# Current Status of Urinary Biomarkers for Detection and Surveillance of Bladder Cancer

Aurélie Mbeutcha, MD[a,b], Ilaria Lucca, MD[a,c], Romain Mathieu, MD[a,d], Yair Lotan, MD[e], Shahrokh F. Shariat, MD[a,e,f,*]

**KEYWORDS**

• Bladder cancer • Transitional cell carcinoma • Urothelial carcinoma • Urinary biomarkers • Urine • Detection • Surveillance • Follow-up

**KEY POINTS**

- Due to its high rate of recurrence, bladder cancer (BC) requires a close follow-up that includes regular cytologic and cystoscopy examinations and leads to expensive lifetime health care expenditures.
- Urinary cytology has a low sensitivity especially for low grade tumors, whereas cystoscopy remains an invasive examination. Therefore, urine-based biomarkers should be considered good alternatives for the detection and follow-up of BC.
- Many biomarkers have shown a higher sensitivity than cytology. Most of them, however, failed to reach its specificity. A combination of biomarkers may increase their performance.
- A standardization of the techniques used for their detection followed by multicenter and prospective analysis needs to be performed before any assessment in large controlled clinical trials.

## INTRODUCTION

With an estimated 74,000 new cases and 16,000 deaths for 2015, BC is the fifth most frequent malignancy in the United States.[1] Urothelial carcinoma of the bladder (UCB) constitutes the most common histologic type and is the dominant histology in more than 90% of cases of BC.[2] Approximately 75% of newly diagnosed BCs are non–muscle-invasive BCs (NMIBCs), of which 70% are Ta, 20% T1, and 10% carcinoma in situ.[3] These lesions are usually treated with

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[a] Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, Vienna 1090, Austria; [b] Department of Urology, Hôpital Archet 2, Centre Hospitalier Universitaire de Nice, University of Nice Sophia-Antipolis, 151 Route de Saint-Antoine, Nice 06200, France; [c] Department of Urology, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, Lausanne 1010, Switzerland; [d] Department of Urology, Rennes University Hospital, 2 Rue Henri le Guilloux, Rennes 35000, France; [e] Department of Urology, University of Texas Southwestern Medical Center, 5303 Harry Hines Boulevard #110, Dallas, TX 75235, USA; [f] Department of Urology, Weill Cornell Medical College, Cornell University, 525 E 68th St, New York, NY 10011, USA
* Corresponding author. Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, Vienna A-1090, Austria.
*E-mail address:* sfshariat@gmail.com

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transurethral resection of the bladder with or without intravesical instillation therapies according to guidelines.[4,5] The remaining 25% of BCs are muscle-invasive BCs (MIBCs) and the standard of care is radical cystectomy and bilateral lymph node dissection with or without perioperative chemotherapy.[6] Although the prognosis of MIBC is poor (5-year mortality rate of 38%),[7] the main issue with NMIBCs is that more than half of the patients experience disease recurrence within a period of 5 years and up to 30% of them experience disease progression to an MIBC despite therapy with curative intent.[8]

This high recurrence rate is the primary reason that BCs have the highest lifetime treatment cost per person of all cancers.[9,10] After initial treatment, patients with NMIBC are committed to a lifelong surveillance to identify recurrence early, with the goal of preventing disease progression to invasive disease. Depending on initial stage and grade, surveillance is of varying intensity but the current recommendation for high-grade tumors is cystoscopy and voided urine cytology every 3 months for 2 years, then every 6 months for 5 years, then yearly.[4,5] Unfortunately, each recurrence restarts the scheduling scheme such that with 50% to 70% recurrence for high-grade tumors, many patients have ever more cystoscopic procedures.

With a sensitivity of 90%, standard white light cystoscopy is the gold standard for detection of BC, but it remains an invasive and costly examination, limiting the compliance of patients for the follow-up.[11] Voided urine cytology is a highly specific test (99% specificity) but is limited by its low sensitivity (34%), especially in low-grade tumors[12,13] and by interobserver variations.[14]

Thus, to improve the management and the quality of life of patients with BC and to decrease the morbidity associated with current diagnostic and follow-up tests, many investigators have searched for a noninvasive, highly sensitive and specific marker of BC. Because urine is in contact with BC and can be collected noninvasively and in large amounts, urine-based assays are a natural and promising source for these biomarkers.

The assessment of a good biomarker should follow international guidelines.[15,16] Guidelines edited by the International Bladder Cancer Network define biomarkers according to their clinical use: detection (screening and assessment of patients with hematuria) and follow-up of patients with BC.[17] For each purpose, the required characteristics of biomarkers are different. To avoid unnecessary investigations and limit cystoscopies, a good diagnostic biomarker should have a low false-positive rate, whereas a good surveillance marker should have a high sensitivity and negative predictive value (NPV).[18]

To date, 6 tests (BTA stat [Polymedco, Cortlandt Manor, New York], BTA TRAK [Polymedco], NMP22 BC test kit [Matritech, Newton, Massachusetts], NMP22 BladderChek Test [Alere, Waltham, MA], uCyt+ [Scimedx, Denville, New Jersey], and UroVysion Bladder Cancer Kit [Abbott Molecular, Des Plaines, Illinois]) have been approved by the Food and Drug Administration (FDA) and are commercially available for clinical use. A multitude of newer markers, however, using genetic testing are currently undergoing validation and have the potential to change clinical practice.

This nonsystematic review summarizes the current data on commercially available and emerging urinary biomarkers for detection and surveillance of BC. Screening for BC is not discussed because this is a complex subject requiring its own review.[19–21]

## MATERIAL AND METHOD

The authors performed a Pubmed/Medline search on articles published in English from 2000 to June 2015 using a combination of the following keywords: bladder cancer, urothelial carcinoma, transitional cell carcinoma, urine, urinary biomarker, marker, surveillance, detection, diagnosis, follow-up, recurrence, and progression.

## COMMERCIALLY AVAILABLE BIOMARKERS

### *Food and Drug Administration–Approved Biomarkers*

#### *Nuclear matrix protein 22*

Nuclear matrix proteins (NMPs) are a family of proteins that play an important role in the structural framework of nucleus and are involved in every step of its function, from DNA replication to regulation of gene expression. NMP22 is specifically involved in mitosis by enabling a correct distribution of chromatin to daughter cells.[22] The urinary concentration of NMP22 is 5-fold higher in patients with BC compared with healthy patients.[23]

Two assays have been developed to detect NMP22 in voided urine. The original assay is the NMP22 BC test kit, a laboratory-based quantitative sandwich ELISA test using 2 antibodies. The NMP22 BladderChek Test is a qualitative immunochromatic assay designed as a point of care (POC) test. A few drops of urine on the cartridge containing NMP22 detection and reporter antibodies provide results within 30 minutes. Both tests have been approved by the FDA for BC surveillance, and the NMP22 BladderChek Test is also approved for detection of BC in patients at risk or presenting suspicious symptoms.