



## Urinary Biomarkers for Urological Cancer

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Received: September 22, 2023

Published: October 01, 2023

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Urinary biomarkers are substances that can be measured in the urine to help diagnose, monitor, or predict the course of urological cancers, such as bladder cancer. Urinary biomarkers can be useful for detecting cancer early, assessing the risk of recurrence or progression, and evaluating the response to treatment. Urinary biomarkers can also reduce the need for invasive procedures, such as cystoscopy or biopsy, which can cause discomfort and complications for patients [1].

There are different types of urinary biomarkers, based on the molecular characteristics of the cancer cells or their products. Some of the most common urinary biomarkers for bladder cancer are:

- **Nuclear matrix protein 22 (NMP22):** This is a protein that is part of the nuclear skeleton of cells. It is released into the urine when cancer cells die or are damaged. NMP22 can be detected by a simple urine dipstick test (NMP22<sup>®</sup>, BladderChek<sup>®</sup>) or by an enzyme-linked immunosorbent assay (ELISA) (NMP22<sup>®</sup>) [2].
- **Bladder tumor antigen (BTA):** This is a protein that is produced by bladder cancer cells and shed into the urine. BTA can be detected by a rapid immunochromatographic test (BTA stat<sup>®</sup>) or by an ELISA (BTA TRAK<sup>®</sup>) [3].
- **Fluorescence in situ hybridization (FISH):** This is a technique that uses fluorescent probes to detect specific chromosomal abnormalities in the DNA of bladder cancer cells in the urine. FISH can identify gains or losses of chromosomes 3, 7, 17, and 9p21, which are associated with bladder cancer. FISH is performed by a specialized laboratory using a commercial kit (UroVysionTM) [4].
- **Cytokeratin fragment test:** This is a test that measures the levels of cytokeratin 8 and 18 fragments in the urine. Cytokeratins are proteins that form part of the cytoskeleton of epithelial cells. They are released into the urine when bladder cancer cells undergo apoptosis or necrosis. Cytokeratin fragment test can be performed by a rapid immunochromatographic test (UBC<sup>®</sup> Rapid) or by an ELISA (UBC<sup>®</sup> Elisa) [5].
- **Multigene RNA test:** This is a test that measures the expression levels of five messenger RNA (mRNA) biomarkers in the urine. These biomarkers are CDK1, MDK, HOXA13, IGFBP5, and CXCR2. They are involved in cell cycle regulation, angiogenesis, invasion, and metastasis of bladder cancer. Multigene RNA test is performed by a specialized laboratory using a commercial kit (Cxbladder<sup>®</sup>) [6].
- **Epigenetic profile test:** This is a test that measures the methylation status of three genes in the urine. These genes are TWIST1, NID2, and OTX1. They are involved in epithelial-mesenchymal transition, extracellular matrix remodeling, and cell differentiation of bladder cancer. Methylation is a chemical modification of DNA that affects gene expression. Epigenetic profile test is performed by a specialized laboratory using a commercial kit (AssureMDxTM) [7].
- **Morpho-histochemical staining test:** This is a test that uses a novel staining method to identify bladder cancer cells in the urine. The staining method combines morphological and histochemical features to differentiate between normal and malignant cells. Morpho-histochemical staining test is performed by a specialized laboratory using a commercial kit (CellDetect<sup>®</sup>).

| Test                          | Sensitivity | Specificity | Cost     | Availability | Ease of use |
|-------------------------------|-------------|-------------|----------|--------------|-------------|
| NMP22                         | 50-70%      | 75-85%      | Low      | High         | High        |
| BTA                           | 60-80%      | 65-75%      | Low      | High         | High        |
| FISH                          | 80-90%      | 80-90%      | High     | Low          | Low         |
| Cytokeratin fragment          | 70-80%      | 70-80%      | Low      | High         | High        |
| Multigene RNA                 | 80-90%      | 80-90%      | High     | Low          | Low         |
| Epigenetic profile            | 90-95%      | 90-95%      | High     | Low          | Low         |
| Morpho-histochemical staining | 85-95%      | 85-95%      | Moderate | Moderate     | Moderate    |

**Table 1:** Available urinary biomarker tests for bladder cancer.

These urinary biomarkers have different advantages and limitations in terms of sensitivity, specificity, cost, availability, and ease of use. Sensitivity refers to the ability of a test to correctly identify patients who have bladder cancer, while specificity refers to the ability of a test to correctly exclude patients who do not have bladder cancer. A high sensitivity means that a negative test result can rule out bladder cancer with high confidence, while a high specificity means that a positive test result can confirm bladder cancer with high confidence.

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