National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Bladder Cancer

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Abbreviations: CFH, complement factor H; CFH-rp, complement factor H-related proteins; FISH, fluorescence in situ hybridization; HA, hyaluronic acid; HAase, hyaluronidase; hTERT, human telomerase reverse transcriptase; hTR, human telomerase; NMP, nuclear matrix protein; TPA, tissue polypeptide antigen; TRAP, telomeric repeat amplification protocol; TURB, transurethral resection of the bladder.
INTRODUCTION

Each year in the United States, nearly 56,000 new cases of bladder cancer are diagnosed and approximately 12,000 people die from this disease (1). The prevalence of bladder cancer in the United States is estimated at almost 500,000 cases. Almost twice as many cases of bladder cancer occur in men as in women, with cigarette smoking its leading cause (2). Other risk factors include exposure to industrial carcinogens and chronic infection with Schistosomiasis haematobium.

The most common symptom of bladder cancer is intermittent hematuria (80-85% of patients). Other urinary tract symptoms include increased frequency, urgency and dysuria (15-20% of patients). In some cases, urine cytology is positive for tumor cells, but the diagnosis is usually established by cystoscopic evaluation, prompted by hematuria or urinary tract symptoms, and biopsy. Bladder cancer is staged on the degree of tumor invasion into the bladder wall (3). Carcinoma in-situ (Tis) and Stages Ta and T1 are grouped as superficial bladder cancers because they are restricted to the inner epithelial lining of the bladder and do not involve the muscle wall. Of the “non-muscle invasive” tumors, Stage Ta tumors are confined to the mucosa, while Stage T1 tumors superficially invade the lamina propria. T1 tumors are regarded as being more aggressive than Ta tumors (4). Invasive tumors (Stages T2, T3 and T4) extend into the muscle (Stage T2) and into the perivesical fat layer beyond the muscle (Stage T3), with metastatic tumors (Stage T4) involving local nodes or distant organs.

The most common cell type of bladder cancer is transitional cell carcinoma, although adenocarcinomas, squamous cell carcinomas and sarcomas also occur. The cellular morphology of superficial bladder tumors is graded on the degree of cellular differentiation. The grading consists of well-differentiated (Grade 1), moderately differentiated (Grade 2) and poorly differentiated (Grade 3) tumors. Grading of cell morphology is important for establishing prognosis, as Grade 3 tumors are the most aggressive and the most likely to become invasive.

Noninvasive (superficial) bladder tumors are generally treated by transurethral resection of bladder (TURB) with or without intravesical treatments with Bacille Calmette-Guérin (BCG) immunotherapy or intravesical chemotherapy. Invasive tumors are usually treated by cystectomy, or with bladder-sparing therapies that consist of chemotherapy and radiation. Patients who have metastatic disease require systemic chemotherapy with multiple anti-cancer agents (5).

The majority of bladder cancer patients are diagnosed with superficial tumors. Even though superficial tumors can be completely resected, there is a high risk of recurrence: 50-70% of these patients will develop tumor recurrence within five years, and almost 90% will have a recurrence of their disease by 15 years. With intensive medical surveillance, the five-year survival rates for these patients range from 95% to 75% for Ta and T1 tumors, respectively.
However, almost 25% of patients with Ta and T1 noninvasive tumors will eventually develop invasive disease. The five-year survival rate decreases with tumor invasiveness and the presence of metastasis. Patients with Stage T2 tumors have a 5-year survival rate of 60%, but only 35% of patients with Stage T3 tumors and 10% of patients with Stage T4 metastatic tumors survive 5 years.

Lifelong surveillance is therefore required for bladder cancer patients who are initially diagnosed with noninvasive disease. Current patient monitoring protocols generally consist of regularly scheduled cystoscopic evaluations, usually together with urine cytology, performed every 3 months during the first two years of follow-up, twice a year during years 3 and 4, and annually thereafter, until disease recurrence is documented (6).

Urine tumor markers have been proposed for use as diagnostic aids in patients who present with hematuria, as prognostic indicators of disease recurrence and survival, and as early detectors of recurrent disease in the monitored patient. There are several potential applications of urine tumor marker tests in patient surveillance, including: a) serial testing to detect recurrent disease earlier, b) as an adjunct to urine cytology in order to improve the detection of disease recurrence, c) providing a less expensive and more objective alternative to urine cytology, and d) directing the frequency of cystoscopy evaluation in the follow-up of patients with bladder cancer.

