Regence

Medical Policy Manual Laboratory, Policy No. 72

Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

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DESCRIPTION

Assays measuring urinary biomarkers have been proposed to aid in the assessment of recurrence risk in bladder cancer, the evaluation of malignancy risk for adrenal tumors, and the screening of asymptomatic patients for bladder cancer and precancerous colonic polyps.

MEDICAL POLICY CRITERIA

The use of urinary biomarkers is considered **investigational** in the diagnosis of, monitoring of, and/or screening for bladder cancer, adrenal tumors, and colonic polyps.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
2. Analysis of Proteomic and Metabolomic Patterns for Cancer Detection, Risk, Prognosis or Treatment Selection, Laboratory, Policy No. 41
3. Protein Biomarkers and Multi-analyte Biomarker Tests for Screening, Detection, and/or Management of Prostate Cancer, Laboratory, Policy No. 69
4. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

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.

The 2012 guidelines from the American Urological Association on the evaluation of microscopic hematuria, which were reviewed and affirmed in 2016, have recommended cystoscopic evaluation of adults older than age 40 years with microscopic hematuria and for those younger than age 40 years with microscopic hematuria and risk factors for developing bladder cancer.[1] Confirmatory diagnosis of bladder cancer is made by cystoscopic examination, considered to be the criterion 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 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 cleared by the U.S. Food and Drug Administration clearance as well as laboratory-developed tests are summarized in the Regulatory Status section.

REGULATORY STATUS

The following urinary tumor marker tests have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for clinical use:

- The BTA stat® test (Polymedco, Cortlandt Manor, NY) is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that has been 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, Cortlandt Manor, NY) provides a quantitative determination of the same protein. This test requires trained personnel and a reference laboratory. Both Polymedco tests have sensitivities comparable with that of cytology for high-grade tumors and better than cytology for low-grade tumors.

- The nuclear matrix protein 22 (NMP22) urine immunoassay (Alere NMP22 BladderChek®; Alere) tests for NMP22, a protein associated with the nuclear mitotic apparatus, which may be released from the nuclei of tumor cells during apoptosis. Elevated urine levels have been associated with bladder cancer. NMP22 may be detected in the urine using an immunoassay.
- Vysis UroVysion® (Abbott Molecular) is a commercially available fluorescence in situ hybridization (FISH) test. 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. DNA FISH probes have been used to detect chromosomal abnormalities in voided urine to assist in bladder cancer surveillance and in the initial identification of bladder cancer.
- The ImmunoCyt™ test (DiagnoCure, Quebec City, QC) uses fluorescence immunohistochemistry to detect antibodies to a mucin glycoprotein and a carcinoembryonic antigen. These antigens are found on bladder tumor cells. DiagnoCure ceased operations in 2016.

With the exception of the ImmunoCyt™ test, which is only cleared for monitoring bladder cancer recurrence, all tests are FDA-cleared as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients.

In addition to FDA-cleared 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 CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test. Laboratory-developed tests include:

- CertNDx™ (Predictive Laboratories) assesses fibroblast growth factor receptor 3 (FGFR3) variants.
- Cxbladder Monitor (Pacific Edge) measures the expression of five genes (MDK, HOXA13, CDC2, IGFBP5, and 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.
- Adrenal Mass Panel (Mayo Clinic Laboratories) is a urinary steroid panel test that uses liquid chromatography–mass spectrometry. The test reports risk values for the probability of a malignant adrenal cortical carcinoma or other malignancy, and also the probability of a benign mass.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic

performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility, which refers to how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on clinical validity and utility, particularly evidence from well designed, studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and
- Improve health outcomes as a result of those decisions.

DIAGNOSIS AND MANAGEMENT OF INDIVIDUALS WITH SYMPTOMS OR HISTORY OF BLADDER CANCER

Systematic Reviews

Several systematic reviews of diagnostic accuracy studies have been published. Chou (2015) reported on a systematic review and meta-analysis of studies of the diagnostic accuracy of urinary biomarkers for the diagnosis or follow-up of non-muscle-invasive bladder cancer (NMIBC), which was done as part of an Agency for Healthcare Research and Quality Comparative Effectiveness Review on the diagnosis and treatment of NMIBC.[2] Two studies were rated as having low risk of bias, three studies at high risk of bias, and the remainder considered to have moderate risk of bias. Only studies that used cystoscopy or histopathology as the reference standard were included in the analysis.

