Urinary Tumor Markers for Bladder Cancer

Description

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.

Background

Urinary bladder carcinoma, 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 common symptom of early bladder cancer is hematuria; however, urinary tract symptoms (i.e., urinary frequency, urgency, and dysuria) may also occur.

For patients with hematuria, American Urological Association (AUA) 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 must be made by cystoscopic examination, considered to be the criterion standard, 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, with or without intravesical therapy, depending on depth of invasion and tumor grade. However, a 50%-75% 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 3 months for 1 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 90–100%), its sensitivity is lower, ranging from 50–60% 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.

Tests cleared by the U.S. Food and Drug Administration (FDA)
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.

In addition to the FDA-cleared tests, clinical laboratories that meet Clinical Laboratory Improvement Act standards are marketing urine-based tests. For example, Predictive Biosciences (Lexington, MA) markets a test, called CertNDx™, to assess Fibroblast Growth Factor Receptor 3 (FGFR3) mutations. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. FGFR3 mutations may be associated with lower-grade bladder tumors that have a good prognosis. In addition, Pacific Edge (New Zealand) is marketing a test in the U.S. called Cxbladder™, which tests for 5 urine-based markers.

Other urinary markers

A number of other urinary tumor markers, not currently commercially available in the United States, are under investigation. These include:

- BLCA-1 and BCLA-4;
- Hyaluronic acid and hyaluronidase;
- Lewis X antigen;
• Microsatellite markers;
• Soluble Fas;
• Survivin (can be isolated from urine and also from tumor samples);
• Telomerase;
• Cytokeratin 8, 18, 19, 20
• Quancyt

Regulatory Status

Urinary tumor marker tests cleared by the U.S. Food and Drug Administration (FDA) and are in clinical use. These tests are:

• The quantitative BTA TRAK® and the qualitative point-of-care BTA (bladder tumor antigen) stat® test, both by Polymedco Inc., Cortlandt Manor, NY.
• The quantitative immunoassay NMP22® and the qualitative, point-of-care test NMP22® BladderChek®, both by Matritech Inc., Newton, MA.
• The UroVysion® Bladder Cancer Kit (Vysis Inc., Downers Grove, IL), a FISH test.
• The ImmunoCyt™ test, also marketed as UCyt+™ (DiagnoCure Inc., Quebec).

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.

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Initial diagnosis

The following urinary bladder tumor markers may be considered medically necessary 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*;

The following urinary bladder tumor marker is considered investigational in the diagnosis of bladder cancer:

• IMMUNOCYT
Bladder cancer monitoring

The following urinary bladder cancer tumor markers may be considered medically necessary as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

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

Bladder cancer screening

The use of urinary tumor markers to screen asymptomatic individuals is considered not medically necessary.

* FDA Approved indications

Rationale

Technical performance

All of the Food and Drug Administration (FDA)-approved tests for urinary tumor markers involve the use of standard laboratory procedures.

Diagnostic performance

Urinary bladder tumor markers [i.e. BTA (bladder tumor antigen) STAT, NMP22 (nuclear matrix protein 22), UroVysion and Immunocyt]

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 criterion standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared to combinations of markers.

There are a number of diagnostic accuracy studies evaluating urinary tumor markers, as well as systematic reviews of these studies. 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 and/or monitoring of recurrence. (1) Selected information from the article is reported in the table below. (Diagnostic accuracy was not reported separately for initial diagnosis versus cancer monitoring).
In 2010, The U.K. Health Technology Assessment Program published a systematic review of studies on the diagnostic performance of the urine biomarkers. (2) The review included 71 studies on the test performance of cytology and urine biomarkers. A majority of the studies included patients both with and without a history of bladder cancer, or included only patients with a history of bladder cancer. Few studies were identified that focused on the evaluation of urinary markers for the initial diagnosis of bladder cancer. Pooled analysis of study findings combined results of tests used for initial diagnosing of bladder cancer and tests used to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard. Results of pooled patient-level analyses are:

