

# MEDICAL POLICY

| MEDICAL POLICY DETAILS |  |
|------------------------|--|
| Medical Policy Title   | URINARY TUMOR MARKERS FOR BLADDER CANCER   |
| Policy Number          | 2.02.12  |
| Category               | Technology Assessment  |
| Effective Date         | 10/18/01   |
| Revised Date           | 06/20/02, 12/20/12   |
| Archived Date          | 05/21/03-12/20/12, 10/17/13  |
| Edited Date            | 11/20/14, 09/17/15, 07/21/16, 07/20/17, 07/19/18, 07/18/19   |
| Product Disclaimer     | <ul style="list-style-type: none"> <li>• If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</li> <li>• If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</li> <li>• If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</li> </ul> |

## POLICY STATEMENT

Based upon our criteria and review of the peer-reviewed literature, the use of urinary tumor markers is considered **investigational** in the diagnosis of, monitoring, and/or screening for bladder cancer.

*Refer to Corporate Medical Policy #2.02.18 regarding Tumor Markers for the Diagnosis and Management of Cancer.*

*Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.*

## POLICY GUIDELINES

The Federal Employee Health benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

## DESCRIPTION

Bladder cancer (transitional cell carcinoma or TCC) typically presents as a tumor confined to the superficial mucosa of the bladder and is treated with transurethral resection. The only symptom of early bladder cancer is hematuria and confirmatory diagnosis of bladder cancer must be made by cystoscopic examination which is considered to be the “gold standard.” There is a 75% incidence of recurrence in these patients, and follow-up care includes surveillance cystoscopy and serial evaluations of urine cytology. While urine cytology is a specific test (90-100%), its sensitivity is lower (50-60%) and is considered even lower for low-grade tumors. Therefore, there has been interest in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

*Bladder Tumor Antigen (BTA) tests.* The *BTA stat*<sup>TM</sup> test is a single-step qualitative test performed on voided urine. It measures human complement factor H related proteins produced by several human bladder cell lines, but not by other epithelial cell lines. The *BTA TRAK*<sup>TM</sup> test provides a quantitative determination of the same protein. The BTA tests have an improved sensitivity compared to cytology, but lower specificities due to high false positive rates associated with recent instrumentation, stones, or inflammatory conditions such as benign prostatic hypertrophy (BPH).

*ImmunoCyt*<sup>TM</sup> test uses fluorescence immunohistochemistry using antibodies to a mucin glycoprotein and a carcinoembryonic antigen (CEA). These antigens are found on bladder tumor cells.

*Nuclear Matrix Protein (NMP-22)* is a quantitative test for tumor related proteins measured in urine. The NMP-22 assay measures nuclear matrix proteins that are involved in DNA replication and RNA synthesis during mitosis. NMP-22 is a protein associated with the nuclear mitotic apparatus. It is thought that this protein is released from the nuclei of tumor

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cells during apoptosis. Normally, only very low levels of NMP-22 can be detected in the urine, but elevated levels may be associated with bladder cancer. The specificity and sensitivity of NMP-22 are similar to BTA stat®.

*Fluorescence in situ hybridization (FISH) DNA* probe technology has 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 that match target sequences. The probes bind to complementary strands of DNA allowing for identification of the location of the chromosomes targeted. The sensitivity and specificity of the FISH assay are proposed to be higher than for the BTA tests.

These tests are proposed for use in conjunction with cystoscopy in the surveillance of patients for recurrent bladder cancer, but not intended to replace the procedure. The BTA, NMP-22 and FISH DNA probe technique tests have additionally been proposed as an initial test in patients with signs and symptoms suggestive of bladder cancer.

### **RATIONALE**

The Bard BTA Stat™ test received approval by the U.S. Food and Drug Administration (FDA) in 1995. The NMP-22 test kit received FDA approval in 1996. The NMP22 BladderChek kit (Matritech, Inc.) was approved by the FDA in 2002. The Vysis UroVysion Bladder Cancer Recurrence Kit was given 510K clearance for marketing by the FDA in August 2001 as a FISH test for monitoring tumor recurrence in conjunction with cystoscopy in patients previously diagnosed with bladder cancer. The FDA approved the ImmunoCyt™ test in February 2000. FDA clearance is only for monitoring bladder cancer recurrence in conjunction with cytology and cystoscopy. In January 2005 the UroVysion Bladder Cancer Kit (also a FISH test) was approved by the FDA for use in assisting in the detection of the initial diagnosis or recurrence of bladder cancer. FDA labeled indications for the UroVysion Bladder Cancer Kit specifies it 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. Results from the UroVysion Kit are intended for use, in conjunction with and in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.”

Published literature has provided data to permit conclusions on the safety and efficacy of the BTA Stat™, the NMP-22 and the AccuDx™ tests on health outcomes. Results of clinical studies indicate that the sensitivity of both BTA Stat™ and NMP-22 is superior to that of urinary cytology, which is considered the gold standard urinary marker for bladder cancer.

