UroVysion FISH for Bladder Cancer

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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<th>Procedures addressed by this guideline</th>
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<td>FISH Analysis for Bladder Cancer (UroVysion), Computer-Assisted</td>
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What is UroVysion FISH testing for bladder cancer

Definition

UroVysion™ was developed to be used with current standard diagnostic tools to aid in initial diagnosis of bladder cancer and monitoring for tumor recurrence in previously diagnosed patients.⁴

- Bladder cancer is one of the most common types of cancer in the U.S., especially among men. Approximately 76,960 new cases of bladder cancer are projected for 2016 (58,950 in men and 18,010 in women).¹ Older individuals (median age, 65 years) are most often affected.
- Bladder cancer is categorized as non-muscle invasive disease (NMID) or muscle invasive disease (MID).² The majority (≈80%) of bladder cancers are NMID.³
- Urothelial carcinoma (UC) accounts for most cases of bladder cancer.²⁴
  - Most cases of UC are low-grade and easily treated.⁴
  - However, UC has a high risk of recurrence (70%), and patients must be monitored for several years after treatment.⁴
- Diagnostic monitoring usually consists of regular testing of cells in the urine (cytology).²⁵ UroVysion FISH (fluorescence in situ hybridization) testing is an alternative to cytology.⁴⁵
**Test information**

- UroVysion testing detects extra or missing chromosomes 3, 7 or 17 and gene changes to a piece of chromosome 9 often found in UC patients.\(^4\)

- Cytology is the standard procedure for diagnosing and monitoring of UC. UroVysion testing can be performed if the cytology returns negative or atypical results.\(^2,4,5\)

- One study showed UroVysion testing to have 85% sensitivity for low-grade UC, and nearly 100% sensitivity for the more rare but serious high-grade UC.\(^4\)

**Guidelines and evidence**

- UroVysion testing is FDA approved,\(^6\) but reviews and guidelines call for additional study before it becomes standard procedure.\(^5\)

- The National Cancer Center Network (NCCN, 2016)\(^2\) has published clinical guidelines on bladder cancer, and state that urinary urothelial tumor markers are classified as category 2B, and an option for follow-up assessment in patients with low to high grade disease who have undergone adjuvant intravesical treatment. They report that urothelial tumor markers have better sensitivity, but lower specificity, for detecting bladder cancer compared with urinary cytology. It is not known whether urinary marker tests add useful clinical information for the detection and management of non-muscle invasive bladder tumors.

- The American Urological Association and the Society of Urologic Oncology (AUA, 2016)\(^7\) recently published clinical practice guidelines regarding microscopic hematuria and the management of non-muscle invasive bladder cancer (NMIB). For urinary markers utilized after diagnosis of bladder cancer, they state the following:
  - "In surveillance of NMIC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation (Strong Recommendation; Evidence Strength: Grade B)"
  - "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. (Expert Opinion)"
  - "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). (Expert Opinion)"

- The National Institute for Health and Care Excellence (NICE, 2015)\(^8\) published a guideline regarding the diagnosis and management of bladder cancer. They stated that urinary biomarker tests (such as UroVysion using FISH, ImmunoCyt or a nuclear matrix protein 22 (NMP22) test may be used for the diagnosis of individuals with suspected bladder cancer.

- The American Urological Association(AUA, 2012)\(^9\) stated the following regarding the management of asymptomatic microhematuria:
"The use of urine cytology and urine markers (NMP22, BTA-stat, and UroVysion FISH) is NOT recommended as a part of routine evaluation of the asymptomatic microhematuria patient. (Recommendation: Evidence Strength C)."


- A systematic review of UroVysion was conducted by the Agency for Healthcare Research and Quality (AHRQ). Based on 11 studies that were reviewed, the following were noted by authors:
  
  Diagnostic testing:
  
  - The sensitivity of Urovysion to detect bladder cancer among undiagnosed patients with clinical signs and symptoms was 63% (95% CI, 50% to 75%) and specificity was 87% (95% CI, 79% to 93%).
  
  - The positive likelihood ratio was 5.02 (95% CI 2.93 to 8.60) (moderate increase in the likelihood of disease). The negative likelihood ratio was 0.42 (95% CI 0.30 to 0.59) (small decrease in likelihood of disease).

  Surveillance testing:
  
  - For individuals being monitored for cancer recurrence the sensitivity was 55% (95% CI, 36% to 72%; 7 studies) and specificity was 80% (95% CI, 66% to 89%; 6 studies).
  
