APPENDIX to Urinary Tumor Markers Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

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

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Moreover, bladder cancer has a very high frequency of recurrence and therefore follow-up cystoscopy, along with urine cytology, is done periodically to identify recurrence early. Urine biomarkers that might be used to either supplement or supplant these tests have been actively investigated.

Urinary bladder cancer, a relatively common form of cancer in the United States, results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma), typically presents as a tumor confined to the superficial mucosa of the bladder. The most frequent symptom of early bladder cancer is hematuria; however, urinary tract symptoms (e.g., urinary frequency, urgency, and dysuria) may also occur.

For patients with hematuria, American Urological Association (AUA) 2012 guidelines 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. Confirmatory diagnosis of bladder cancer is made by cystoscopic examination and biopsy. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. Non-muscle invasive disease is usually treated with transurethral resection (TUR), with or without intravesical therapy, depending on depth of invasion and tumor grade. However, a 50 to75% incidence of recurrence has been noted in these patients, with 10% to 15% progressing to muscle invasion over a 5 year period. Current follow-

up protocols include flexible cystoscopy and urine cytology every three months for one to 3 years, every 6 months for an additional 2 to 3 years, and then annually thereafter, assuming no recurrence.

While urine cytology is a specific test (from 90 to100%), its sensitivity is lower, ranging from 50 to 60% 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.

Review of Literature

Urinary Tumor Markers

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.

Bladder Tumor Antigen (BTA) STAT®, Nuclear Matrix Protein 22 (NMP-22)BladderChek® , UroVysion® and Immunocyt®

A 2011 article by Parker and Spiess reviewed the published literature and summarized the sensitivity and specificity of several urine tumor markers in bladder cancer for diagnosis or monitoring of recurrence. Selected information from the article is reported in the following table:

Test	Sensitivity Range (%)	Specificity Range (%)
Cytology	12 to 79	78 to 99
BTA STAT	50 to 70	67 to 78
NMP22	50 to 92	66 to 87
ImmunoCyt	67 to 85	62 to 85
FISH (UroVysion)	69 to 92	89 to 95

FISH, fluorescence in situ hybridization

In 2010, The United Kingdom Health Technology Assessment Program published a systematic review of studies on the diagnostic performance of several urine biomarkers (Mowatt et al., 2010). 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
Number of studies	12	8	28
Number of patients	3,101	3,041	10,565
Sensitivity % (95% CI)	76 (65-84)	84 (77-91)	68 (62-74)
Specificity % (95% CI)	85 (78-92)	75 (68-83)	79 (74-84)

CI, confidence interval

Representative Studies Comparing the Diagnostic Accuracy of Two or More Urinary Markers Compared to a Reference Standard

A cross-sectional study from Germany, published by Horstmann and colleagues in 2009, compared the performance of UroVysion® , ImmunoCyt® and NMP-22 BladderChek® 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 resection 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.

Cytology was the most sensitive single marker (84%) but was less specific than ImmunoCyt® (62% and 72%, respectively). The authors commented that the performance of cytology was better than in previous similar studies, and the performance of other single markers was similar to previous studies. All combinations of 2 tests increased the sensitivity. Sensitivities varied from 94%, with a combination of cytology and NMP-22 BladderChek®, to 87% for the combination of cytology and UroVysion®. Combining 2 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% and a specificity of 56%. Combining 3 tests increased the sensitivity even further. Two combinations attained a sensitivity of 98%, NMP-22 BladderChek® and ImmunoCyt® combined with either cytology or UroVysion®. Specificity of these combinations was low, 31 to 32%. The best tradeoff with 3 markers was the combination of cytology, ImmunoCyt®, and UroVysion®, which had a sensitivity of 93% and a specificity of 49%. Combining all 4 tests did not substantially improve the diagnostic performance.

In 2009, Sullivan and colleagues published a cross-sectional study that compared the urinary tumor markers ImmunoCyt® and UroVysion®. 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, 2 were considered inadequate for cytology, 2 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% for cytology, 76% for ImmunoCyt®, and 13% for UroVysion®. Specificities were 97% for cytology, 63% for ImmunoCyt®, and 90% for UroVysion®. Diagnostic performance of the combination of cytology and ImmunoCyt®, but not cytology and UroVysion®, was reported. In the analysis of 2 tests, sensitivity was calculated with either test positive or specificity with both tests negative. For the combination of cytology and ImmunoCyt®, the sensitivity was 75% and specificity was 63%. The specificity of this combination of tests was similar to that found by Horstmann and colleagues (2009), described above, 56%. The combined sensitivity was lower than in the Horstmann study (93%), likely due to the higher sensitivity of urinary cytology found. The study by Sullivan et al. (2009) was limited by a small sample size. Moreover, the

study was supported by DiagnoCure, Inc. (Quebec, Canada), the manufacturer of ImmunoCyt® ; the Horstmann study did not receive industry funding.