<table>
<thead>
<tr>
<th>No. studies</th>
<th>12</th>
<th>8</th>
<th>28</th>
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<tr>
<td>No. patients</td>
<td>3,101</td>
<td>3,041</td>
<td>10,565</td>
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<tr>
<td>Sensitivity % (95% CI)</td>
<td>76 (65-84)</td>
<td>84 (77-91)</td>
<td>68 (62-74)</td>
</tr>
<tr>
<td>Specificity % (95% CI)</td>
<td>85 (78-92)</td>
<td>75 (68-83)</td>
<td>79 (74-84)</td>
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A 2014 meta-analysis by Guo et al focused on the diagnostic accuracy of BTA stat. (3) The authors identified 13 studies comparing BTA stat and cytology. Studies were published between 1998 and 2006 and included a total of 3462 patients. Findings were similar to previous meta-analyses. In pooled analyses, BTA stat had a higher sensitivity than cytology but lower specificity (see Table 3).

### Table 3. Results of Pooled Analyses in Guo et al (2014)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BTA stat</th>
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<tbody>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>67 (64 to 69)</td>
<td>43 (40 to 46)</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>75 (73 to 77)</td>
<td>97 (96 to 98)</td>
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Representative studies focusing on the diagnostic accuracy of urinary tumor markers for the initial detection of bladder cancer are described below:

In 2013, Todenhöfer and colleagues published a prospective study including 2113 individuals suspected of having bladder cancer. (4) All patients underwent cystoscopy and upper urinary tract imaging, and urine samples were analyzed. A total of 502 (24%) of patients were found to have bladder
cancer. The sensitivities of cytology, FISH and UCyt+ (also known as ImmunoCyt) for detecting bladder cancer were 80%, 69% and 72%, respectively. Specificities were 83%, 83% and 79%, respectively.

In a related study, in 2014, Todenhofer et al published findings of a study conducted with 483 patients who were undergoing surveillance for nonmuscle invasive bladder cancer. Patients underwent cystoscopy and imaging of the upper urinary tract (UUT). Urine samples were taken before cystoscopy and tested for urine tumor markers. Performance of individual markers and combinations of markers was evaluated. Test combinations with the highest overall accuracy were cytology and FISH, cytology and uCyt, and FISH and uCyt. When positivity was defined by having at least 1 positive marker, sensitivities ranged from 80.5% to 86.7%, and specificities ranged from 56.5% to 64.2. When both markers needed to be positive, sensitivities for these 2-marker combinations ranged from 51.6% to 63.3%, and specificity ranged from 80.8% to 86.2%.

A prospective study by Kamat and colleagues evaluated the accuracy of 5 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 NMP22; cystoscopy and Urovysion; and 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 NMP22 test was positive. After an initial evaluation, patients were followed with routine cystoscopy every 3-6 months. For patients with a negative cystoscopy at baseline and in whom a tumor was detected at the first follow-up (ie, 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 NMP22, 30 of 43 (70%) positives with cystoscopy and Urovysion, 14 of 27 (52%) positives with cystoscopy and cytology, and 6 of 19 (32%) positives with cystoscopy and NMP22, followed by Urovysion if the NMP22 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.

Section Summary: Numerous studies have evaluated the accuracy of the urinary tumor markers BTA STAT, NMP22, UroVysion and ImmunoCyt for diagnosing and/or monitoring bladder cancer. Several systematic reviews of these studies have been published. In studies on the initial diagnosis of bladder cancer and/or detection of recurrent bladder cancer, urinary tumor markers tend to have higher sensitivity but not higher specificity than cytology. Combining tumor markers with cytology can improve overall diagnostic accuracy.