CURRENTLY AVAILABLE TUMOR MARKERS FOR BLADDER CANCER

Currently available bladder cancer tumor markers and some of those in development are listed in Table 1, with an assessment of each marker and the level of evidence (LOE) for its clinical use. The LOE grading system is based on that of Hayes et al [see Section 1]. As indicated in Table 1, the United States Food and Drug Administration (FDA) has cleared six tumor marker tests for use in routine patient care.
URINE TUMOR MARKERS IN BLADDER CANCER: NACB RECOMMENDATIONS

At this time, no tumor markers tests can be recommended for use in the diagnosis and clinical management of bladder cancer. This includes tests for making a differential diagnosis, assessing prognosis, staging of the disease or monitoring patients for the early detection of recurrent disease. There are no prospective clinical trial data that establish the utility of any of the FDA cleared markers or the proposed markers for increasing survival time, decreasing the cost of treatment or improving the quality of life of bladder cancer patients. In the following report, we describe the FDA cleared markers and the variety of newly proposed markers.

FDA CLEARED MARKERS FOR BLADDER CANCER

BTA-Stat and Trak tests for complement factor H and related proteins

The BTA-Stat test (Polymedco, Courtlandt Manor, NY) detects complement factor H (CFH) and related proteins (CFH-rp) in urine (7). Factor H, a 155-kDa protein, has a central role in regulating the alternate pathway of complement activation to prevent complement-mediated damage to healthy cells. At least four other factor H-related proteins have been identified as products of a cluster of genes on chromosome 1 called the regulators of complement activation (RCA) locus, and while some of these proteins possess complement regulatory activity, others do not (8).

The BTA-Stat test provides semi-quantitative detection of CFH and the CFH-rp antigens using a double monoclonal antibody, immunochromatographic point-of-care device. The BTA-Stat test is reported to have 50-60% sensitivity for both superficial (Tis, Ta, T1) and invasive (T2-T4) tumors and a specificity of 72%. False-positive test results are reported to occur in some patients with infection of the bladder or urinary tract, nephritis, urinary calculi, or BPH and following trauma (9).

The BTA-Trak test is a quantitative enzyme immunoassay version of the BTA-Stat test. The manufacturer reports a sensitivity of 67% (Tis), 59% (Ta), 92% (T1), and 89% (T2-T4) for the stages of bladder cancer indicated. Specificities of 60% are observed in benign renal disease, urinary tract infections and sexually transmitted diseases, and rise to 80-90% in various other genitourinary diseases. Confirmatory reports have validated the high sensitivity of the BTA-Trak test in patients with recurrent disease (10,11). However, the test has not been generally accepted for patient surveillance due to its high false-positive rate (11,12).
Nuclear Matrix Protein
The nuclear matrix protein 22 (NMP22) test (Matritech, Newton, MA) is a double monoclonal antibody test designed to measure quantitatively the nuclear mitotic apparatus (MUMA) protein. This component of the nuclear matrix is over expressed by bladder cancer and is released into the urine in increased quantity. NMP-22 is not stable in urine and the use of a protein preservative is recommended. Clinical trial data showed that the NMP22 test, when performed 6-40 days post-surgery, correctly predicted the presence of recurrent disease at the first cystoscopic follow-up visit in 71% (24/34) of the patients with positive NMP-22 results (13). Of the subjects who had negative NMP22 test values, 86% (61 of 71), had no clinical evidence of disease at the first follow-up cystoscopy. Miyanaga (14) reported similar results for the NMP22 test but with a 35% false positive rate. In that study and a follow up report (15) NMP22 clearly performed better than voided urine cytology in detecting bladder cancer. Similar results were also reported by Stampfer et al in a multicenter study involving 171 patients with 274 cystoscopies (16), and by other groups (17,18).

A point-of-care version of the NMP22 test called Bladder Chek NMP22 test is available (19). One published report has addressed the false positive effect of red blood cells on this test (20), while another recent report suggested that the presence of white blood cells was responsible for false positive NMP22 results (21). In a recent comparison of Bladder Chek with cytology in which 1331 subjects with hematuria were tested, the Bladder Chek test had a sensitivity of 55.7% while cytology detected 15.8% of the cancers. The specificity of Bladder Chek was 85.7% compared with 99.2% specificity for urine cytology (22). The high false positive rate of NMP based tests has limited their general acceptance for routine use in patient care.