A prospective study by Kamat and colleagues (2011) evaluated the accuracy of five bladder cancer surveillance protocols for identifying recurrence in patients with a history of bladder cancer. Four patient management strategies were compared:

- Cystoscopy alone
- Cystoscopy and NMP-22 BladderChek®
- Cystoscopy and Urovysion®
- Cystoscopy and cytology

In addition, a fifth hypothetical protocol was evaluated; cystoscopy and contingent strategy in which a Urovysion® test was only performed if the NMP-22 BladderChek® test was positive. After an initial evaluation, patients were followed with routine cystoscopy every 3 to 6 months. For patients with a negative cystoscopy at baseline and in whom a tumor was detected at the first follow-up (e.g., within 6 months), it was assumed that this was a true result reflecting a missed diagnosis at the initial examination. Cancer was detected in 13 of 200 (6.5%) patients at the baseline evaluation and in 12 of 187 (6.4%) initially negative patients at first follow-up. Each of the patient management strategies described above correctly identified all 13 patients diagnosed with cancer at study entry. The proportion of false-positives at baseline was

- 2 of 15 (13%) patients testing positive using cystoscopy alone
- 19 of 32 (59%) positives with cystoscopy and NMP-22 BladderChek®
- 30 of 43 (70%) positives with cystoscopy and Urovysion®
- 14 of 27 (52%) positives with cystoscopy and cytology
- 6 of 19 (32%) positives with cystoscopy and NMP-22 BladderChek® (followed by Urovysion® if the NMP-22 BladderChek® test was positive)

The number of initial false-positives that were confirmed positive at the first follow-up for each strategy was 0, 1, 5, 2, and 1, respectively. The 2 invasive tumors (out of 12 total tumors) identified at first follow-up were missed by all 5 surveillance strategies; urinary tumor markers only detected non-invasive tumors.

Fibroblast Growth Factor Receptor 3 (FGFR3) mutations

Several studies have evaluated urine based assays for identifying FGFR3 mutations. A 2012 study was published by Fernandez and colleagues; several authors involved in this study were employees of Predictive Biosciences, Inc. (Cleveland, OH) the manufacturer of the CertNDx test. The study included 323 individuals who had been treated for bladder cancer; 48 of these had a recurrence of bladder cancer and the remaining 275 had no current evidence of disease. Seven patients without disease did not have sufficient DNA for FGFR3 mutation testing and were excluded from further analysis. FGFR3 mutations were detected in 15 samples, 5 from patients with cancer recurrence and 10 from individuals without evidence of disease. This resulted in a sensitivity of 5 of 48 (10%) and a specificity of 258 of 268 (96%). When results of FGFR3 mutation analysis were combined with the findings of other tests (matrix metalloproteinase 2 (MMP2), Twist 1 and Nid2 methylation), the markers had a 92% sensitivity (44 of 48) and 51% specificity (136 of 268) for detecting cancer recurrence.

In a retrospective study, Rieger-Christ and colleagues (2003) compared the accuracy of FGFR3 mutation analysis, cytology and the combination of the two in identifying bladder tumors. The study included 192 patients with bladder cancer, 72 who underwent TURB (Group A) and 120 who underwent cystectomy (Group B). Urine samples were collected prior to surgery. DNA preparations were screened for FGFR3 mutations using single-strand conformation polymorphism (SSCP) and DNA sequencing (the study did not appear to use the CertNDx test). Cytology results were available for 62 of 72 (86%) in the TURB group and 62 of 120 (52%) in the cystectomy group. Sensitivity of the FGFR3 test alone was 68% for Group A and 24% for Group B. The sensitivity of cytology alone was 32% for Group A and 90% for Group B. For the combination of FGFR3 and cytology, the sensitivity was 78% for Group A and 93.5% for Group B.