Urinary Bladder Tumor Markers For Detecting Upper Urinary Tract (UUT) Tract Disease In Patients With A History Of Bladder Cancer And A Negative Cystoscopy

No studies were identified that specifically addressed the diagnostic accuracy of urinary tumor markers for diagnosing upper urinary tract (UUT) cancers in patients with a history of bladder cancer. Several studies have addressed the accuracy of urinary tumor markers for diagnosing UUT diseases. However,
the populations included in this study were either patients with suspected disease or a mixed group of patients with suspected disease and a history of bladder cancer or UUT cancer. For example, Lodde et al in Austria evaluated the accuracy of Immunocyt for detecting upper urinary tract transitional cell carcinoma (UT-TTC). (7) The study included 37 patients with signs or symptoms suggestive of UT-TCC; 14 patients (38%) had a history of bladder cancer. Sixteen of 37 patients (43%) were found to have UT-TCC. All patients also underwent cystoscopy, renal ultrasonography and intravenous excretory urography. Using voided urine samples, Immunocyt had 75% sensitivity and 95% specificity for identifying UT-TCC. This compares to a sensitivity of 50% and specificity of 100% for cytology. Using ureteral urine samples, Immunocyt had a sensitivity of 91% and cytology had a sensitivity of 82%. Both tests had 100% specificity using ureteral urine. The combination of Immunocyt and cytology had a sensitivity of 88% in voided urine samples and a sensitivity of 100% in ureteral urine. In 2011, Xu et al in China reported on the diagnostic accuracy of UroVysion FISH for detecting upper tract urothelial carcinoma. (8) The study included urine specimens from 85 patients suspected of having upper urinary tract disease. Patients underwent cystoscopy after urine collection. Seventeen patients (20%) had a history of UT urothelial carcinoma and 8 (9%) had a history of bladder cancer. The remaining patients had signs or symptoms of disease such as hematuria. The sensitivity of FISH for diagnosing UT carcinoma was 79% and the sensitivity of cytology was 45%. Specificity was 98% for FISH and 100% for cytology. When findings from cytology and FISH were combined, the sensitivity was 86% and the specificity was 98%. Neither study separately reported findings for detection of recurrence in patients with a history of urinary tract cancer, or for patients with a negative cystoscopy.

In 2012, Picozzi and colleagues published a systematic review of studies that reported data related to upper urinary tract recurrence following radical cystectomy for bladder cancer. (9) Upper tract recurrence was defined as any documented recurrence in the renal collecting system or ureter. The authors identified 27 studies with a total of 13,185 participants. The overall prevalence of UT in the studies ranged from 0.75% to 6.4% and, among the cancers detected, 64.6% were advanced and 35.6% were metastatic. The Picozzi review also reported on the diagnostic yield of protocols used to follow patients after treatment for bladder cancer. As reported in the review, in 14 studies, 63 of 166 patients (38%) with upper urinary tract recurrence were identified by follow-up investigations and in the remaining 103 (62%) of patients, diagnosis was based on symptoms. In 9 studies that used urine cytology, 10 of 112 (9%) patients with recurrence were identified by positive cytology. In 13 studies that used upper tract imaging, 40 of 161 (25%) patients with recurrence were identified by imaging. Put another way, approximately 2,000 urine cytology examinations or 800 radiological examinations were performed to identify 1 patient with UT recurrence. The authors stated that they were not able to determine whether there was a survival advantage in patients whose tumors were identified by cytology or UT imaging compared to symptoms because the data on this subject were poor. The Picozzi review did not discuss the use of urinary tumor markers for diagnosis of UUT recurrence.

Section Summary: No studies were identified that focused specifically on the use of urinary tumor markers for detecting UUT recurrences in patients with a history of bladder cancer. Several studies have evaluated urinary tumor markers for detecting UUT disease in samples of patients both with and without a history of urinary carcinoma. Available studies generally found that urinary tumor markers had higher sensitivity but not higher specificity than cytology, and combining urinary markers and cytology improved diagnostic accuracy.
FGFR3 (Fibroblast Growth Factor Receptor 3) mutations

Several studies have evaluated urine-based assays for identifying FGFR3 mutations. A 2012 study was published by Fernandez et al; several authors were employees of Predictive Biosciences, the manufacturer of the CertNDx test. (10) 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 5/48 (10%) and a specificity of 258/268 (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 (44/48) and 51% specificity (136/268) for detecting cancer recurrence.