Results of pooled analyses of diagnostic accuracy in patients with symptoms of bladder cancer are displayed in Table 1, and results in patients with a history of bladder cancer are displayed in Table 2.

Table 1. Diagnostic Accuracy of Urinary Biomarkers in Patients with Symptoms of Bladder Cancer

Test	TP/n	Pooled Sensitivity (95% CI)	Number of Studies	Pooled Specificity (95% CI)	Number of Studies
BTA stat®					
Quantitative test	37/49	76% (61% to 87%)	1	53% (38% to 68%)	1
Qualitative test	275/372	76% (67% to 83%)	8	78% (66% to 87%)	6
NMP22 BladderChek®					
Quantitative test	235/368	67% (55% to 77%)	9	84% (75% to 83%)	7
Qualitative test	69/145	47% (33% to 61%)	2	93% (81% to 97%)	2
FISH (e.g., UroVysion®)	82/144	73% (50% to 88%)	2	95% (87% to 98%)	1
ImmunoCyt™	334/401	85% (78% to 90%)	6	83% (77% to 87%)	7
Cxbladder	54/66	82% (70% to 90%)	1	85% (81% to 88%)	1

CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives

Table 2. Diagnostic Accuracy of Urinary Biomarkers in Patients with a History of Bladder Cancer

Test	TP/n	Pooled Sensitivity 95% CI)	Number of Studies	Pooled Specificity (95% CI)	Number of Studies
BTA stat®					
Quantitative test	39/67	58% (46% to 69%)	2	79% (72% to 85%)	2
Qualitative test	325/544	60% (55% to 65%)	11	76% (69% to 83%)	8
NMP22 BladderChek®					
Quantitative test	235/368	61% (49% to 71%)	10	71% (60% to 81%)	8
Qualitative test	99/159	70% (40% to 89%)	2	83% (75% to 89%)	2
FISH (e.g., UroVysion®)	189/299	55% (36% to 72%)	7	80% (66% to 89%)	6
ImmunoCyt™	302/406	75% (64% to 83%)	7	76% (70% to 81%)	8

CI: confidence interval; FISH: fluorescence in situ hybridization; TP: true positives

Table 3. Sensitivity and Specificity Ranges of Select Biomarkers (Parker and Spiess)

Test	Sensitivity Range	Specificity Range
Cytology	12% to 79%	78% to 99%
BTA stat®	50% to 70%	67% to 78%
NMP22 BladderChek®	50% to 92%	66% to 87%
FISH (UroVysion®)	69% to 92%	89% to 95%
ImmunoCyt™	67% to 85%	62% to 85%

FISH: fluorescence in situ hybridization

In addition, in 2010, the U.K. Health Technology Assessment Program published a systematic review of studies on the diagnostic performance of several urine biomarkers.[3] Reviewers included 71 studies on the test performance of cytology and urine biomarkers. Most included patients both with and without a history of bladder cancer or included only patients with a history of bladder cancer. Few studies were identified that focused on the evaluation of urinary markers for the initial diagnosis of bladder cancer. Pooled analyses of study findings combined results of tests used for initial diagnosis of bladder cancer and tests used to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard (see Table 4).

Table 4. Results of Pooled Patient-Level Analyses (Mowatt, 2010)[3]

Variables	FISH	ImmunoCyt	NMP22
No. of studies	12	8	28
No. of patients	3,101	3,041	10,565
Sensitivity (95% CI)	76% (65% to 84%)	84% (77% o 91%)	68% (62% to 74%)
Specificity (95% CI)	85% (78% to 92%)	75% (68% to 83%)	79% (74% to 84%)

CI: confidence interval; FISH: fluorescence in situ hybridization

Wang (2017) published a systematic review and meta-analysis focused on NMP22 BladderChek.[4] There were 23 studies (n=8,724 patients) included in the review, 19 of which (n=5,291 patients) were included in the meta-analysis. Eleven of the studies were performed in Asian populations, and the other 12 were predominantly Caucasian. All studies in the meta-analysis compared BladderChek to cytology or cystoscopy, and these studies were reported to be of generally high quality, though there was significant heterogeneity observed which was associated with study quality. Based on the meta-analysis, sensitivity and specificity of the test

was 56% (95% confidence interval [CI] 52% to 59%) and 88% (95% CI 87% to 89%), respectively, the negative likelihood ratio was 0.51 (95% CI 0.40 to 0.66), and the positive likelihood ratio was 4.36 (95% CI 3.02 to 6.29). There was some evidence that test performed better in Asian populations than Caucasians.

