



Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

UroVysion FISH Test

- Assay Tests for the Diagnosis of Bladder Cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Bladder/Urothelial Tumor Markers (L36680)
Local Coverage Article	Billing and Coding: Lab: Bladder/Urothelial Tumor Markers (A55029)

For Non-Medicare Members

UroVysion FISH test is covered for members with a suspected new diagnosis of bladder cancer or known prior history of bladder cancer, who have an atypical cytology in spite of normal cystoscopy and upper tract imaging.

A negative test will preclude further evaluation and a positive test either increases the frequency of surveillance or prompts urothelial biopsy.

The FISH test is not covered when used for all other indications, such as, screening for bladder cancer or for the evaluation of hematuria. The tests below are not covered for any indication:

- BTA Stat test
- NMP22 test
- Aura-Tek FDP test

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

In 2012, cancer of the urinary bladder accounted for 73,510 new cases and 14,880 deaths in the USA, making it the sixth most common and tenth most lethal malignancy in the country (Siegel, Naishadham et al. 2012). Most patients present with superficial low-grade transitional cell carcinoma which is readily resectable and, in some cases, requires additional chemotherapy or immunotherapy (Rouprêt, Babjuk et al. 2013). Although these tumors have a high recurrence, they usually do not invade the bladder wall or metastasize. One third of incident bladder cancers, however, progress into invasive cancer presenting as solid, nonpapillary tumors with a high propensity for metastasis

requiring radical therapy. The five year survival rate for these tumors is only 30-50% (Arentsen, de la Rosette et al. 2006). Thus, patients with a history of bladder cancer are routinely monitored for recurrence

At present, the diagnosis of both primary and recurrent bladder tumors relies upon both cystoscopy and cytology, of which, neither is completely accurate (Mian, Lodde et al. 2003). Cystoscopy is an efficient method; however, it is invasive, causes patient discomfort, may be associated with a risk of urethral and bladder neck stricture and might not detect flat tumors or carcinoma in situ (false negative rate of 30%) (Danilchenko, Riedl et al. 2005; Denzinger, Burger et al. 2007). Cytology, often used as an adjunct to cystoscopy, has a poor sensitivity for low grade tumors and frequently the results are inconclusive for malignancy (Nabi, Greene et al. 2004). In addition, patients with atypical cytology pose a challenging problem due to uncertainty about the presence of cancer.

Options for management of this predicament include observation with the possibility of missing a diagnosis or biopsying every patient.

Due to the limitations of cytology, molecular-based detection techniques represent potentially attractive strategies for noninvasive detection of aggressive bladder cancer using urine as the specimen source. Among these is the UroVysion™ Kit, a multi-target, multicolor FISH assay designed to detect aneuploidy for chromosomes 3, 7, 17 or the loss of the 9p21 locus (Sarosdy, Schellhammer et al. 2002). Better performance has been reported in detecting carcinoma in situ and high-grade tumors (Lokeshwar, Habuchi et al. 2005).

UroVysion (Abott-Vysis, Wiesbaden, Germany) was approved by the FDA in January 2005 for the cytologic detection of cancer cells in voided urine specimens.

Medical Technology Assessment Committee (MTAC)

UroVysion FISH Test

10/13/2004: MTAC REVIEW

Evidence Conclusion: The studies reviewed compared the performance of the UroVysion FISH test to the other noninvasive tests used to detect new or recurrent urinary bladder carcinoma, using voided urine specimens. Cystoscopic evaluation (or bladder resection) with histopathologic studies for the suspicious cases was used as gold standard. All studies were conducted among patients referred to cystoscopy for a history of bladder carcinoma, or urinary signs/symptoms. Sarosdy's study only included patients with a history of transitional cell carcinoma, and Halling as well as Placer included patients with either a history of urothelial carcinoma or other genitourinary symptoms and signs. The ages of the study subjects ranged from 28 to 98 years, and the majority were men. Patient characteristics and inclusion criteria provided were insufficient, exclusion criteria were not discussed, and except for one study with consecutive patients, the authors do not explain how the subjects were selected for the studies. None of the studies evaluated the test as a screening tool, and none evaluated its role in improving the management of urothelial carcinomas. Overall, the studies reviewed showed that FISH test was more sensitive than urine cytology in detecting new or recurrent bladder carcinomas among the patients studied. The specificity of the two tests was similar. Compared to the gold standard of cystoscopy/histopathologic evaluation, the overall sensitivity of FISH assays ranged from 71% to 81%, and the overall specificity ranged from 66% in Sarosdy et al's study to 96% in Halling et al's study. The test appears to be more sensitive in detecting later stages, and higher grades of the disease however; the numbers of patients in the subgroups were too small.