ImmunoCyt test
The ImmunoCyt test (Diagno-Cure Inc., Sainte-Foy, Quebec Canada) detects bladder cancer markers present on exfoliated cells using a cocktail of fluorescent antibodies (19A211, M344 and LDQ10) (23). The monoclonal antibody 19A211 detects high molecular weight carcinoembryonic antigen, while M344 and LDQ10 detects a cancer related mucin. One recent report has shown that the test has a sensitivity of (81%) and specificity of 75% in detecting bladder cancer (24). The ImmunoCyt test was evaluated in several earlier reports (25,26) with similar findings (25,26). When used with cytology, the ImmunoCyt test appears to improve the detection of low-grade tumors (27).
UroVysion test

Multi-target fluorescence in situ hybridization (FISH) detects cancer cells based on the aneuploidy of selected chromosomes. The UroVysion test (Vysis Chicago, IL) employs centromere probes specific to chromosomes 3, 7, 17 and 9 to detect aneuploidy associated with bladder cancer (28). A multi-site study of the UroVysion test demonstrated 71% sensitivity and 94.5% specificity for bladder cancer, which is much better than that of the BTA stat test (29). A similar finding was reported by Friedrich et al in a comparison of UroVysion with BTA stat and NMP22 (30).

PROPOSED BIOMARKERS NOT CLEARED BY THE FDA

Cytokeratins

Cytokeratins (CKs) are intermediate filament proteins characteristic of epithelial cells. Overexpression of certain cytokeratins occurs in transitional cell carcinoma of the bladder (31). The tissue polypeptide antigen (TPA) test (Sangtec Medical, Sweden) employs polyclonal antisera for detection of CK 8, 18 and 19. While the overall sensitivity is reported to be 80%, a false positive rate of 30-40% has limited its use in routine patient care (32). Subsequently, a tissue polypeptide specific (TPS) test (IDL Biotech, Sweden) was developed employing monoclonal antibodies against CK 8 and 18 (33). Another version, called the urinary bladder cancer (UBC) test (IDL, Sweden), also detects CK 8 and 18. A preliminary report suggests a sensitivity of 65% and specificity of 92% for this test (32,34). In one method comparison study, the UBC test out-performed the BTA Stat and NMP22 tests showing higher sensitivity and specificity for bladder cancer (35). A specific assay for urinary CK19 (Cyfra 21-1) has also been shown to give high sensitivity and specificity for bladder cancer (36).

Telomerase

Telomeres are regions located at the end of human chromosomes and are composed of many identical short repetitive sequences of TTAGGG. Their function is to stabilize and protect chromosomes (37,38). With each cell cycle, the ends of the telomeres shorten, until a critical length is reached after which cell division leads to breakdown of the telomere. Telomerase is a ribonucleoprotein enzyme that adds telomere repeats to maintain telomere length. Telomerase is inactivated in normal human epithelial tissue, but is reactivated in neoplasia (37). Telomerase has two major components, an RNA template and an enzymatic subunit.

The Telomeric Repeat Amplification Protocol (TRAP) assay (Geron, San Francisco, CA) measures enzymatic activity of telomerase. Telomeric repeats are synthesized in vitro, amplified by PCR and the products are visualized by various methods (37). In a tissue study of bladder
tumors, 86% (48/56) were shown to be telomerase-positive, but no activity was detected in non-neoplastic bladder tissue. The same study evaluated exfoliated cells in 109 urine samples from urological patients, 26 of which had bladder cancer. The authors reported 62% sensitivity and 96% specificity for telomerase activity in exfoliated urothelial cells (38). Advances in the measurement of telomerase include RT PCR assays for the telomerase RNA (hTR) and M-RNA for telomerase reverse transcriptase (hTERT). These assays have demonstrated a sensitivity of 83% for hTR and 80% for hTERT (39,40). Sanchini et al compared the TRAP and hTERT assays and confirmed the high sensitivity of both assays for telomerase, but suggested that the hTERT assay may be subject to a high false positive rate in patients with inflammation of the urinary tract (41). Saad et al reported that the combined use of the TRAP assay with NMP22 gave sensitivity and specificity comparable to that of voided urine cytology (42).