In addition, Zuiverloon and colleagues (2010) applied FGFR3 mutation analysis to the detection and prediction of bladder cancer recurrence. The research team, based in the Netherlands, developed an assay to identify common FGFR3 mutations in urine samples. This assay validation study identified the FGFR3 mutation status of tumors in 200 patients with low grade non-muscle invasive bladder cancer. FGFR3 mutations were identified in 134 (67%) patients. The 134 patients with an FGFR3 mutant tumor provided 463 urine samples, and 45 concomitant histologically proven recurrences of bladder cancer were found. The sensitivity of the assay to detect concomitant recurrences was 26 of 45 (58%). After at least 12 months of follow-up from the time of the last urine sample, an additional 34 recurrences were identified. Overall, 85 of 105 (81%) FGFR3 positive urine samples were associated with a bladder cancer recurrence compared to 41 of 358 (11%) FGFR3 negative urine samples. In a Cox time-to-event analysis, a FGFR3 positive urine sample was associated with a 3.8 fold higher risk of having a recurrence ($p < 0.0001$).

Other Urinary Bladder Tumor Markers

A 2009 review article on potential new tumor markers comments that bladder cancer tumor markers is a rapidly evolving field in which new markers are constantly identified (Shirodkar and Lokeshwar, 2009). The review concluded; "there exists a dizzying number of markers identified using newer expertise, and much more work will need to be done to delineate which markers may be clinically applicable and which will be discarded."

Regarding the variety of other potential tumor markers in bladder cancer, most of the published studies evaluating them have included small numbers of patients and were preliminary investigations. Literature searches identified 1 meta-analysis and several larger prospective studies on additional markers. The meta-analysis, published in 2012 by Ku and colleagues, addressed using urine survivin as a marker for diagnosing bladder cancer and used cystoscopy and/or histopathology as a reference standard. They identified 14 studies, 3 of which were conducted in the United States and 3 of which identified recruitment as prospective. A meta-analysis of data from the studies found a pooled sensitivity for the urine survivin test of 0.77 (95% [CI]: 0.74 to 0.80) and a pooled specificity of 0.92 (95% CI: 0.90 to 0.93). In a pre-planned subgroup analysis comparing the diagnostic accuracy of survivin and cytology, a pooled analysis of data from 6 studies found that survivin had a significantly better sensitivity than cytology, but a significantly lower specificity; the sensitivity and specificity of cytology for diagnosing bladder cancer was 0.43 and 0.98, respectively.

Among the prospective studies evaluating potential tumor markers, Eissa and colleagues (2010) in Egypt aimed to determine the ability of HYAL1 and survivin to identify malignant bladder tumors. A total of 278 patients underwent urine analysis and cystoscopy, and 100 healthy volunteers who did not undergo cystoscopy served as controls. Among patients, 166 were found to have bladder cancer, and 112 had benign bladder lesions. Using qualitative real-time polymerase chain reaction (RT-PCR) analysis, HYAL1 was identified in 153 (92%) malignant samples and 12 (11%) of benign samples, and survivin in 126 (76%) of malignant samples and 12 (11%) 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% at 94.3% specificity. This was higher than a comparable analysis of survivin, which had 75.9% sensitivity and 94.3% specificity. Using semi-quantitative RT-PCR analysis, the sensitivity of HYAL1 was 91% and of survivin was 95.9%; specificity in both cases was 100%.

Similarly, Passerotti and colleagues (2011) in Brazil evaluated urinary hyaluronate for diagnosing transitional cell carcinoma (TCC). Urine samples were taken from 350 patients prior to surgery (cystoscopy, cystectomy or transuretheral resection for bladder cancer). Postoperatively, a total of 160 patients (46%) were found to have TCC. Using area under the curve analysis, the investigators identified the optimal urinary hyaluronan cutoff to be 13.0 microgram (mcg); with this cutoff, the test had a sensitivity of 82.3% and a specificity of 81.2% for identifying the presence of TCC.

