

Protocol

Urinary Tumor Markers for Bladder Cancer

(20407)

Medical Benefit	Effective Date: 01/01/13	Next Review Date: 09/14
Preatuthorization	No	Review Dates: 03/12, 09/12, 09/13

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preatuthorization is not required but recommended if, despite this Protocol position, you feel this service is medically necessary; the ordering/requesting physician should submit documentation to Utilization Management. 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.

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 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, 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 is made by cystoscopic examination, 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 50–75% 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 90–100%), 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, Predictive Biosciences (Lexington, MA) is marketing a urine-based 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. It is being offered through Predictive Bioscience's network of Clinical Laboratory Improvement Amendment (CLIA) laboratories. FGFR3 mutations may be associated with lower-grade bladder tumors that have a good prognosis.

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;
- Quanticyt.

Regulatory Status

Urinary tumor marker tests cleared by the FDA and in clinical use include:

- 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.

Corporate Medical Guideline

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

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.

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