UM-CDG-080 Bladder Urothelial Tumor Markers	Approved By: Director, Health Services	Effective Date: 10/20/2025

This Policy applies to all SECUR affiliates, associates, and subsidiaries.

Approved by Courtney Gonzales, Director of Health Services on behalf of the Utilization Management Committee.

PURPOSE

This coverage determination guideline serves to address bladder/urothelial tumor markers. Bladder or urothelial tumor markers are substances found in urine, blood, or tissue that can indicate the presence of bladder cancer. These markers are typically proteins or genetic material released by cancer cells or produced by the body in response to the tumor. Doctors use them alongside other diagnostic tools to help detect bladder cancer, monitor for its return after treatment, and, in some cases, assess how aggressive the cancer might be.

While not used as a stand-alone test, tumor markers can provide valuable information when combined with imaging and cystoscopy (a procedure that looks inside the bladder). They offer a non-invasive or minimally invasive way to support diagnosis and ongoing care, especially in patients at higher risk for bladder cancer or those undergoing regular surveillance.

For SECUR Health Plan members, National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) will be applied to requests when applicable. SECUR Health Plan Coverage Determination Guidelines (CDG) will be utilized in the absence of an appropriate NCD and/or LCD.

DEFINITIONS

None

POLICY

SECUR Health Plan recognizes the following as covered indications:

Gross painless hematuria is often the first manifestation of an urothelial tumor. Since the degree of hematuria bears no relation to the seriousness of the underlying disease, the microscopic finding of blood in the urine is a serious symptom until significant pathology has been excluded.

At this time, there is no published consensus from the following national organizations: National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Urological Association (AUA) and the International Bladder Cancer Consensus Group (IBCCG) regarding the management of persistent asymptomatic microscopic hematuria. Due to insufficient supporting data, the AUA's 2001 best practices policy could not recommend routine use of voided urinary markers in the evaluation of patients with microscopic hematuria.[3]

Recommended surveillance schedules for patients with a previous negative evaluation for unexplained microscopic hematuria include annual urinalysis and voided urinary cytology until the hematuria resolves, or for up to 3 years if microscopic hematuria persists. The AUA has been silent regarding practice guidelines due to the paucity of prevalence studies on asymptomatic microscopic hematuria.

Cystoscopy in conjunction with bladder tumor markers is the standard practice to evaluate patients with symptoms suggesting bladder cancer and to monitor treated patients for recurrence or progression. Although cystoscopy is considered the "gold standard", studies have shown that up to 20% of tumor can be missed. Urinary cytology has close to a 90%-100% specificity, but only 10%-50% sensitivity for low grade urinary cancer (UC) detection. Due to this deficit, clinicians have sought noninvasive tumor markers detectable in urine.

Upwards of 50% of patients have recurrence of bladder cancer within 5 years.

After initial diagnosis and treatment, patients with UC are frequently monitored every 3 months for the first 2 years, every 4 months for the third, year then usually twice a year for the fourth year. Annual monitoring is recommended during years 5 through 15.

Diagnostic and Surveillance Tests

- BTA TRAK® - a quantitative determination of human complement factor H-related protein
- Nuclear matrix protein 22 (NMP-22) – detects nuclear mitotic apparatus protein believed to be released during apoptosis; a quantitative assay, which is either positive of negative
- NMP-22® BladderChek® – a CLIA-waved assay, point of care test with an immunochromographic qualitative format taking 20 minutes to perform
- The UroVysion® Bladder Cancer Kit is fluorescence in situ hybridization (FISH) DNA probe technology. It is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus. This assay involves visualization of nucleic acid sequences within cells by creating short sequences of fluorescently labeled, single-strand DNA probes that match target sequences. The probes bind to complementary strands of DNA to identify the targeted chromosome(s) location. It is 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.

Scientific studies demonstrate the sensitivity of BTA and NMP-22® are superior to urinary cytology.[1] Studies affirm the adjunctive value of BTA stat® and NMP-22® in suspected and known bladder cancer in conjunction with cystoscopy. However, false positive results occur more frequently in the presence of hematuria, nephrolithiasis, recent GU instrumentation, inflammation and other urological malignancies. Administration of bacillus Calmette-Guerin (BCG) within 2 years of testing decreases specificity to 28%.