Moreover, a 2010 study by Li and colleagues in China prospectively evaluated the cytokeratin 20 (CK20) test for detecting urothelial carcinoma. Diagnostic accuracy of CK20 was compared to cytology and the Immunocyt® test, using cystoscopy with histological diagnosis as the reference standard. The study included 169 patients who were hospitalized for a urological condition; 22 healthy individuals were included as controls. Thirty-four of 169 (20%) patients were excluded from the analysis due to missing data. Of the remaining 135 patients, 93 had urothelial carcinoma (primary tumors in 68 and recurrent tumors in 25), 26 had other urogenital malignancies, and 16 had benign lesions. A total of 132 patients had findings available on all 3 tests. The sensitivity of liquid-based cytology alone was 49.4% and the specificity was 91.1%. The combination of cytology and CK20 yielded a sensitivity of 81.6% and a specificity of 88.9%. When all 3 tests were used together (any positive test scored as positive), the sensitivity was 90.8% and the specificity was 84.4%. It is worth noting that the Immunocyt® test is approved by the United States FDA for use in patients already diagnosed with bladder cancer, not for initial diagnosis. The authors did not specify whether or not all study participants, who were inpatients in a department of urology, had previously received a diagnosis for their condition.

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 urinary marker/markers approaches 100%. However, some authors 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 (Grocela and McDougal; 2000).

No studies were identified that prospectively evaluated health outcomes in patients who were managed with and without the use of urinary tumor marker tests. In addition, there were no published studies to date comparing different cystoscopy protocols, used in conjunction with urinary markers, to monitor recurrence.

A 2011 study by Shariat and colleagues used a decision-curve analysis to assess the impact of urinary marker testing on the decision to refer for cystoscopy and concluded that the marker did not aid clinical decision making in most cases. The study included 2,222 patients with non-muscle invasive bladder cancer and negative cytology, at various stages of surveillance. (Patients with positive urinary cytology were excluded, since standard practice is to refer these patients for cystoscopy). According to the study protocol, all patients underwent cystoscopy, and 581 (26%) were found to have disease recurrence; of these, 234 (40%) had disease progression. NMP-22 BladderChek® level was found to be significantly associated with both disease recurrence and progression ($p < 0.001$ for both). In the analysis, clinical net benefit of the NMP-22 BladderChek® test was evaluated by summing the benefits (true-positives), subtracting the harms (false-positives), and weighing these values by the "threshold probability," defined as the minimum probability of bladder cancer or recurrence at which a patient or clinician would opt for cystoscopy. The investigators found only a small clinical net benefit of the NMP-22 BladderChek® test over the strategy of "cystoscopy for all patients," and this benefit occurred only at threshold probabilities over 8%. For example, for patients with at least a 15% risk of recurrence, using a model containing age, sex, and NMP-22 BladderChek®; 229 (23%) cystoscopies could be avoided, 236 (90%) recurrences would be identified and 25 (15%) recurrences would be missed.

Thus, for clinicians or patients who would opt for a cystoscopy even if patients had a low risk of recurrence (e.g. 5%), NMP-22 BladderChek® would not add clinical benefit and the optimal strategy would be to offer cystoscopy to all at-risk patients. The authors attributed the low clinical net benefit to the high risk of bladder cancer recurrence in patients with negative cytology

Urinary Markers for Screening Asymptomatic Individuals for Bladder Cancer

In 2010, the United States Preventive Services Task Force (USPSTF) published an updated evidence review on screening adults for bladder cancer (Chou and Dana, 2010). The quality of direct evidence that screening for bladder cancer reduces morbidity or mortality was poor. There were no randomized controlled trials (RCTs), and only one prospective study, which was rated as being poor quality. The systematic review did not identify any studies evaluating the sensitivity or specificity of diagnostic tests for bladder patients in asymptomatic average risk patients. Moreover, the review did not identify any suitable studies on whether treatment of screen-detected bladder cancer reduces disease-specific morbidity and mortality, or on potential harms of screening for bladder cancer. The authors concluded that "major gaps in evidence make it impossible to reach any reliable conclusions about screening."

A modeling study 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 (Svatek et al., 2006).

In 2009, Lotan and colleagues published a prospective study in which 1,502 individuals at high risk of bladder cancer due to age plus smoking and/or occupational exposures were screened. Approximately 60% of the sample was recruited from a Veterans Administration hospital and 1,175 (78%) of the study population was male. Approximately 73% of participants had undergone urinalysis within 3 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 NMP-22 BladderChek test and was supported by Matritech, Inc. (Newton, MA) 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.

