Protocol

Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance

(20407)

Medical Benefit		**Effective Date**: 01/01/19	**Next Review Date**: 09/20
Preauthorization	No	**Review Dates**: 03/12, 09/12, 09/13, 09/14, 09/15, 09/16, 09/17, 09/18, 09/19	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With signs and/or symptoms of bladder cancer	Interventions of interest are: • Urinary tumor marker tests in addition to cytology	Comparators of interest are: • Cytology • Cystoscopy • Biopsy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Resource utilization
Individuals: • With a history of bladder cancer	Interventions of interest are: • Urinary tumor marker tests in addition to cytology	Comparators of interest are: • Cytology • Cystoscopy • Biopsy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Resource utilization
Individuals: • Who are asymptomatic and at a population-level risk of bladder cancer	Interventions of interest are: • Urinary tumor marker tests	Comparators of interest are: • Standard surveillance without testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity
Individuals: • Who are asymptomatic and at a population-level risk of colon cancer	Interventions of interest are: • Urinary tests for precancerous polyps	Comparators of interest are: • Colonoscopy • Fecal testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

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 who receive urinary tumor marker tests in addition to cytology, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have 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 cytology, 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. 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 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; i.e., 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. Relevant outcomes are overall survival, 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 randomized controlled trials, the preferred trial design to evaluate the impact of population-based screening and found only one 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, evidence includes a validation study. Relevant outcomes are overall survival, 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.

POLICY

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

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. Cigarette smoking is an important risk factor for urothelial carcinoma.

Diagnosis

The criterion standard for a confirmatory diagnosis of bladder cancer is cystoscopic examination with 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 approved or cleared by the U.S. Food and Drug Administration (FDA) as well as laboratory-developed tests are summarized in the Regulatory Status section.

REGULATORY STATUS

Table 1 lists urinary tumor marker tests approved or cleared for marketing by 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

Test	Manufacturer	Type	Detection	Indication
BTA stat®	Polymedco	Point of care immunoassay	Human complement factor H-related protein	Qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer
BTA TRAK®	Polymedco	Reference laboratory immunoassay	Human complement factor H-related protein	Quantitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer
Alere NMP22®	Alere	Immunoassay	NMP22 protein	in vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy
BladderChek®	Alere	Point of care immunoassay	NMP22 protein	Adjunct to cystoscopy in patients at risk for bladder cancer
UroVysion®	Abbott Molecular	FISH[a]	Cell-based chromosomal abnormalities	Cell-based chromosomal abnormalities

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NMP: nuclear matrix protein

[a] 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, FDA has chosen not to require any regulatory review of these 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 the CLIA. Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of these tests. Laboratory-developed tests include:

- Cxbladder Monitor (Pacific Edge) measures the expression of five 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.

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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