In a retrospective study, Rieger-Christ and colleagues compared the accuracy of FGFR3 mutation analysis, cytology and the combination of the two in identifying bladder tumors. (11) 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 before 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 62/72 (86%) in the TURB group and 62/120 (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 have 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. An study published in 2010 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. (12) 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 26/45 (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, an FGFR3-positive urine was associated with a 3.8-fold higher risk of having a recurrence (p<0.0001). Another study by this research team was published in 2012. (13) A total of 716 urine samples were collected from 136 patients with non-muscle invasive bladder cancer (at least 3 samples per patient were required for study entry. During a median of 3 years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity of FGFR3 for detecting a recurrence was 201/408 (49%) and 124/187 (66%), respectively. In comparison, the sensitivity of cytology was 211/377 (56%) and the specificity was 106/185 (57%). Combining FGFR3 and cytology increased sensitivity to 76% but lowered specificity to 42%.
Other Urinary Bladder Tumor Markers

Most of the published studies evaluating other potential tumor markers have included small numbers of patients and were preliminary investigations. Examples include a study by Passerotti et al. (14) on urinary hyaluronate, a study by Abd El-Hakim on surviving (15) and a study by Li et al. (16) on the cytokeratin 20 test. One meta-analysis was identified. This was a 2012 meta-analysis by Ku et al that examined literature on urine survivin as a marker for diagnosing bladder cancer and used cystoscopy and/or histopathology as a reference standard. (17) The investigators 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 preplanned subgroup analysis comparing the diagnostic accuracy of survivin and cytology, a pooled analysis of data from 6 studies found that surviving 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.

Section Summary: Studies have evaluated various other potential urinary tumor markers but there is insufficient evidence on the diagnostic accuracy of any particular marker.

Impact Of Urinary Tumor Marker Tests 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. (18)

No controlled 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 using the NMP22 test on the decision to refer for cystoscopy and concluded that the marker did not aid clinical decision making in most cases. (19) The study included 2,222 patients with nonmuscle-invasive bladder cancer and negative cytology, at various stages of surveillance. (Patients with positive urinary cytology were excluded, because 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. NMP22 level was found to be significantly associated with both disease recurrence and progression (p<0.001 for both).

In the analysis, the clinical net benefit of the NMP22 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 NMP22 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 NMP22, 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%, NMP22 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.

A 2013 study by Kim et al examined data on the FISH test with the aim of determining whether the urinary marker could modify the surveillance cystoscopy. (20) The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every 3 to 6 months. A total of 243 patients who met the above criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy 2 to 6 months after reflex FISH. The cystoscopy was positive in 17 (7%) patients. FISH results were not significantly associated with the results of the next cystoscopy (odds ratio [OR] = 0.84, 95% CI, 0.26 to 2.74, p=1.0). Because of this lack of short-term association between FISH results and cystoscopy, the authors concluded that FISH has limited ability to modify the surveillance schedule in nonmuscle invasive bladder cancer.

Section Summary: There is a lack of evidence that health outcomes are improved in patients managed with urinary tumor marker tests compared to those managed without tumor marker tests and a lack of direct evidence that cystoscopy protocols can be changed when urinary tumor marker tests are used. The available studies have found low potential clinical benefit of urinary tumor marker testing for patients with nonmuscle invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

Urinary markers for screening asymptomatic individuals for bladder cancer

The ideal study for evaluating the effectiveness of a screening program is a randomized controlled trial (RCT) comparing outcomes in patients who did and did not participate in a screening program. In 2010, the U.S. Preventive Services Task Force (USPSTF) published an updated evidence review on screening adults for bladder cancer. (21) The quality of direct evidence that screening for bladder cancer reduces morbidity or mortality was poor. There were no RCTs, and only one prospective study, which were 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."