*BTA tests.* The sensitivity of the BTA stat™ test was evaluated in a study of 220 patients with confirmed bladder cancer. Overall sensitivity was 67%, ranging from 51% in those with bladder cancer stage Ta (noninvasive papillary) to 88% in those with higher stages. When categorized according to tumor grade, sensitivity ranged from 42% for those with grade I tumors to 83% for those with grade 3 tumors. A subset of 131 patients also had voided urine cytology performed on the same sample as the BTA. With the exception of those with carcinoma in situ, the BTA test was more sensitive than urine cytology. The combination of the two tests increased the sensitivity slightly compared to the BTA test alone. The most significant improvement was noted in those with carcinoma in situ, in which the sensitivity of the BTA alone was 53%, rising to 80% when combined with the results of cytology.

*NMP-22.* A study of 231 patients with a history of transitional cell cancer reports collected samples prior to a scheduled cystoscopic examination. Voided urine cytology was also performed in a subset of 200 of the patients. Using an NMP-22 cut off of 6.4 units/ml, the overall sensitivity compared to pathologic diagnosis was 68%. In contrast, the sensitivity of cytology was 31-40%, depending on the definition of a positive cytology examination.

*FISH Technology.* A comparison of cystoscopy with biopsy or tumor resection to urine cytology and FISH analysis in urine sample of 86 patients reported finding overall sensitivity of FISH to be 80.4% vs. 63.8% for urine cytology. Sensitivities reported by tumor grade 1, 2 and 3 were 53.3%, 83.3% and 100% for FISH and 25%, 66% and 94.7% for urine cytology, respectively. Two multicenter trials compared FISH to the BTA Stat® test and voided urine cytology. In the first study of 176 patients with known transitional cell carcinoma (TCC), sensitivities were 71% for FISH, 50% for BTA Stat® and 26% for cytology. In the second study of 275 healthy volunteers and patients with conditions other than TCC, the specificity of FISH was 94.5%.

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While the 2007 American Urological Association's best practices policy indicates that 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.

*ImmunoCyt™ immunohistochemical assay.* A multi-center study using the ImmunoCyt™ assay in 341 patients with a history of bladder cancer reported sensitivity and specificity similar to the other medically appropriate markers in this policy. Overall sensitivity was 81% and specificity was 75%. For most grades and stages of tumors, the ImmunoCyt™ assay was more sensitive than urine cytology. As with other markers for bladder cancer, the low specificity of this test (dealing with false-positive results) can be problematic.

Studies have been published with other potential tumor markers in bladder cancer. These potential new markers include: telomerase, soluble FAS, TATI (tumor-associated trypsin inhibitor), soluble e-cadherin, and BLCA-1 and BLCA-4 (bladder cancer specific biomarkers). Studies describing these markers generally involve limited numbers of patients. Therefore, additional studies are needed before their use would be considered medically appropriate. There have not been clinical trials to demonstrate if any of these markers can change the current role or frequency of cystoscopy in monitoring patients with bladder cancer. There are also limited studies that compare one marker to another.

The U.S. Preventive Services Task Force (USPSTF) concluded that tumor markers do not have a proven role in *screening of asymptomatic* persons for early detection of bladder cancer. The August 2011 USPSTF recommendation statement, Screening for Bladder Cancer, concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults.

In July 2012, the Blue Cross Blue Shield Association (BCBSA) re-evaluated the evidence on the use of urinary tumor markers with focus on whether clinical utility has been established. The BCBSA stated that "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. It was concluded that, due to continued lack of evidence of clinical utility, mixed support from clinical vetting and a lack of support of use from clinical practice guidelines, the evidence doesn't meet the current threshold for concluding that the use of the technology results in an improvement in health outcomes. Thus, use of urinary tumor markers for diagnosing, monitoring and/or screening for bladder cancer is considered investigational".

### CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

#### CPT Codes

| Code        | Description   |
|-------------|---|
| 86294 (E/I) | Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)  |
| 86386 (E/I) | Nuclear Matrix Protein 22 (NMP22), qualitative  |
| 88120 (E/I) | Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual |
| 88121 (E/I) | Using computer-assisted technology  |

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| <b>Code</b> | <b>Description</b>   |
|-------------|--|
| 88367 *     | Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), using computer-assisted technology, per specimen; initial single probe stain procedure (*with 188.0-188.9, 233.7, 239.4,599.7, V10.51, C67.0-C67.9, D09.0, D49.4, R31.0-R31.9, Z85.51) <b>(E/I for listed diagnosis codes)</b>  |
| 88368       | Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each additional single probe stain procedure (List separately in addition to code for primary procedure) (*with 188.0-188.9, 233.7, 239.4,599.7, V10.51, C67.0-C67.9, D09.0, D49.4, R31.0-R31.9, Z85.51) <b>(E/I for listed diagnosis codes)</b> |

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**HCPCS Codes**

| <b>Code</b> | <b>Description</b> |
|-------------|--------------------|
| No codes    |                    |

**ICD10 Codes**

| <b>Code</b> | <b>Description</b>                                |
|-------------|---|
| C67.0-C67.9 | Malignant neoplasm of bladder (code range)        |
| D09.0       | Carcinoma in situ of bladder                      |
| D49.4       | Neoplasm of unspecified behavior of bladder       |
| R31.0-R31.9 | Hematuria (code range)                            |
| Z85.51      | Personal history of malignant neoplasm of bladder |

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\*Key Article

### **KEY WORDS**

Bladder tumor antigen, BTA, Fibrin/fibrinogen degradation (FDP), ImmunoCyt, NMP-22.

### **CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Urinary Markers for Bladder Cancer.