  - For evaluation of symptoms, sensitivity was 73% (95% CI, 50% to 88%), based on two studies.

  - The sensitivity of the test increased with higher tumor stage and grade.

  A prior systematic review and meta-analysis provided a comparison of Urovysion with cystoscopy for diagnosing UC.
  
  - Pooled sensitivity of UroVysion was 72% (95% CI, 69% to 75%) compared with 42% (95% CI, 38% to 45%) for cytology.
  
  - Specificity of UroVysion was 83% (95% CI, 82% to 85%) and 96% (95% CI, 95% to 97%) for cytology.

  - Sensitivity increased if earlier stage tumors (Ta) were excluded: Urovysion, 86% (95% CI, 82% to 89%) and cytology, 61% (95% CI, 56% to 66%).

  - The overall diagnostic performance was higher for Urovysion (area under the curve [AUC], 0.867, standard error [SE], 0.021) versus cytology (AUC, 0.626 (SE 0.091). However, these differences in diagnostic accuracy disappeared when Ta cases were excluded, indicating that the tests may be more comparable for accurately detecting later stage disease.
A prospective, blinded study compared results of ImmunoCyt and UroVysion with urine cytology to detect recurrent UC. A total of 100 patients with a history of bladder cancer submitted a single voided urine sample, immediately followed by cystoscopy and biopsy.

- The overall results of sensitivity for low- and high-grade UC for the various tests were as follows: Cytology, 15% and 27%; ImmunoCyt, 62% and 91%; and UroVysion, 8% and 18%.
- Specificity of the tests were: Cytology, 97%; ImmunoCyt, 63%; UroVysion, 90%.
- Positive predictive value (PPV) and negative predictive value (NPV) of each test demonstrated: Cytology 71% and 78%; ImmunoCyt 43% and 88%; UroVysion 33% and 72%
- ImmunoCyt had significantly better sensitivity at detecting low-grade tumors compare with cytology or UroVysion (76% vs 21% and 13%, respectively; P<0.001 for both). However, specificity for ImmunoCyt was significantly lower than for cytology and UroVysion (63% vs 97% and 90%; P<0.001 for both).
- The authors concluded that UroVysion and cytology had comparably high rates of specificity for patients with negative cystoscopy, and as a result, UroVysion may have value to confirm cytology or ImmunoCyt.

A retrospective study evaluating the ability of UroVysion to predict recurrence and progression in NMIBC with suspicious cytology and negative cystoscopy results was undertaken due to the high rate of recurrence and frequent cystoscopic monitoring required in this disease. Authors evaluated predictors for recurrence, progression and findings on subsequent cystoscopy.

- A positive UroVysion result was a significant predictor for recurrence (hazard ratio [HR], 2.35; 95% CI, 1.42 to 3.90; P=0.001) and for progression (HR, 3.01; 95% CI, 1.10 to 8.21; P=0.03).
- A positive UroVysion result, however, was not significantly associated with evidence of tumor on subsequent surveillance cystoscopy compared with negative UroVysion results (odds ratio [OR], 0.80; 95% CI, 0.26 to 2.74; NS).
- The authors concluded that an “anticipatory positive” UroVysion result can predict recurrence and progression in patients with NMIBC when cystoscopy results are negative and cytology results are suspicious.
- The lack of association between UroVysion results and tumor recurrence on cystoscopy during the immediate follow-up period, however, suggests that UroVysion has limited value to modify surveillance regimens in these patients.

Criteria

- Previous Testing:
o No repeat UroVysion® testing on the same sample when a result was successfully obtained, AND

• Diagnosis
  o UroVysion is not indicated for the routine evaluation of hematuria or microhematuria and will not be reimbursed when billed with an ICD10 code in the R31 Hematuria range. Exceptions may be made for uncertain or equivocal results on standard diagnostic assessments, such as cytology, OR

• Surveillance
  o UroVysion is indicated when the individual has a personal history of bladder cancer defined by ICD10 code of Z85.51 (Personal history of malignant neoplasm of bladder) or C67.0-C67.9 (Malignant neoplasm of the bladder, range), AND
  o The member is being monitored for cancer recurrence, AND
    ▪ Member had been diagnosed with low grade bladder cancer and the results of cytology are equivocal, or
    ▪ Member had been diagnosed with high grade bladder cancer and the results of cytology are negative or equivocal, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy

References