Several uncontrolled studies evaluating screening protocols have been published. In 2013, Bangma et al reported on a population-based program with men in The Netherlands. (22) The purpose of the study was to evaluate the feasibility of screening using urine-based markers and to examine performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least one positive home hematuria test underwent screening for 4 urine-based
molecular markers. Men with at least 1 positive urine-based test were recommended to undergo cystoscopy. Out of 6500 men invited to participate in screening, 1984 (30.5%) agreed and 1747 (88.1%) underwent hematuria testing. Of these, 409 (23.4%) tested positive for hematuria and 385 (94%) underwent urine-based marker testing. The number of men testing positive for each marker was 14 (3.6%) for NMP22, 33 (8.6%) for microsatellite analysis, 6 (1.6%) for FGFR3, and 40 (10.4%) for CH3. Cystoscopy was recommended for 75 men, and 71 actually underwent cystoscopy. Cancer was diagnosed in 4 of 1747 men who underwent screening (3 bladder cancers and 1 kidney cancer). Although men in the study who tested negative on screening tests did not receive further testing, the investigators were able to link participants’ data to a Dutch cancer registry data. They determined that 2 cancers (1 bladder cancer and 1 kidney cancer) had been diagnosed in men who completed the protocol; these were considered to be false negatives. Considering these data, the sensitivity of any urine-based marker was 80% (95% CI, 28.4-99.5) and the specificity was 95.9% (95% CI, 94.9 to 96.8). The sensitivity and specificity of the FDA-approved NMP22 test was 25% (95% CI, 0.63 to 80.6) and 96.6% (95% CI, 94.2 to 98.2). The screening program had low diagnostic yield.

In 2009, Lotan et al published a prospective study in which 1,502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure were screened. The study used the NMP22 BladderChek test and was supported by 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 retested; 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 1502 participants had a positive BladderChek test. Two of the 85 patients were found to have bladder cancer (noninvasive), yielding a positive predictive value of 2.4%. There was also 1 case of atypia. Follow-up at a mean of 12 months was obtained for 1309 of 1502 (87%) screened patients. 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 1 cm. Because 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 (eg, sensitivity) cannot be calculated.

Section Summary: There are no RCTs evaluating the impact of screening for bladder cancer on health outcomes in asymptomatic individuals. There is also insufficient observational evidence on the diagnostic accuracy of urinary tumor markers used to screen asymptomatic individuals for bladder cancer.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) 2015 bladder cancer guideline included the following statement regarding monitoring patients with high-grade bladder tumors:
“…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 nonmuscle invasive bladder tumors. Therefore, the NCCN Bladder Cancer panel members consider this a category 2B recommendation.” (24)

National Academy of Clinical Biochemistry Laboratory Medicine
The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend use of any Food and Drug Administration (FDA)–approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients. (25) 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.”

American Urological Association
The American Urological Association’s 2007 guideline 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 nonmuscle invasive bladder cancer.”(26)

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force concluded in 2011 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. (27)

Summary
Numerous well-designed studies evaluated the diagnostic performance of the FDA-approved urinary tumor markers. Overall, studies found reasonable sensitivities and specificities, and a recent study found that one or two of these urinary tumor markers can enhance the sensitivity of urinary cytology. 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.

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, and thus these 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, use of urinary tumor markers to screen asymptomatic individuals is considered not medically necessary.

Medicare National Coverage

No Medicare national coverage determination.

References


Policy History

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<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, policy statement unchanged.</td>
</tr>
</tbody>
</table>

Keywords

Bladder Tumor Antigen
BTA Test
FISH, Bladder Cancer Testing
ImmunoCyt
NMP-22
Tumor Marker, Bladder Cancer
UroVysion
BTA Stat

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on File

Deborah M. Smith, MD, MPH