Randomized Controlled Trials

No randomized controlled trials (RCTs) of urinary tumor marker tests for bladder cancer in patients that were symptomatic or had a history of bladder cancer were identified.

Nonrandomized Studies

Bladder EpiCheck™

The Bladder EpiCheck™ DNA methylation biomarker test was evaluated in two prospective clinical trials which have only been described in the FDA review of data for the 510(k) premarket submission.[5] One clinical trial enrolled 674 adults with urothelial carcinoma who had undergone resection within 12 months prior and were undergoing cystoscopy surveillance. Patients provided voided urine specimens at up to three study visits (baseline and two surveillance visits). Valid Bladder EpiCheck and gold standard (cytology or combined cystoscopy/pathology) results were obtained for 449 patients. Bladder EpiCheck™ was found to have an accuracy of 78.8%, sensitivity of 66.7%, and specificity of 84.2%, with positive and negative predictive values of 65.3% and 85.1%, respectively. In the second study, Bladder EpiCheck™ was compared to the predicate approval device, UroVysion® in 352 matched patients (specific patient characteristics and matching criteria not described) using the same gold standard reference. Bladder EpiCheck™ was found to be similar to UroVysion®, with a higher reported sensitivity (difference 4.82%, 95% CI -5.7 to 15.3) and lower specificity (difference -2.97%, 95% CI -7.8 to 1.9) that were not statistically significant.

Cxbladder™

Breen (2015) compared Cxbladder™ to three other urinary marker tests (UroVysion®, FISH, NMP22) using samples from five datasets.[6] The datasets included 939 patients, 89 of whom had urothelial carcinoma (UC). In addition to cytology, between one and three additional diagnostic tests were performed on each sample; a single study (124 samples, nine cancers) performed all three tests. Cxbladder™ results were obtained in 746 (79.4%) of samples. The authors proposed a "methodology for comparative analysis and ranking" to evaluate the different tests despite not all tests being performed on all samples. The approach required imputing results in studies not conducting particular tests using different imputation methods. Next, a signal-to-noise ratio (SNR) for each test was calculated as the mean difference in a test result for patients with or without UC and dividing by the sum of the two standard deviations. Although similar to a standard effect size, the summed standard deviations do not account for small sample sizes (e.g., UC samples), making the SNR somewhat difficult to interpret. Analysis of the imputed data suggested Cxbladder™ has higher sensitivity but lower specificity than the other tests. For example, in the comparison of Cxbladder™ and cytology, sensitivities were 73.6% (95% CI 65.1% to 81.7%) versus 46.0% (95% CI 36.3% to 55.8%) and specificities were 81.7% (95% CI 78.7% to 84.4%) versus 95.3% (95% CI 93.7% to 96.6%), respectively. Cxbladder™ was also accompanied by the largest point estimate (presumably a median but not stated) ranking for the SNR. However, the novel methodology and the absence of reported confidence intervals for the rankings limit any conclusions about the relative diagnostic accuracy of Cxbladder™.

A 2018 study authored by employees of Pacific Edge Ltd. (the company that markets Cxbladder™), assessed changes in physician-patient decisions based on Cxbladder™ results.[7] Twelve physicians each evaluated case notes from 33 patients with asymptomatic microscopic hematuria, and made recommendations for tests and procedures. The physicians then received the results of the Cxbladder™ test and re-evaluated their recommendations. Negative Cxbladder™ results led to a net reduction in recommended diagnostic procedures, and positive Cxbladder™ results lead to a net increase, the impact of this testing on patient health outcomes was not evaluated.

FGFR3 Variants

A study was published by Fernandez (2012), in which several coauthors were employees of Predictive Biosciences, the manufacturer of the CertNDx™ test.[8] The study included 323 individuals who had been treated for bladder cancer; 48 had recurrence of bladder cancer and the remaining 275 had no current evidence of disease. Seven patients without disease did not have sufficient DNA for *FGFR3* variant testing and were excluded from further analysis. *FGFR3* variants were detected in 15 samples, five from patients with cancer recurrence and 10 from patients without evidence of disease. This resulted in a sensitivity of five (10%) of 48 and a specificity of 258 (96%) of 268. When results of *FGFR3* variant analysis were combined with the findings of other tests (matrix metalloproteinase 2 [MMP2], Twist 1, Nid2 methylation), the markers had a 92% (44/48) sensitivity and 51% (136/268) specificity for detecting cancer recurrence.