BLCA-4

Getzenberg et al (43,44) have described a bladder cancer specific nuclear matrix protein (BLCA-4). The BCLA proteins were identified on 2D gels and sequenced; and antibodies were subsequently raised to synthetic peptides corresponding to those sequences. Preliminary immunoassay data showed the BLCA-4 protein to be present in the urine of 53 of 54 bladder cancer patients (4 Stage Tis, 25 Stage Ta-T1, 13 Stage T2-T3 and 6 Stage T4). BLCA-4 urine levels in all 51 healthy control subjects were below the upper limit of normal. However, 38 of 202 spinal chord injured patients had elevated values. Superficial tumor was subsequently found in only 1 of these 38 cases (45). Since spinal chord injury patients are at high risk for developing bladder cancer, these subjects will require additional follow-up to assess the diagnostic role of BLCA-4. Clinical studies are under way to confirm the encouraging preliminary data on the utility of BLCA-4 in bladder cancer.

Survivin

The protein survivin is an inhibitor of apoptosis that is associated with the mitotic spindle (46). The expression of survivin is low in normal adult tissues but high in cancer tissues and transformed cell lines (47). Smith et al have developed a polyclonal semi-quantitative immunoassay to assess the role of survivin as a urine marker for bladder cancer. The protein was detected in all 46 new and recurrent cases of bladder cancer, but in none of 17 healthy subjects. Survivin was present in 3 of 35 patients who had previously been treated for bladder cancer but who had negative cystoscopic evaluations (48). More recently, Shariat et al reported figures for sensitivity and specificity, and positive and negative predictive values for the survivin protein of 64%, 93%, 92% and 67% respectively in pre-cystoscopy urine samples. In this study, urine survivin outperformed the NMP22 test in detecting bladder cancer (49). The detection of
mRNA survivin transcripts in exfoliated cells and bladder washings rather than the survivin protein may further improve the detection of bladder cancer (49).

**Microsatellite detection**

Repetitive sequences of DNA, each containing from 1 to 4 base pairs, are present throughout the genome and may undergo mutational changes associated with neoplasia, thereby serving as genetic cancer markers. The most common genetic change seen in bladder cancer is loss of heterozygosity (LOH) in chromosome 9. From 60 to 70% of bladder neoplasms show LOH in either the long or the short arm of chromosome 9, indicating that loss of suppressor genes may be the early initiating event in bladder carcinogenesis (50,51).

Using 20 microsatellite DNA markers, Mao et al (52) detected 95% of patients with bladder cancer. Steiner et al (53) tested two microsatellite markers in serial urine samples from 21 patients who had been treated for bladder cancer. Recurrent lesions were detected in 10 of 11 patients independently verified to have recurrent disease. Several other studies (54,55,56) using different panels of DNA markers suggest that it may be possible to identify a small set of microsatellite markers that reflect key DNA alterations specific and sensitive for bladder cancer. All of these reports suggest that microsatellite analysis of exfoliated cells is potentially useful to detect bladder cancer.

**Hyaluronic acid and hyaluronidase**

Hyaluronic acid (HA), the glycosaminoglycan ligand for CD44, has the ability to promote tumor cell adhesion, migration and angiogenesis. Hyaluronidase (HAase) degrades HA into angiogenically active fragments. Lokeshwar et al (57) have demonstrated that the HA test has a sensitivity of 83% and specificity of 90% for detecting bladder cancer. In addition, they found that hyaluronidase was elevated 5-fold to 8-fold in the urine of patients with Grade 2 and 3 tumors compared to normal individuals. Urinary hyaluronidase measurement has demonstrated a sensitivity of 100% and a specificity of 89% in detecting these high-grade bladder tumors in 139 patients (58). Hautmann and co-workers have used these analytes together in a combined HA-HAase test (59). In two method comparison studies, the HA-HAase test outperformed the ImmunoCyt test (59) and BTA-Stat and UBC tests (60) in the detection of bladder cancer.

**Other proposed markers**

DD 23 monoclonal antibody recognizes a 185 kDa antigen expressed by bladder cancer cells and has been proposed as an adjunct to cytology for the detection of bladder cancer (61,62). Urine fibronectin (63,64) and chorionic gonadotropin (protein and mRNA transcript) may also be markers for transitional cell carcinoma of the bladder (65). Detection of
hypermethylation of promoter regions of tumor suppressor genes and apoptosis genes also appears to have diagnostic value for bladder cancer (66,67,68). Recently, the use of urine proteomic profiles has been suggested as a diagnostic approach for bladder cancer (69,70).

