This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<tr>
<td>• With signs and/or symptoms of bladder</td>
<td>• Urinary tumor marker tests</td>
<td>• Cytology</td>
<td>• Overall survival</td>
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<td>• Cystoscopy</td>
<td>• Disease-specific survival</td>
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</tr>
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<td>• Who are asymptomatic and at a population-</td>
<td>• Urinary tumor marker tests</td>
<td>• Standard surveillance without</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>level risk of bladder cancer</td>
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<td>testing</td>
<td>• Disease-specific survival</td>
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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.

Summary of Evidence

For individuals who have signs and/or symptoms of bladder cancer or a history of bladder cancer who receive urinary tumor marker tests, the evidence includes a number of diagnostic accuracy studies, meta-analyses, as well as a decision curve analysis and retrospective study examining the clinical utility of urinary tumor marker tests. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource
utilization. The diagnostic accuracy studies found that urinary tumor marker tests tend to have higher sensitivity but lower or similar specificity than cytology. Also, they found that combining tumor marker tests with cytology can improve overall diagnostic accuracy. 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; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without 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. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The 2010 systematic review (conducted for the U.S. Preventive Services Task Force [USPSTF]) did not identify any randomized controlled trials, the preferred trial design to evaluate the impact of population-based screening, and found only one prospective study that USPSTF 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.

Policy

The use of urinary tumor markers is considered investigational in the diagnosis of, monitoring, and/or screening for bladder cancer.

Policy Guidelines

For the purpose of this protocol, standard diagnostic procedures for bladder cancer consist of urine cytology and cystoscopy, with or without biopsy.

The BTA (bladder tumor antigen) stat® and nuclear matrix protein 22 (NMP22) are immunoassay tests.

Background

Urinary Bladder Cancer

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

Diagnosis

The 2012 guidelines from the American Urological Association on the evaluation of microscopic hematuria, which were reviewed and affirmed in 2016, have recommended cystoscopic evaluation of adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with microscopic hematuria and risk factors for developing bladder cancer.¹ Confirmatory diagnosis of bladder cancer is 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 the depth of invasion and tumor grade. However, a 50% to 75% incidence of recurrence has been noted in these
patients, with 10% to 15% progressing to muscle invasion over a five-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every three months for one to three years, every six months for an additional two to three years, and then annually thereafter, assuming no recurrence.

While urine cytology is a specific test (from 90% to 100%), its sensitivity is lower, ranging from 50% to 60% overall, and it 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.

Adjunctive testing to urine cytology has used a variety of nuclear and cytoplasmic targets, and a range of molecular pathology and traditional (e.g., immunohistochemistry) methods.

Commercially available tests cleared by the U.S. Food and Drug Administration as well as laboratory-developed tests are summarized in the Regulatory Status section.

Regulatory Status

The following urinary tumor marker tests have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for clinical use:

- The BTA stat® test (Polymedco, Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H–related protein that has been 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, Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both Polymedco tests have sensitivities comparable with that of cytology for high-grade tumors and better than cytology for low-grade tumors.

- The nuclear matrix protein 22 (NMP22) urine immunoassay (Alere NMP22® BladderChek®; Alere) tests for NMP22, a protein associated with the nuclear mitotic apparatus, which may be released from the nuclei of tumor cells during apoptosis. Elevated urine levels have been associated with bladder cancer. NMP22 may be detected in the urine using an immunoassay.

- Vysis UroVysion® (Abbott Molecular) is a commercially available fluorescence in situ hybridization (FISH) test. 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. DNA FISH probes have been used to detect chromosomal abnormalities in voided urine to assist in bladder cancer surveillance and in the initial identification of bladder cancer.

- The ImmunoCyt™ test (DiagnoCure, Quebec City, QC) uses fluorescence immunohistochemistry to detect antibodies to a mucin glycoprotein and a carcinoembryonic antigen. These antigens are found on bladder tumor cells. DiagnoCure ceased operations in 2016.

With the exception of the ImmunoCyt™ test, which is only cleared for monitoring bladder cancer recurrence, all tests are FDA-cleared as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients.

In addition to FDA-cleared tests, clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Urine-based tests are available under the auspices of
CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

For example, Predictive Laboratories (Lexington, MA) markets the CertNDx™ test; it assesses fibroblast growth factor receptor 3 (FGFR3) variants. The test is intended to be used in combination with cytology for identifying patients with hematuria at risk of bladder cancer. FGFR3 variants 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 United States called Cxbladder™, which tests for five urine-based markers.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