Zuiverloon (2010) applied *FGFR3* variant analysis to the detection and prediction of bladder cancer recurrence.[9] The research team, based in the Netherlands, developed an assay to identify common *FGFR3* variants in urine samples. They identified tumor *FGFR3* variant status in 200 patients with low-grade NMIBC. *FGFR3* variants were identified in 134 (67%) patients. The 134 patients with an *FGFR3*-variant tumor provided 463 urine samples, and 45 concomitant histologically proven recurrences of bladder cancer were detected. The sensitivity of the assay to detect concomitant recurrences was 26 (58%) of 45. After at least 12 months of follow-up from the last urine sample, an additional 34 recurrences were identified. Overall, 85 (81%) of 105 *FGFR3*-positive urine samples were associated with a bladder cancer recurrence compared with 41 (11%) of 358 *FGFR3*-negative urine samples. Using a Cox time-to-event analysis, an *FGFR3*-positive urine test was associated with a 3.8-fold higher risk of recurrence ($p<0.001$). Another study by this research team was published in 2013.[10] A total of 716 urine samples were collected from 136 patients with NMIBC (at least three samples per patient were required for study entry). During a median of three years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity and specificity of *FGFR3* for detecting a recurrence were 201 (49%) of 408 and 124 (66%) of 187, respectively. In comparison, the sensitivity of cytology was 211 (56%) of 377 and the specificity was 106 (57%) of 185. Combining *FGFR3* and cytology increased sensitivity to 76% but lowered specificity to 42%.

In a retrospective study, Rieger-Christ (2003) compared the accuracy of *FGFR3* variant analysis, cytology, and the combination of both in identifying bladder tumors.[11] The study included 192 patients with bladder cancer, 72 who underwent transurethral resection of the bladder (group A) and 120 who underwent cystectomy (group B). Urine samples were collected before surgery. DNA preparations were screened for *FGFR3* variants using single-strand conformation variant and DNA sequencing. (The study did not appear to use the CertNDx™ test.) Cytology results were available for 62 (86%) of 72 in the group A and 62

(52%) of 120 in group B. Sensitivity of the *FGFR3* test alone was 68% for group A and 24% for group B. The sensitivity of cytology alone was 32% for group A and 90% for group B. For combination *FGFR3* plus cytology, the sensitivity was 78% for group A and 93.5% for group B.

FISH (UroVysion®)

Lotan (2019) published a prospective multi-center study assessing the predictive value of the UroVysion® test for patients with primary high-grade NMIBC treated with bacillus Calmette-Guérin therapy.[12] There were 150 patients enrolled in the study, and after nine months of follow-up, 37 had disease recurrence and nine had disease progression. UroVysion® results were associated with recurrence/progression with a hazard ratio (HR) of 2.59 (95% CI 1.42 to 4.73) for the baseline test (prior to bacillus Calmette-Guérin therapy), 1.94 (95% CI 1.04 to 3.59) for the six-week test, and 3.22 (95% CI 1.65 to 6.27) for the three-month test. The NPV for patients who had no positive results was 76%. The authors stated that, “using the test to change management decisions is limited due to the discordance between results and outcomes as well as the variance of tests results with time.”

Virk (2017) evaluated the use of the UroVysion® test to risk-stratify patients with “atypical urothelial cells” by cytology.[13] The sensitivity, specificity, and positive and negative predictive values (PPV, NPV) for the test were calculated based on histological diagnosis of UC within 12 months of the cytology analysis. The study included 377 patients with atypical cytology results, 62 (16.45%) of whom had UC diagnosis within 12 months. In this setting, the UroVysion® test had a sensitivity of 44.6%, a specificity of 81.8%, a PPV of 47.2%, and an NPV of 80.2%. The authors noted a high false positive rate (52.8%), which remained high after extended follow-up, limiting the usefulness of the test.

A study by Kim (2014) examined data on the FISH test with the aim of determining whether the urinary marker could modify the surveillance schedule in patients with NMIBC who had suspicious cytology but a negative surveillance cystoscopy.[14] The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every three to six months. A total of 243 patients who met the previous criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy two to six months after reflex FISH. Cystoscopy findings were positive in 17 (7%) patients. FISH results were not significantly associated with the results of the next cystoscopy (odds ratio [OR], 0.84; 95% CI 0.26 to 2.74; p=1.0). Because of this lack of short-term association between FISH results and cystoscopy, the authors concluded that FISH has limited ability to modify the surveillance schedule in NMIBC.

