FEP Medical Policy Manual

FEP 2.04.07 Urinary Biomarkers for Cancer Diagnosis and Surveillance

Effective Policy Date: April 1, 2020

Original Policy Date: December 2011

Related Policies:
None

Urinary Biomarkers for Cancer Diagnosis and Surveillance

Description
The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. 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 supplement or supplant these tests have been actively investigated.

OBJECTIVE
The objective of this evidence review is to evaluate whether the diagnostic use of urinary tumor markers improves the net health outcome for patients with suspected or history of bladder cancer.

POLICY STATEMENT
The use of urinary tumor markers is considered not medically necessary in the diagnosis of, and monitoring for bladder cancer.

POLICY GUIDELINES
None

BENEFIT APPLICATION
Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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FDA REGULATORY STATUS

Table 1 lists urinary tumor marker tests approved or cleared for marketing by the FDA. The FDA-approved or cleared tests are indicated as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer or surveillance of bladder cancer patients.

**Table 1. FDA-Approved or -Cleared Urinary Tumor Marker Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Detection</th>
<th>Indication</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat</td>
<td>Polymedco</td>
<td>Point of care immunoassay</td>
<td>Human complement factor H-related protein</td>
<td>Qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer</td>
<td>510(k)</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>Polymedco</td>
<td>Reference laboratory immunoassay</td>
<td>Human complement factor H-related protein</td>
<td>Quantitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer</td>
<td>510(k)</td>
</tr>
<tr>
<td>Alere NMP22</td>
<td>Alere</td>
<td>Immunoassay</td>
<td>NMP22 protein</td>
<td>In vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy</td>
<td>Premarket Approval (PMA)</td>
</tr>
<tr>
<td>BladderChek</td>
<td>Alere</td>
<td>Point of care immunoassay</td>
<td>NMP22 protein</td>
<td>Adjunct to cystoscopy in patients at risk for bladder cancer</td>
<td>PMA</td>
</tr>
<tr>
<td>UroVysion</td>
<td>Abbott Molecular</td>
<td>FISH⁸</td>
<td>Cell-based chromosomal abnormalities</td>
<td>Aid in the initial diagnosis of bladder cancer (P030052) and monitoring patients with previously diagnosed bladder cancer (K033982)</td>
<td>PMA</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein.

⁸ FISH is a molecular cytogenetic technology that can be used with either DNA or RNA probes to detect chromosomal abnormalities. DNA FISH probe technology involves the creation of short sequences of fluorescently labeled, single-strand DNA probes that match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Urine-based tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. Laboratory-developed tests include:

- CxBladder Monitor (Pacific Edge) measures the expression of 5 genes (MDK, HOXA13, CDC2, IGFBP5, CXCR2). Pacific Edge also has CxBladder Detect and CxBladder Triage tests.
- Xpert Bladder Cancer Monitor (Cepheid) measures mRNA (ABL1, CRH, IGF2, UPK1B, ANXA10) in voided urine by rtPCR.
- PolypDx™ (Metabolomic Technologies) is a urine metabolite assay that uses liquid chromatography-mass spectrometry. An algorithm compares urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.

**RATIONALE**

**Summary of Evidence**

For individuals who have signs and/or symptoms of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. The relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have a sensitivity ranging from 47% to
85% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a history of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies, meta-analyses, as well as a decision curve analysis and a retrospective study examining the clinical utility of urinary tumor marker tests. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. The diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 46% to 84% and pooled specificity ranging from 71% to 91%. The decision analysis found only a small clinical benefit for use of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies using the preferred trial design to evaluate clinical utility were identified; ie, controlled studies prospectively evaluating health outcomes in patients managed with and without the use of urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A 2010 systematic review (conducted for the U.S. Preventive Services Task Force) did not identify any RCTs, the preferred trial design to evaluate the impact of population-based screening and found only 1 prospective study that the Task Force rated as poor quality. A more recent retrospective study, assessing a population-based screening program in the Netherlands, reported low diagnostic yield. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at a population-level risk of colon cancer who receive urinary tests for precancerous polyps, the evidence includes a validation study. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A urine metabolite assay for adenomatous polyps is at a very early stage of development, with a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v.4.2019) bladder cancer guidelines include consideration for urinary urothelial tumor markers every 3 months along with urine cytology for the first 2 years of follow-up for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation). The guidelines include the following statement: "Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumors may be considered during surveillance of high-risk non-muscle-invasive bladder cancer. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors.”

American Urological Association et al

The guidelines from the American Urological Association and Society of Urologic Oncology (2016) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review completed by the Agency for Health Care Research and Quality. Table 2 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

Table 2. Guidelines for Urine Tumor Markers After the Diagnosis of Bladder Cancer

<table>
<thead>
<tr>
<th>Guidance Statement</th>
<th>SOR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>&quot;In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation.”</td>
<td>Strong</td>
<td>B</td>
</tr>
<tr>
<td>&quot;In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance.”</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>&quot;In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion FISH) and adjudicate equivocal cytology (UroVysion FISH and ImmunoCyt™).”</td>
<td>Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

The 2012 guidelines from the American Urological Association (reviewed and affirmed in 2016) on the evaluation of microscopic hematuria recommended cystoscopic evaluation for the following individuals:

- Individuals who are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a validation study. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A urine metabolite assay for adenomatous polyps is at a very early stage of development, with a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine the effects of the technology on health outcomes.

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- Older than age 40 with microscopic hematuria; and
- Younger than age 40 with microscopic hematuria and risk factors for developing bladder cancer.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2011) concluded that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was based on insufficient evidence (grade I).

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE

ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>June 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review, policy statement unchanged.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review. Policy statement unchanged. References 4, 23, &amp; 25 added; others renumbered or removed.</td>
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<tr>
<td>October 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 9, 2018; references 1, 8, 11-12, and 20 added; some references removed. Urinary bladder cancer tumor markers as an adjunct in the monitoring of bladder cancer changed from “medically necessary” to “not medically necessary”. Title changed to “Urinary Biomarkers for Cancer Diagnosis and Surveillance.”</td>
</tr>
<tr>
<td>March 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 4, 2018; references 5-6 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>March 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 30, 2019; no references added. Title revised to remove “screening” as policy does not address due to screening benefit language. Policy statement unchanged.</td>
</tr>
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