Role of urine markers in early detection of bladder cancer

Almost all cases of bladder cancer are found during the work-up of patients who present with hematuria (71), but most cases of hematuria are not caused by bladder cancer. Urologic disease is detected in 10% of subjects who present with hematuria, and bladder cancer is detected in fewer than half of these subjects (72,73,74). The work-up of patients with hematuria is costly and may require cytology, cystoscopy, intravenous urography or computed tomography (75). Thus, tumor markers could be useful in identifying the patients in this high-risk group, which requires more intensive clinical work-up for bladder cancer. Zippe et al reported on the value of the urine NMP22 test in the evaluation of 330 patients with hematuria (76). The NMP22 test when used with a cut-off value of 10.0 u/ml detected all 18 cases of bladder cancer with 45 false positive cases (sensitivity, 100%; specificity, 85%). In this study, 267 unnecessary cystoscopies could have been avoided if cystoscopy had been directed by the NMP22 test. In a clinical trial submitted to the Food and Drug Administration (as Pre-Market Approval Data), the NMP22 test was elevated in 69.6% of 56 bladder cancer that were detected in the high risk group. In this report, the specificity was 67.7% (77). The NMP22 test has been cleared by the FDA for use as an aid to diagnose bladder cancer in individuals with risk factors or who have symptoms of bladder cancer. It is highly likely that other urine markers (e.g. BTA, UroVysion and Immunocyt) may also have value for cancer detection in subjects who present with hematuria. The high false positive rate is the major criticism of the urine-based tests when they are used to assess patients who present with hematuria or are used in patient surveillance. The low false negative rate of these tests is their strength, leading to a high negative predictive value that effectively rules out disease in a significant proportion of patients, thereby eliminating unnecessary clinical work-ups for bladder cancer.

Role of tissue markers for prognosis

Considerable research effort continues to be directed towards the identification of markers that predict the aggressive potential of superficial bladder tumors. Such information could lead to more effective surveillance protocols and permit more aggressive treatment of those patients with tumors most likely to progress to invasive or metastatic disease (78). Stein et al have performed an exhaustive review of a variety of biological markers reported to have prognostic value (45). More recently, p53 and other cell cycle control genes (79,80), chorionic gonadotropin beta gene transcripts (81), various cell matrix and adhesion proteins and differentially expressed
genes (early vs late stage tumors) have all been reported to have prognostic value (82). However, at the present time, none of these markers have yet been validated for use in routine patient care.

**Role of urine markers for patient surveillance**

Many reports have established the value of urine tumor marker tests in the early detection of recurrent bladder tumors, but as yet these urine tests cannot replace routine cystoscopy and cytology in the management of bladder cancer patients. Instead, they may be used as complementary adjuncts that direct more effective utilization of clinical procedures, thus reducing the cost of patient surveillance. Patients with superficial lesions of low grade (Ta, Grade 1 and II) are at lower risk for recurrence than patients with Ta Grade III and T1 tumors, and these lower-risk patients may need less intensive follow-up (16).

The urine markers used in patient surveillance have on occasion been criticized for their low sensitivity in detecting disease (86,87), but in most studies they have significantly improved the detection of bladder cancer when used in conjunction with cytology and cystoscopy. Voided urine cytology has its own limitations in detecting carcinoma in situ (Tis) and low-grade bladder tumors (88). It appears that urine markers can assist in the early detection of recurrence in patients with carcinoma in situ and low-grade superficial tumors (89).

**CONCLUSION**

The availability of many new markers for bladder cancer raises the possibility of improving the rate of cancer detection by combined use of selected markers, measured either simultaneously or sequentially (83). The objective of such panel testing should be to improve both the sensitivity and the specificity for bladder cancer detection. Prospective clinical trials are undoubtedly necessary to prove their clinical value, before such panels could be implemented in routine patient care (84). It should also be noted that the stability of these tumor marker analytes must be better defined in order to minimize false negative test results. Improved definition of the disease conditions which can produce false positive test results for urine based markers could lead to more effective use of these tests for cancer detection (85).
### Table 1. Currently available urine markers for bladder cancer.

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<th>Cancer Marker</th>
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<th>FDA approved?</th>
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HCG, human chorionic gonadotropin; HTR, human telomerase; hTERT, human telomerase reverse transcriptase; TRAP, telomeric repeat amplification protocol; LOE, Levels of evidence
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