Xu (2011) in China reported on the diagnostic accuracy of FISH (UroVysion®) for detecting upper tract UC.[15] The study included urine specimens from 85 patients suspected of having UUT disease. Patients underwent cystoscopy after urine collection. Seventeen (20%) patients had a history of urinary tract UC and eight (9%) had a history of bladder cancer. The remaining patients had signs or symptoms of disease such as hematuria. The sensitivity of FISH for diagnosing urinary tract carcinoma was 79% and the sensitivity of cytology was 45%. Specificity was 98% for FISH and 100% for cytology. When findings from cytology and FISH were combined, the sensitivity was 86% and the specificity was 98%. Neither study separately reported findings for detection of recurrence in patients with a history of urinary tract cancer or for patients with a negative cystoscopy.

ImmunoCyt

Lodde (2001) in Austria evaluated the accuracy of ImmunoCyt™ for detecting UUT transitional cell carcinoma (UUTTCC).[16] The study included 37 patients with signs or symptoms suggestive of UUT-TCC; 14 (38%) patients had a history of bladder cancer. Sixteen (43%) of 37 patients were found to have UUT-TCC. All patients also underwent cystoscopy, renal ultrasonography, and intravenous excretory urography. Using voided urine samples, ImmunoCyt™ had a 75% sensitivity and a 95% specificity for identifying UUT-TCC. This compares to a sensitivity of 50% and specificity of 100% for cytology. Using ureteral urine samples, ImmunoCyt™ had a sensitivity of 91% and cytology had a sensitivity of 82%. Both tests had 100% specificity using ureteral urine. Combination ImmunoCyt™ plus cytology had a sensitivity of 88% in voided urine samples and a sensitivity of 100% in ureteral urine.

NMP22

A study by Shariat (2011) used a decision curve analysis to assess the impact of urinary marker testing using the NMP22 assay on the decision to refer for cystoscopy and concluded that the marker did not aid clinical decision making in most cases.[17] The study included 2,222 patients with NMIBC and negative cytology, at various stages of surveillance. (Patients with positive urinary cytology were excluded, because standard practice is to refer those patients for cystoscopy.) According to the study protocol, all patients underwent cystoscopy, and 581 (26%) were found to have disease recurrence; of these, 234 (40%) had disease progression. NMP22 level was found to be significantly associated with both disease recurrence and progression ($p<0.001$ for both).

In the analysis, the clinical net benefit of the NMP22 test was evaluated by summing the benefits (true positives), subtracting the harms (false positives), and weighing these values by the “threshold probability,” defined as the minimum probability of bladder cancer or recurrence at which a patient or clinician would opt for cystoscopy. The investigators found only a small clinical net benefit for the NMP22 test over the strategy of “cystoscopy for all patients,” and this benefit occurred only at threshold probabilities over 8%. For example, for patients with at least a 15% risk of recurrence, using a model containing age, sex, and NMP22, 229 (23%) cystoscopies could be avoided, 236 (90%) recurrences would be identified, and 25 (15%) recurrences would be missed. Thus, for clinicians or patients who would opt for cystoscopy even if patients had a low risk of recurrence (e.g., 5%), NMP22 would not add clinical benefit and the optimal strategy would be to offer cystoscopy to all at-risk patients. The authors attributed the low clinical net benefit to the high risk of bladder cancer recurrence in patients with negative cytology.]

Xpert Bladder Cancer Monitor

Four studies prospectively evaluated the use of Xpert Bladder Cancer Monitor in follow up of patients with a history of NMIBC. D’Elia (2018) followed 230 patients, of whom 52 patients had a new recurrence of non-muscle invasive bladder cancer.[18] In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 46.2% and specificity of 77%; cytology demonstrated an overall sensitivity of 11.5% and specificity of 97.2%. Pichler (2018) followed 140 patients, of whom 43 patients had a new recurrence of non-muscle invasive bladder cancer.[19] In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 84% and specificity of 91%; cytology demonstrated an overall sensitivity of 33% and specificity of 94%. Blinding was not discussed for either study; studies were further limited by a short follow up period. Valenberg (2019) followed 239 patients with 43 cases of recurrence, and reported a sensitivity of 74% (95% CI 60% to 85%) and specificity of 80% (95% CI 73% to

85%).[20] Hurle (2020) followed 106 patients that had recurrent NMIBC and were undergoing active surveillance, 22 of whom required treatment during the study due to cystoscopic changes in size and/or number of lesions.[21] The authors reported that use of the test with a cutoff value of 0.4, approximately 34% of the cystoscopies could have been avoided.