The DNA probe assay has high sensitivity (81%) and specificity (96%) for high grade tumors, but lower sensitivity (36-57%) for low grade and stage tumors. The assay specificity approaches that of cytology, and can be utilized in patients recently treated with intravesical BCG. This can result in a positive UroVysion® test with a negative study for UC. This assay has also been shown to be useful in predicting tumor recurrence following BCG therapy.

At present the IBCCG has recommended that tumor markers be used in conjunction with cystoscopy. They also concluded that routine screening for bladder cancer is not cost-effective.[3] The US Preventive Services Task Force

concluded bladder tumor markers do not have a proven role in screening of asymptomatic patients for early detection of bladder cancer.[3] NCCN, ASCO, and AUA are silent regarding the utilization of these bladder tumor markers.

Surveillance Tests

- BTA (bladder tumor antigen) stat® - a qualitative CLIA-waved test that identifies a human complement factor H-related protein produced by several human bladder cell lines
- The ImmunoCyt™ test is cleared for monitoring bladder cancer recurrence only in conjunction with cytology and cystoscopy. The assay uses fluorescent labeled antibodies to 3 markers (carcinoembryonic antigen, and mucins LDQ10 and M344) commonly found on malignant exfoliated urothelial cells. The ImmunoCyt™ assay has also been shown to be more sensitive than urine cytology.

Coverage Limitations

Cystoscopy in conjunction with bladder tumor markers is standard practice to evaluate patients with symptoms suggesting bladder cancer and to monitor treated patients for recurrence or progression. Exceptions, such as high grade bladder cancers s/p radical cystectomy, do exist which preclude cystoscopy prior to testing. Testing indications, limitations and frequency do not apply to urine cytology.

Bladder cancer tumor markers performed by any technology, immunoassay, molecular or FISH testing, are not covered for screening of all patients with hematuria. Bladder tumor markers are not expected to be performed until other diagnostic studies fail to identify the etiology of the hematuria. Urine cytology is not considered a bladder tumor marker.

All other bladder cancer marker assays, including but not limited to the following, regardless of the methodology are considered investigational and not covered by SECUR Health Plan:

- BCLA-4
- BLCA-1
- Hyaluronic acid
- Hyaluronidase
- Lewis X antigen
- Microsatellite markers
- Quanticyt
- Soluble FAS TATI (tumor associated trypsin inhibitor)
- Soluble e-cadherin
- Survivin
- Telomerase
- UBC™ Rapid Test (urinary bladder cancer test for cytokeratins 8 and 18)

Utilization Guidelines

- Only 1 bladder cancer test per single date of service (e.g., FISH then reflex cytology) are considered reasonable and necessary.
- For high risk patients with persistent hematuria and a negative FISH assay following a comprehensive diagnostic (no tumor identified) workup, ONE repeat FISH testing in conjunction with cystoscopy is considered reasonable and necessary within 1 year of the original attempted diagnosis.

- Maximum of 4 bladder tumor marker studies per year for years 1-2
- Maximum of 3 bladder tumor marker studies per year for year 3
- Maximum of 2 bladder tumor marker studies for year 4 and
- Maximum of 1 bladder tumor marker studies follow-up annually for up to 15 years

References:

1. Polymedco, Inc. 2008. BTA stat®Test . Cortlandt, NY.
2. Grossfeld GD, Litwin MS, Wolf JS Jr, et al. Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association best practice policy part II: Patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. *Urology.* 2001;57(4):604-10.
3. Guide to Clinical Preventive Services, U.S. Preventive Services Task Force Accessed on January 13, 2021.
4. Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. *Urology.* 2005;66:35-63.
5. Messing EM, Teot L, Korman H, et al. Performance of urine test in patients monitored for recurrence of bladder cancer: A multicenter study in the United States. *J Urol.* 2005;174(4 pt 1):1238-41.
6. Local Coverage Determination Guideline (LCD) L36975, Bladder/Urothelial Tumor Markers,