# Novel Biomarkers to Predict Response and Prognosis in Localized Bladder Cancer

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**KEYWORDS**

• Nonmuscle invasive bladder cancer • Diagnostic biomarkers • Prognostic biomarkers • DNA • RNA • Protein • Urine

**KEY POINTS**

- Urothelial carcinoma of the bladder (UCB) is the most expensive solid tumor to treat because of its high recurrence rate and the need of continued cystoscopic surveillance.
- Cystoscopy has a high sensitivity and specificity, but is a costly and invasive procedure; urinary cytology is noninvasive and highly specific and shows very low overall sensitivity, in particular in low-grade nonmuscle invasive bladder cancer (NMIBC).
- Several biomarkers may have better sensitivity than voided urinary cytology, but they are not accurate enough to replace cystoscopy and cytology.
- *NMP22, BTA*, ImmunoCyt/uCyt+ and UroVysion/FISH have been approved by the Food and Drug Administration for screening and follow-up of patients with NMIBC in combination with cystoscopy.
- The long interval required for validation, testing, and approval of the assays and the lack of standardization could explain the present failure of biomarkers to predict NMIBC development, recurrence, and progression.

## INTRODUCTION

Urothelial carcinoma of the bladder (UCB) is the most expensive solid tumor to treat because of its high recurrence rate and need of continued surveillance, with an estimated annual cost of $3.7 billion in the United States.[1] More than 400,000 patients are newly diagnosed with UCB worldwide every year, and more than 150,000 die from the disease.[2]

The standard evaluation of a suspected UCB consists of cystoscopy and urinary cytology.[3] Although cystoscopy has a high sensitivity and

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specificity, it is a costly and invasive procedure, with a risk of complications, such as urinary infections, pain, and bleeding. Urinary cytology has a low overall sensitivity rate of only 33% to 48%, but a higher specificity of 86% to 90% in the detection of nonmuscle invasive bladder cancer (NMIBC).[4,5] Its predictive accuracy improves in high-grade tumors to approximately 90%, whereas it does not go beyond 60% in low-grade NMIBC.[6] Urinary cytology after bladder washing seems to have a higher sensitivity than from voided urine.[7]

In UCB, the TNM staging together with various prognostic models, such as the European Organization for the Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) scoring systems, allow defining the risk of recurrence and progression after the surgery.[3,8] However, among patients with UCB staged similarly, there is still a considerable variation in rates of recurrence, disease progression, and response to treatment. Therefore, biomarkers are needed to improve prognostication.

Intense work is being done in the field of NMIBC biomarkers with the main goals of reducing the number of invasive cystoscopic evaluations through early diagnosis and identifying those patients with a higher risk of disease progression. The identification of valuable NMIBC biomarkers would improve our understanding of the biological pathways involved in the genesis and progression of the tumor, but would also add information about UCB outcomes.

A biomarker is an indicator of biological and pathogenic processes or pharmaceutical responses to a therapeutic intervention.[9] The ideal biomarker should be noninvasive, rapid to analyze, objective, easy to perform, sensitive, specific, reproducible, and, above all, cost-effective. However, to date, the available biomarkers are all lacking one or more of these characteristics. Several biomarkers showed a higher sensitivity than voided urinary cytology, but they are not accurate enough to replace it. Indeed, although several studies have been published on NMIBC biomarkers in recent years, none of them is recommended for use in clinical practice.

The classification of UCB biomarkers is relatively complex. They could be classified according to (1) the sample used for their identification, (2) their objective, (3) the biomolecule, or (4) the type of measurements applied (**Fig. 1**).[10]

Because the literature on this topic is vast, the aim of this review was to provide a summary of the most relevant biomarkers investigated in the last period as predictor of NMIBC, recurrence, and aggressiveness.

## DIAGNOSTIC BIOMARKERS FOR EARLY DETECTION OF NONMUSCLE INVASIVE BLADDER CANCER

Diagnostic biomarkers aim to detect the disease in symptomatic patients or in those having an increased risk, if possible at early stages.[11] NMIBC is an attractive tumor for screening because of its well-known risk factors and its favorable outcomes when diagnosed at early stages. Macrohematuria is the most common symptom, but it is not specific and is not related to the pathologic stage. Madeb and Messing[12] screened 1575 men aged 50 years or older without a history of UCB,

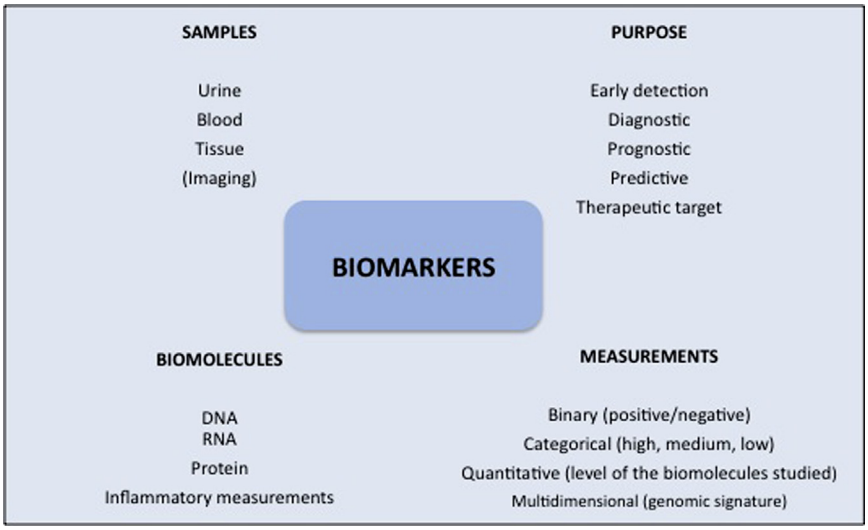


**Fig. 1.** Classification of biomarkers for NMIBC.