A multi-center study by van Valenberg (2021) evaluated the use of the Xpert test in patients without a history of bladder cancer who were undergoing cystoscopy for hematuria.[22] Of the 1,124 patients who were enrolled, 925 were eligible for inclusion in this study which compared the Xpert test to cytology and to the UroVysion® test. Individuals with invalid or inconclusive results for the UroVysion® or Xpert test or who did not have cytology results available were excluded, leaving 828 patients in the analysis. Compared with histology/cytology, the Xpert test had a reported sensitivity of 78% (95% CI 66% to 87%) and specificity of 84% (95% CI 81% to 86%).

Comparison Studies

Lotan (2017) published an industry-sponsored study comparing Cxbladder™ to NMP22 Bladderchek, NMP22 enzyme-linked immunosorbent assay (ELISA), and UroVysion®.[23] The patients in this study all had a history of bladder cancer and were undergoing testing to rule out recurrent disease. There were 1,016 samples from 748 patients that had Cxbladder™, NMP22 Bladderchek, and NMP22 ELISA assays. These samples were used previously for the development and validation of the Cxbladder™ test. A much smaller number of samples (n=91) had UroVysion® results from routine clinical workup. The authors reported sensitivities and NPVs of 91% and 96% for Cxbladder™, 22% and 87% for cytology, 26% and 87% for NMP22 ELISA (positive >10.0U/ml), and 11% and 86% for NMP22 BladderChek, respectively. They separately reported a sensitivity of 33% and an NPV of 92% for UroVysion®. The specificities, PPVs, and false-positive rates were not reported. Employees of Pacific Edge Ltd., the company that markets Cxbladder™, performed statistical analyses for the article, and editorial assistance was also funded by the company. These limitations, along with the re-analysis of samples previously used for the development and validation of the Cxbladder™ assay, limit the conclusions that can be drawn from the study results.

The study by van Valenberg (2021) described above included an indirect comparison between the Xpert and Urovysion® tests.[22] When compared with cytology/histology, Urovysion® had a higher sensitivity than the Xpert test (59% vs. 44%) but a lower specificity (88% vs. 97%).

Section Summary

Numerous studies have evaluated the accuracy of the urinary tumor markers BTA stat, NMP22, UroVysion®, and ImmunoCyt™ for diagnosing and/or monitoring bladder cancer. Several systematic reviews of these studies have been published. In studies on the initial diagnosis of bladder cancer and/or detection of recurrent bladder cancer, urinary tumor marker tests were found to have reasonably high sensitivity and specificity compared with standard diagnostic approaches. Diagnostic performance studies on *FGFR3* or Cxbladder™ for identifying or monitoring bladder cancer generally showed that the markers had higher sensitivity than cytology. Specificity was compared with cytology in an analysis of Cxbladder™ data and found to be lower. No studies were identified that focused specifically on the use of urinary tumor markers for detecting UUT recurrences in patients with a history of bladder cancer.

There is a lack of direct evidence that health outcomes improve in patients managed with urinary tumor marker tests compared with those managed without tumor marker tests. Additionally, there is a lack of direct evidence that cystoscopy protocols can be changed when urinary tumor marker tests are used. The available studies have found low potential clinical benefit of urinary tumor marker testing for patients with NMIBC in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

URINARY MARKERS FOR SCREENING ASYMPTOMATIC INDIVIDUALS FOR BLADDER CANCER

Systematic Reviews

The ideal study for evaluating the effectiveness of a screening program is a randomized controlled trial (RCT) comparing outcomes in patients who did and did not participate in a screening program. In 2010, the U.S. Preventive Services Task Force updated its evidence review on screening adults for bladder cancer.[24] The quality of evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only one prospective study, rated as poor quality. The systematic review did not identify any studies evaluating the sensitivity or specificity of diagnostic tests for bladder patients in asymptomatic average-risk patients. Moreover, reviewers did not identify any suitable studies on whether treatment of screen-detected bladder cancer reduces disease-specific morbidity and mortality, or on potential harms of screening for bladder cancer. Reviewers concluded: “major gaps in evidence make it impossible to reach any reliable conclusions about screening.”

