Urinary Tumor Markers for Bladder Cancer
Archived Medical Policy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Initial Diagnosis
Based on review of available data, the Company may consider the use of any of the following bladder tumor markers to be eligible for coverage 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 BladderChek®;
- UroVysion®

Bladder Cancer Monitoring
Based on review of available data, the Company may consider the use of any of the following bladder tumor markers to be eligible for coverage when used as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures:

- BTA-Stat, BTA-TRAK;
- ImmunoCyt™;
- NMP22, NMP22 BladderChek;
- UroVysion

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Initial Diagnosis
Based on review of available data, the Company considers the use of the ImmunoCyt urinary bladder tumor marker in the diagnosis of bladder cancer to be investigational.*
Screening for bladder cancer in asymptomatic persons
Based on review of available data, the Company considers the use of urinary bladder tumor markers for screening for bladder cancer in asymptomatic persons to be investigational.*

Based on review of available data, the Company considers the use of all other bladder cancer tumor markers in the diagnosis, monitoring, or screening for bladder cancer to be investigational.*

Background/Overview
The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Moreover, bladder cancer has a very high frequency of recurrence and therefore requires follow-up cystoscopies, along with urine cytology, as periodic surveillance to identify recurrence early. Consequently, urine biomarkers that might be used to either supplement or supplant these tests have been actively investigated.

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; however, urinary tract symptoms (i.e., 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. Confirmatory diagnosis of bladder cancer must be made by cystoscopic examination, which is considered to be the gold 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 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.
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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.

The following table reflects the sensitivities and specificities of urine tumor markers in bladder cancer as reported in various publications.

| Commercially available marker | Sensitivity (%) mean / range | Specificity (%) mean / range |
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<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>48 / 16 - 89</td>
<td>96 / 81 - 100</td>
</tr>
<tr>
<td>Hematuria Dipstick</td>
<td>68 / 40 - 93</td>
<td>68 / 51 - 97</td>
</tr>
<tr>
<td>BTA-Stat</td>
<td>68 / 53 - 89</td>
<td>74 / 54 - 93</td>
</tr>
<tr>
<td>BTA-TRAK</td>
<td>61 / 17 - 78</td>
<td>71 / 51 - 89</td>
</tr>
<tr>
<td>NMP22</td>
<td>75 / 32 - 92</td>
<td>75 / 51 - 94</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td>55.7</td>
<td>85.7</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>74 / 39 - 100</td>
<td>80 / 73 - 84</td>
</tr>
<tr>
<td>UroVysion</td>
<td>77 / 73 - 81</td>
<td>98 / 96 - 100</td>
</tr>
</tbody>
</table>

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
As of March 2010, 6 urinary tumor marker tests have been 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.

Centers for Medicare and Medicaid Services (CMS)
No Medicare national coverage determination.

Rationale/Source
The discussion below focuses on the fundamental attributes of any diagnostic test: technical performance; diagnostic performance (sensitivity, specificity, positive and negative predictive values) compared to a gold standard; and data demonstrating how the results of the test can be used to benefit patient outcomes.

1. Technical performance
All of the FDA-approved tests for urinary tumor markers involve the use of standard laboratory procedures.
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2. Diagnostic performance
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:

<table>
<thead>
<tr>
<th>Marker</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>12</td>
<td>3,101</td>
<td>76 (65-84)</td>
<td>85 (78-92)</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>8</td>
<td>3,041</td>
<td>84 (77-91)</td>
<td>75 (68-83)</td>
</tr>
<tr>
<td>NMP22</td>
<td>28</td>
<td>10,565</td>
<td>68 (62-74)</td>
<td>79 (74-84)</td>
</tr>
</tbody>
</table>

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%; T1 (n=171), 38%; T2-3 (n=7), 1.6%; carcinoma in situ (CIS; n=15), 3.4%; and classification unknown (n=37), 8.3%. A majority of patients (n=327, 67%) had no prior history of intravesical instillation treatments; 97 patients (20%) had past (at least 3 months from the last) instillation (Group B); 66 patients (14%) had present instillations. Patients with missing instillation information (n=9) and patients with urine infection (n=6) 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%)
- In the remaining 368 patients, 96 (26.1%) had a positive BTA test result
An additional 9 (16.4%) recurrences were detected at further examinations. The overall sensitivities were 56.0% and 19.2%, and specificities were 85.7% and 98.3% 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% 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 3 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%, 50%, and 26% 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:

