markers are used mainly to assess the patient's response to treatment and to identify recurrence early.

The safety and effectiveness of urinary tumor markers have been established. They may be considered a useful diagnostic and monitoring option when used as an adjunct in the diagnosis of bladder cancer or when used as an adjunct in the monitoring of bladder cancer.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Initial diagnosis:

When used as an adjunct in the diagnosis of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA STAT*, BTA TRAK*
- NMP22*, NMP22 BLADDER CHEK*
- UROVYSION*

Bladder cancer monitoring:

When used as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA STAT* and BTA TRAK*
- IMMUNOCYT*

- NMP22* and NMP22 BLADDER CHEK*
- UROVYSION*

Exclusions:
Initial Diagnosis:
- IMMUNOCYT

Screening for bladder cancer:
- Screening for bladder cancer in asymptomatic and low risk persons
- Routine screening for bladder cancer

*** indicates FDA Approved indications**

Related Policies

N/A

Medicare Information

There is no LCD or NCD that covers urinary tumor markers for bladder cancer.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

References

- American Urological Association Education and Research, Inc., Chapter 1: The management of bladder cancer: Diagnosis and treatment recommendations, 2007, pp. 1-51, available online at: < http://www.auanet.org/content/guidelines-and-qualitycare/clinical-guidelines/main-reports/bladcan07/chapter1.pdf >.
- Blue Cross Blue Shield Association, "Urinary tumor markers for bladder cancer" *Medical Policy Reference Manual,* Policy #2.04.07, Issue 5:2010, original policy date 1/30/1998, last review date 12/9/2010.
- Chou, R., et al., "Screening adults for bladder cancer: A review of the evidence for the U.S. Preventive Services Task Force," *Annals of Internal Medicine*, 2010, Vol. 153, pp. 461-468.
- Eissa, S., et al., "Expression of HYAL1 and survivin RNA as diagnostic molecular markers for bladder cancer," *Journal of Urology*, 2008, Vol. 183, No. 2, pp. 493-498.
- Grocela, J., et al., "Utility of nuclear matrix protein (NMP22) in the detection of recurrent bladder cancer," *Urologic Clinics of North America*, 2000, Vol. 27, No. 1, pp. 47-51.
- Hortsmann, M., et al., "Clinical experience with survivin as a biomarker for urothelial bladder cancer," *World Journal of Urology*, 2010, Vol. 28, No. 3, pp. 399-404.

- Hortsmann, M., et al., "Combinations of urine based tumour markers in bladder cancer surveillance," *Scandinavian Journal of Urology and Nephrology*, 2009, Vol. 43, No. 6, pp. 461-466.
- Lai, Y., et al., "UPK3A - A promising novel urinary marker for the detection of bladder cancer," 2010, Vol. 76, No. 2, pp. 6-10.
- Lotan, Y., et al., "Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker," *Journal of Urology*, 2009, Vol. 182, No. 1, pp. 52-58.
- Mowatt G., et al. "Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer," Health Technology Assessment 2010; Vol. 14, No. 4, pp. 1-331, < www.hta.ac.uk >.
- National Cancer Institute (NCI) "Bladder and other urothelial cancers PDQ®" available at: < http://www.cancer.gov/cancertopics/pdq/screening/bladder/HealthProfessional/page1 > Updated 10/22/10.
- National Comprehensive Cancer Network® "NCCN Clinical Practice Guidelines in Oncology™. Bladder Cancer including upper tract tumors and urothelial carcinoma of the prostate,".2009, available at: < http://www.nccn.org/index.asp >.
- Nisman, B., et al., "The follow-up of patients with non-muscle-invasive bladder cancer by urine cytology, abdominal ultrasound and urine CYFRA 21-1: A pilot study, *Anticancer Research*, 2009, Vol. 29, No. 10, pp. 4281-4285.
- Raitanen, M., et al., "The role of BTA stat test in follow-up of patients with bladder cancer: results from FinnBladder studies," *World Journal of Urology*, 2008, Vol. 26, No. 1, pp. 45-50.
- Sarosdy, M., et al., "Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer," *Journal of Urology*, 2002, Vol. 168, No. 5, pp. 1950-1954.
- Shirodkar, S., et al., "Potential new urinary markers in the early detection of bladder cancer," *Current Opinions in Urology*, 2009, Vol. 19, No. 5, pp. 488-493.
- Sturgeon, C., et al., "National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines for use of tumor markers in liver, bladder, cervical and gastric cancers," *Clinical Chemistry*, 2010, Vol. 56, No. 6, pp. e1-e48.
- Svatek, R., et al., "Economic impact of screening for bladder cancer using bladder tumor markers: A decision analysis," *Urologic Oncology: Seminars and Original Investigations*, 2006, Vol. 24, No. 4, pp. 338-343.
- U.S. Preventive Services Task Force, "Screening for bladder cancer in adults: Recommendation statement," June 2004, Agency for Healthcare Research and Quality, Rockville, MD, available at: < http://www.ahrq.gov/clinic/3rduspstf/bladder/blacanrs.pdf >.

*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through **12/8/11**, the date the research was completed.*

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/11	4/19/11	5/3/11	Joint policy established
5/1/12	2/21/12	2/21/12	Routine maintenance, CPT code 86386 added to policy

Next Review Date: 1st Qtr, 2013

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: URINARY TUMOR MARKERS FOR BLADDER CANCER

I. Short Description:

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. As bladder cancer has a high recurrence rate, follow-up cystoscopies and urine cytology help to identify recurrence. Urinary tumor markers are used to detect higher-than-normal levels of specific proteins that may indicate the presence of a certain types of cancer. Urinary tumor markers are used mainly to assess the patient's response to treatment and to identify recurrence early.

The safety and effectiveness of urinary tumor markers have been established. They may be considered a useful diagnostic and monitoring option when used as an adjunct in the diagnosis of bladder cancer or when used as an adjunct in the monitoring of bladder cancer.

II. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Covered, criteria apply
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service
BlueCaid	Covered, criteria apply

III. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate benefits and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.

IV. Effective Dates:

Policy updated: 5/1/12
JUMP policy effective date: 7/1/11