Randomized Controlled Trials

No randomized controlled trials of urinary tumor marker tests for bladder cancer screening in asymptomatic patients were identified.

Nonrandomized Studies

Several uncontrolled studies have reported findings of screening studies. Bangma (2013) reported on a population-based program with men in The Netherlands.[25] The study evaluated the feasibility of screening using urine-based markers and examined performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least one positive home hematuria test underwent screening for four urine-based molecular markers. Men with at least one positive urine-based test were recommended to undergo cystoscopy. Of 6,500 men invited to participate in screening, 1,984 (30.5%) agreed and 1,747 (88.1%) underwent hematuria testing. Of these, 409 (23.4%) tested positive for hematuria and 385 (94%) underwent urine-based marker testing. The number of men testing positive for each marker was 14 (3.6%) for NMP22, 33 (8.6%) for microsatellite analysis, six (1.6%) for *FGFR3*, and 40 (10.4%) for CH3. Cystoscopy was recommended for 75 men, and 71 actually underwent the procedure. Cancer was diagnosed in four (0.002%) of 1747 men who underwent screening (three bladder cancers, one kidney cancer). Although men in the study who tested negative on screening tests did not receive further testing, the investigators were able to link participants’ data to a Dutch cancer registry data. They determined that two cancers (one bladder cancer, one kidney cancer) had been diagnosed in men who completed the protocol; they were considered false negatives. Considering these data, the sensitivity of any urine-based marker was 80% (95% CI 28.4% to 99.5%) and the specificity was 95.9% (95% CI 94.9% to 96.8%). The sensitivity and specificity of the FDA-

approved NMP22 test was 25% (95% CI 0.63% to 80.6%) and 96.6% (95% CI 94.2% to 98.2%). The screening program had low diagnostic yield.

Lotan (2009) published a prospective study in which 1,502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure were screened.[26] The study used the NMP22 BladderChek® test and was supported by the test manufacturer. Individuals with positive BladderChek® tests underwent additional testing, beginning with urinalysis. Those found to have infection on urinalysis were treated and their urine was retested; others who tested positive received cystoscopy and cytology. Individuals with a negative BladderChek® test did not have to undergo additional testing. Eighty-five (5.7%) of the 1,502 participants had a positive BladderChek® test. Two of the 85 patients were found to have bladder cancer (noninvasive), yielding a positive predictive value of 2.4%. There was also one case of atypia. Follow-up at a mean of 12 months was obtained for 1,309 (87%) of 1,502 screened patients. No additional cancers were diagnosed in the group that had had positive BladderChek® tests. Two participants with negative BladderChek® screen had been diagnosed with bladder cancer; both tumors were less than one cm. Because no follow-up tests were done on participants who initially tested negative, it is unclear whether these were false-negative findings or new cancers. The authors report that the cancer prevalence in this population was lower than expected, which could be due in part to the large proportion who had previously undergone urinalysis. Study limitations included lack of follow-up testing on approximately 20% of participants who tested positive and lack of early cystoscopy and incomplete one-year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Section Summary

No RCTs were found that evaluated the impact of screening for bladder cancer on health outcomes in asymptomatic individuals. There is also insufficient observational evidence on the diagnostic accuracy of urinary tumor markers used to screen asymptomatic individuals for bladder cancer.

URINARY MARKERS FOR SCREENING ASYMPTOMATIC INDIVIDUALS FOR PRECANCEROUS COLONIC POLYPS

Nonrandomized studies

Deng (2017) published a report on the development and validation of PolypDx™.[27] Urine and stool samples were prospectively collected from 695 individuals who were participating in a colorectal cancer screening program to undergo colonoscopy. Metabolites in urine that were associated with adenomatous polyps were determined from 67% of the samples using nuclear magnetic resonance spectroscopy. Blinded testing on the validation set was performed in 33% of the samples using mass spectrometry, with a resulting area under the curve of 0.692.

Section Summary

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. There is insufficient evidence on the diagnostic accuracy of urinary tumor markers used to screen asymptomatic individuals for precancerous colon polyps.