Articles: The search yielded 29 articles. There were 14 studies that compared the FISH test with cytologic analysis and/or other tests. In five of these studies the urine specimens were obtained from bladder washings during cystoscopy. These studies were excluded as this review deals specifically with the noninvasive UroVysion FISH test using voided urine specimens. Nine studies on UroVysion FISH test in voided urine were identified. Sensitivity and/or specificity of the test was/were not reported in three of the studies. Four of the remaining studies that had a gold standard, and reported sensitivity and specificity were critically appraised. Selection of these studies for critical review was based on the sample size and validity of the study methodology. *The following articles were critically appraised**: Sarosdy MF, Schellhammer P, Bokinsky, et al. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for the detection of bladder cancer. *J Urol* 2002; 168:1950-1954. See [Evidence Table](#) Halling KC, King W, Sokolova I, et al. A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. *J Urol* 2000; 164:1768-1775. See [Evidence Table](#) Halling KC, King W, Sokolova I, et al. A comparison of BTA stat, hemoglobin dipstick, telomerase and Vysis assays for the detection of urothelial carcinoma in urine. *J Urol* 2002; 167:2001-2006. See [Evidence Table](#) Placer J, Espinet B, Salido M, et al. Clinical utility of a multiprobe FISH assay in voided urine specimens for the detection of bladder cancer and its recurrence, compared with urinary cytology. *Eur Urol* 2002; 42:547-552. See [Evidence Table](#)

The use of UroVysion FISH test in the evaluation of new or recurrent urinary bladder carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

UroVysion FISH Test

6/17/2013: MTAC REVIEW

Evidence Conclusion: The accuracy of the UroVysion FISH assay for the diagnosis of bladder cancer in patients with atypical cells has two major components, validity and precision. In this context, the validity of the UroVysion FISH assay refers to the degree to which it does what it is designed to do (i.e. detect urothelial carcinoma of the bladder) and the precision refers to its reliability or its consistency from one application to the next. In both of the selected studies, the validity of the FISH assay was measured by testing every patient who underwent cystoscopy and cytology with atypical cells within a certain time frame and then reviewing the clinical and pathological data on each patient for congruence. The end result, in both studies, was sensitivity and specificity which allows us to measure how well the test classifies people with the cancer as sick and those without cancer as healthy. In addition, two other measures, positive and negative predictive values, were determined to measure how well the test performed in the given population. Both of the selected studies employed similar methodologic techniques. The UroVysion test was performed on all patients presenting with atypical cytology, both with and without cancer history, within a certain time frame. Results were reviewed comprehensively to evaluate the clinical and pathological data on each patient. Clinical stage was assigned by the operative surgeon and all cytology results were interpreted by an experienced cytopathologist, who was blinded to clinical findings. Cytology results were considered atypical if it was not unequivocally positive or negative. The results of both studies show that the use of the UroVysion test is beneficial in patients with equivocal and negative cystoscopy. Lotan and colleagues found in patients with no cancer history the sensitivity was 77.8% and the specificity was 100% and in patients with cancer history the sensitivity and specificity were both 100%. These findings were validated by Schlomer and colleagues results which show that in patients with cystoscopically visualized lesions UroVysion had a positive predictive value of 100% but there were false negative results. In patients with equivocal cystoscopy and a history of cancer all four high grade tumors were detected and there were no false negative findings. In patients with equivocal cystoscopy and no prior cancer the positive predictive value was 100% and there were no false negative results. In patients with negative cystoscopy the UroVysion test detected all cancers but the positive predictive value was 10% and 29% in patients with and without a history of cancer, respectively. Although these prospective studies indicate that the use of UroVysion in patients with atypical cytology is beneficial in identifying cancer in patients with atypical results they come with limitations. First and foremost, both studies are working with relatively small samples threatening the generalizability of the study. In addition to the small samples, both studies yielded and excluded uninformative UroVysion results. Furthermore, both studies employed more than one diagnostic technique which leads to potential bias. It should also be noted that the UroVysion FISH assay has been approved by the FDA as a noninvasive tool for the detection of cancer cells through voided urine. A portion of the sample collections described in the two prospective studies included specimens that were obtained via bladder washings during cystoscopy which makes comparison difficult with studies that solely used voided urinary samples.

Articles: Lotan Y, Bensalah, Ruddell T, Shariat S, Sagalowsky A, Ashfaq R. Prospective evaluation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. *The Journal of Urology* 2008; 179:2164-2169. [See Evidence Table](#) Schlomer BJ, Ho R, Sagalowsky A, Ashfaq R, Lotan Y. Prospective Validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. *The Journal of Urology* 2010; 183:62-67. [See Evidence Table](#)

The use of UroVysion FISH test in the evaluation of new or recurrent urinary bladder carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
88120	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

**To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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10/13/2004	04/04/2011 ^{MDCRPC} , 02/07/2012 ^{MDCRPC} , 12/04/2012 ^{MDCRPC} , 08/06/2013 ^{MPC} , 09/03/2013 ^{MPC} , 07/01/2014 ^{MPC} , 05/05/2015 ^{MPC} , 03/01/2016 ^{MPC} , 11/07/2017 ^{MPC} , 09/04/2018 ^{MPC} , 09/03/2019 ^{MPC} , 09/01/2020 ^{MPC} , 09/07/2021 ^{MPC} , 09/06/2022 ^{MPC} , 09/05/2023 ^{MPC}	09/01/2020

^{MPC} Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34067
09/01/2020	Removed CPT code 88271