<table>
<thead>
<tr>
<th>Single Tests</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>84</td>
<td>62</td>
</tr>
<tr>
<td>NMP22</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>UroVysion</td>
<td>76</td>
<td>63</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination of 2 Tests</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology + NMP22</td>
<td>93</td>
<td>34</td>
</tr>
<tr>
<td>Cytology + UroVysion</td>
<td>87</td>
<td>54</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Combination of Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology + ImmunoCyt</td>
<td>93</td>
<td>56</td>
</tr>
<tr>
<td>NMP22 + UroVysion</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>NMP22 + ImmunoCyt</td>
<td>91</td>
<td>38</td>
</tr>
<tr>
<td>UroVysion + ImmunoCyt</td>
<td>93</td>
<td>53</td>
</tr>
</tbody>
</table>

Combination of 3 Tests

<table>
<thead>
<tr>
<th>Combination</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology, NMP22 and UroVysion</td>
<td>96</td>
<td>28</td>
</tr>
<tr>
<td>Cytology, NMP22 and ImmunoCyt</td>
<td>98</td>
<td>31</td>
</tr>
<tr>
<td>Cytology, UroVysion and ImmunoCyt</td>
<td>93</td>
<td>49</td>
</tr>
<tr>
<td>UroVysion, ImmunoCyt and NMP22</td>
<td>98</td>
<td>32</td>
</tr>
</tbody>
</table>

Combination of all 4 tests | 98 | 31 |

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 were similar to previous studies. All combinations of two tests increased the sensitivity. Sensitivities varied from 94%, with a combination of cytology and NMP22, to 87% 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% and a specificity of 56%. Combining three tests increased the sensitivity even further. Two combinations attained a sensitivity of 98%, NMP22 and ImmunoCyt combined with either cytology or UroVysion. Specificity of these combinations was low, 31%-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 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, 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 and 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, described above, 56%. The combined sensitivity was lower than in the Horstmann study (93%), 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%. 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. Other authors comment 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 Fas, tumor-associated trypsin inhibitor (TATI), soluble e-cadherin, bladder cancer specific biomarkers BLCA-1 and BLCA-4, cytokeratins 8 18 19 and 20, surviving, 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 on potential new tumor markers comments that bladder cancer tumor markers is a rapidly evolving field in which new markers are constantly identified. The review concludes, “1) there exists a dizzying number of markers identified using newer expertise, and 2) 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. 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
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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%) 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 a 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%. 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 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% of the sample was recruited from a Veterans Administration hospital and 1175 (78%) 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 10-year or greater smoking history, and 513 had a greater than 15-year occupational exposure. Approximately
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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 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%) of the 1502 participants had a positive 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 1309 of 1502 (87%) 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 1cm. 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% 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.

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 1 or 2 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 eligible for coverage 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
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Asymptomatic individuals. Thus, urinary tumor markers to screen asymptomatic individuals is considered investigational.

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>86294, 86316, 88120, 88121, 88271, 88367, 88368</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No Code</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>188.0 thru 188.9, 233.7, 239.4, 599.7, V10.51</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No Code</td>
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</table>

Policy History

Policy History

<table>
<thead>
<tr>
<th>Original Effective Date: 09/18/2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/18/2002 Managed Care Advisory Council approval</td>
</tr>
<tr>
<td>12/07/2004 Medical Director review</td>
</tr>
<tr>
<td>12/14/2004 Medical Policy Committee Review. Format revision - Rationale and source added to policy.</td>
</tr>
<tr>
<td>01/31/2005 Policy archived. Managed Care Advisory Council approval. Archived.</td>
</tr>
<tr>
<td>03/05/2010 Medical Policy Committee approval</td>
</tr>
<tr>
<td>03/19/2010 Medical Policy Implementation Committee approval. Returned to active status.</td>
</tr>
<tr>
<td>03/03/2011 Medical Policy Committee review</td>
</tr>
<tr>
<td>03/16/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
</tr>
<tr>
<td>05/05/2011 Medical Policy Committee review</td>
</tr>
<tr>
<td>05/18/2011 Medical Policy Implementation Committee approval. Archived policy.</td>
</tr>
<tr>
<td>Next Scheduled Review Date: Archived</td>
</tr>
</tbody>
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Urinary Tumor Markers for Bladder Cancer

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified. Claims processing edits based on the medical policy will be removed at the time a medical policy is changed to archived status.

Policy # 00129
Original Effective Date: 09/18/2002
Archived Date: 01/31/2005
Returned to Active Status: 03/19/2010
Archived Date: 05/18/2011

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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