URINARY MARKERS FOR ASSESSING MALIGNANCY RISK OF ADRENAL TUMORS

Urinary testing of steroid metabolite levels has been proposed as a method for distinguishing malignant from benign adrenal tumors.[28] However, no studies have been published assessing the clinical validity or utility of this test.

PRACTICE GUIDELINE SUMMARY

National Comprehensive Cancer Network (NCCN)

Bladder Cancer

The NCCN bladder cancer guidelines (v.4.2024) state that providers may consider testing for urinary urothelial tumor markers every three months along with urine cytology for the first two years of follow-up for high-risk patients with NMIBC (category 2B recommendation).[29]

Adrenal Tumors

The NCCN guidelines for adrenal gland tumors (v.2.2024) recommend a biochemical workup for hyperaldosteronism, Cushing's syndrome, pheochromocytoma, and suspected adrenocortical carcinoma.[30] For suspected or confirmed adrenal cortical carcinoma, the guidelines recommend testing for Cushing's syndrome or hyperaldosteronism, testosterone, and DHEA-S.

Colorectal Cancer

The NCCN colorectal cancer screening guidelines (v.1.2024) do not mention use of urinary tumor markers for detection of colon cancer in asymptomatic individuals at population-level risk of colon cancer.[31] Colonoscopy or fecal testing are recommended for screening purposes in these individuals.

AMERICAN UROLOGICAL ASSOCIATION AND SOCIETY OF UROLOGIC ONCOLOGY

The 2016 (amended 2020) guidelines from the American Urological Association and Society of Urologic Oncology addressed the diagnosis and treatment of NMIBC, based on a systematic review completed by the Agency for Health Care Research and Quality.[32] The guidelines state:

- In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of a cystoscopic evaluation. (strong recommendation, evidence level 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)

AMERICAN UROLOGICAL ASSOCIATION/SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE AND UROGENITAL RECONSTRUCTION

In 2020, the American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a guideline on the diagnosis, evaluation, and follow-up of microhematuria.[33] This guideline recommended the following with regard to urinary markers:

- Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria [Strong recommendation; Evidence level: Grade C]
- Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ [Expert opinion]

U.S PREVENTIVE SERVICES TASK FORCE

The U.S. Preventive Services Task Force concluded in 2011 that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults. The recommendation was based on insufficient evidence (grade I).[34] In April 2019, a literature surveillance report was published that scanned for relevant literature in PubMed and PubMed databases and the Cochrane library from 2009 to present.[35] The researchers found "no relevant systematic reviews on the impact of screening for bladder cancer on morbidity and mortality, outcomes of treatment of screen-detected bladder cancer, or harms of screening for or treatment of screen-detected bladder cancer." Additionally, "no randomized, controlled trials or controlled observational studies compared the benefits or harms of treatment of screen-detected bladder cancer with no treatment."

The USPSTF (2021) recommendation for screening for colorectal cancer "does not include serum tests, urine tests, or capsule endoscopy for colorectal cancer screening because of the limited available evidence on these tests and because other effective tests are available."[36]

SUMMARY

There is not enough research to show that urinary biomarker tests for bladder cancer or adrenal tumors can improve health outcomes for patients suspected of having adrenal or bladder cancer, or that using these tests or urinary biomarker tests for colonic polyps to screen patients can improve patient health outcomes. Therefore, the use of urinary tumor markers is considered investigational in the diagnosis of and monitoring for bladder cancer and adrenal tumors, and screening for colonic polyps.

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CODES

Codes	Number	Description
CPT	0012M	Oncology (urothelial), mRNA, expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
	0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
	0015M	Adrenal cortical tumor, biochemical assay of 25 steroid markers, utilizing 24-hour urine specimen and clinical parameters, prognostic algorithm reported as a clinical risk and integrated clinical steroid risk for adrenal cortical carcinoma, adenoma, or other adrenal malignancy
	0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps
	0363U	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
	0365U	Oncology (bladder), 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm including patient's age, race and gender reported as a probability of harboring urothelial cancer
	0366U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer
	0367U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection
	0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs)

Codes	Number	Description
		genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma
	0452U	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer
	0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative
	0467U	Oncology (bladder), DNA, next generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
	0549U	Oncology (urothelial), DNA, quantitative methylated real-time PCR of TRNA-Cys, SIM2, and NKX1-1, using urine, diagnostic algorithm reported as a probability index for bladder cancer and/or upper tract urothelial carcinoma (UTUC)
HCPCS	None	

Date of Origin: *April 2018*