Eighty-five (5.7%) of the 1,502 participants had a positive NMP-22 BladderChek® test. Of these, 69 (81%) underwent cystoscopy; 14 refused, and 2 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%. There was also one case of atypia. Follow-up at a mean of 12 months was obtained for 1,309 of 1,502 (87%) screened individuals. No additional cancers were diagnosed in the group that had had positive NMP-22 BladderChek® tests. Two participants with negative NMP-22 BladderChek® screen had been diagnosed with bladder cancer; both tumors were less than 1 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 the cancer prevalence in this population was lower 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% of participants who tested positive and lack of early cystoscopy and incomplete 1 year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network (NCCN)® 2012 Practice Guidelines in Oncology for Bladder Cancer included the following statement 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. They [urinary tumor marker tests] are not used to guide treatment decisions outside of the experimental protocol setting”

In 2010, the USPSTF concluded that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was graded

as an “I” recommendation, indicating insufficient evidence. This statement replaced a 2004 recommendation against routine screening for bladder cancer.

The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend using any of the FDA approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients. The guideline stated:

“At this time, no tumor markers tests can be recommended for use in the diagnosis and clinical management of bladder cancer. This includes tests for making a differential diagnosis, assessing prognosis, staging of the disease or monitoring patients for the early detection of recurrent disease. 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” (Sturgeon et al., 2010 and Fritsche et al., 2010).

The AUA 2007 guidelines on management of bladder cancer included 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 non-muscle invasive bladder cancer.”

An ongoing clinical trial sponsored by the Baylor College of Medicine (2010) is evaluating screening for bladder cancer in men age 60 years and older with a history of smoking. The estimated patient enrollment is 1,500 individuals and the estimated study completion date is February, 2015 (ClinicalTrials.gov, NCT0084867).

Clinical Input Received through Specialty Medical Societies and Academic Medical Centers

In 2012, in response to requests for vetting from the Blue Cross Blue Shield Association (BCBSA), input was received through two physician specialty societies and five academic medical enters. The results showed unanimous support for the medically necessary statements and unanimous or near-unanimous support for the investigational statements. There was mixed support but no uniform consensus on issues regarding the incremental value of urinary tumor markers compared to urinary cytology alone and whether urinary tumor markers lead to changes in patient management.

Summary

Numerous studies have evaluated the diagnostic performance of various urinary tumor markers for diagnosing and/or monitoring bladder cancer. However, there is little evidence on the impact of urinary bladder tumor marker tests on patient management, (e.g., the frequency of cystoscopy, or on the impact of tests on health outcomes). There is also a lack of evidence on the impact of screening asymptomatic individuals for bladder cancer using urinary tumor markers.

The available evidence does not establish the clinical utility of urinary tumor markers for diagnosing, monitoring and/or screening for bladder cancer and therefore is considered investigational and experimental.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	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	Immunofluorescent study, each antibody; direct method
	88367	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology
	88368	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual
HCPC	None	
ICD9	None	

Type	Number	Description
ICD10 Procedure	N/A	
ICD9 Diagnosis	All Diagnoses	
ICD10 Diagnosis	N/A	
Place of Service	All Places of Service	

Tables

N/A

Definitions

Bladder tumor antigen (BTA) - A qualitative, point-of-care test used to identify human complement factor H-related protein shown to be produced by bladder cell lines but not other epithelial cell lines.

Florescence In Situ Hybridization (FISH) - A technique used to visualize nucleic acid sequences within cells by creating short sequences of fluorescently labeled single strand DNA called probes, which match target sequences. DNA probe technology is used to detect chromosomal abnormalities in voided urine and assist in bladder cancer detection and surveillance.

Nuclear Matrix Protein (NMP-22 Bladder Chek® test) - A urine assay for identifying patients possibly at risk for recurrent bladder cancer.

UroVysion® Bladder Cancer Kit - A urinary tumor marker used in conjunction with standard diagnostic procedures to aid in diagnosis or monitoring of bladder cancer.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

N/A

Key / Related Searchable Words

- Bladder Tumor Antigen (BTA)
- Fluorescence in situ hybridization (FISH)
- ImmunoCyt®
- NMP-22 Bladder Chek®

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Policy History

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

Effective Date	Action	Reason
12/7/2006	Policy Adopted - BCBSA MPP	Medical Policy Committee
1/7/2011	Policy title change from Urinary Tumor Markers for Bladder Cancer Policy revision with position change	Medical Policy Committee
1/21/2011	Coding Update	Administrative Review
3/13/2012	Coding Update	Administrative Review
10/5/2012	Policy revision with position change	Medical Policy Committee
12/14/2012	Policy revision with position change	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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