Urinary markers for bladder cancer
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F1000Prime Reports 2013, 5:21 (doi:10.12703/P5-21)

Abstract
Bladder cancer has the fifth highest incidence of all malignancies in the United States, with a propensity to recur, requiring lifelong surveillance after diagnosis. Urinary markers of disease have been of extreme interest in this field in an effort to simplify surveillance schedules and improve early detection of tumors. Many markers have been described, but most remain investigational. However, some markers have undergone clinical trials and are approved for clinical use. In this review, urinary markers and their application for screening and surveillance of bladder cancer are discussed.

Introduction
Bladder cancer (urothelial carcinoma) has the fifth highest incidence of all malignancies in the United States, with an estimated 72,570 new cases and 15,210 deaths in 2013 [1]. At presentation, approximately 70% are non-muscle-invasive (stage Tis, Ta, T1) and 30% muscle-invasive (stage T2, T3, T4) [2]. Of the non-muscle-invasive tumors, 50-70% will recur despite conservative measures such as transurethral and intravesical therapy [3,4]. It is because of this natural history that, once diagnosed, bladder cancer requires lifelong surveillance. Unfortunately, this management paradigm contributes to bladder cancer carrying the highest cost from diagnosis to death of all cancers, ranging from $96,000 to $187,000 (2001 values) in the United States [5]. Consequently, there is a need for an accurate marker of disease in order to decrease the cost associated with surveillance. An accurate marker would also have the added benefit of improving quality of life by potentially minimizing the number of invasive endoscopic evaluations.

An accurate bladder cancer marker should ideally be capable of both screening high risk populations as well as surveillance of patients with a known history of bladder cancer. Given the relatively low overall prevalence of bladder cancer in the general population, widespread screening is not cost effective and, therefore, not recommended at this time [6,7]. However, screening individuals who are at high risk for bladder cancer, such as those with a history of tobacco abuse, high risk occupational exposure, cyclophosphamide exposure, or pelvic radiation, may be beneficial for early detection of bladder cancer.

Recent advances
For decades, cystoscopy with the addition of urine cytology has been the gold standard in the detection and surveillance of bladder cancer. Current surveillance protocols after initial diagnosis typically include cystoscopy and urine cytology every 3 months for the first 1 to 3 years, every 6 months for an additional 1 to 3 years, and then annually thereafter. Cystoscopy is a minimally traumatic office procedure and is successful in identifying most bladder tumors. However, it may be inconclusive if a patient has a grossly abnormal appearance to their bladder mucosa, such as patients with an indwelling catheter or an active inflammatory condition. While still the gold standard for diagnosis, cystoscopy has a false-negative rate either from operator error, or from small areas of sessile tumor (carcinoma in situ), which may be difficult to detect [8,9]. Additionally, although cystoscopy is a minor procedure, it can still cause significant patient discomfort, stress, and anxiety [10,11].
An abundance of data supports the idea that urine cytology with cystoscopy is superior to cystoscopy alone in detecting high-grade urothelial carcinoma, as well as upper tract tumors [12,13]. Accordingly, any new marker must have its performance considered against this current gold standard. A meta-analysis of 36 studies found a sensitivity and specificity of 44% and 96%, respectively, for urine cytology [14]. Additionally, the positive predictive value of cytology is approximately 90% [15,16]. However, one major limitation of urine cytology is its low sensitivity for the detection of low-grade tumors, at approximately 4% to 31% [17]. Unfortunately, thus far, a similar correlation is being identified in the current investigational urinary markers as well.

Therefore, the addition of a commercially available bladder tumor marker would add to the armamentarium of bladder cancer detection. The ideal screening and surveillance test should be non-invasive, rapid, easily accessible to providers and patients, and have high sensitivity and specificity. Because urine comes into direct contact with bladder tumors, urinary markers have been of extreme interest in this field. Many markers have been described, but most of them remain investigational and are still undergoing preclinical evaluation (see Table 1). Few have undergone clinical trials and are approved for clinical use.

When investigating the utility of a new marker, it is important to delineate the difference between screening and surveillance applications. One function of an accurate urinary marker for bladder cancer would be in surveillance of patients with a history of bladder cancer, with the goal of detecting early recurrence of disease and potentially minimizing the need for invasive testing. The other use would be in screening the general population, or patients at high risk, for bladder cancer. When examining the current literature on the various urinary markers, it must be understood that the overwhelming majority of studies have used mixed population cohorts (i.e. patients with history of bladder cancer, patients at risk of getting bladder cancer, and asymptomatic low risk patients). Few studies have evaluated markers in purely surveillance or purely screening populations and this limits the analysis of the sensitivity and specificity of these assays. When evaluating the performance of a marker, one must be careful to consider the study population in which it is being applied as disease prevalence will impact the performance of the marker. Although low in number, some of these markers have undergone focused studies, and we have attempted to segregate these data in Table 2, accepting that uniform data are not available for each marker.

A recent analysis of 21 screening cohort studies examined the use of these markers for screening [18]. Using various methods and markers in addition to cystoscopy, bladder cancer was diagnosed in 0.0% to 51.2% of high-risk screening populations (removing the single highest outlier, the range was 0.0% to 1.64%), with a median

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**Table 1. Summary of urinary markers for bladder cancer**

| Test (Manufacturer) | Marker detected                                      | Assay type                                      | FDA approval |
|---------------------|------------------------------------------------------|------------------------------------------------|--------------|
| Cytology            | Tumor cells                                          | Microscopy                                     | N/A          |
| BLCA-4              | Nuclear matrix protein                               | Sandwich ELISA (rabbit polyclonal antibody)    | –            |
| BTA sta® (Polymedco)| Complement factor H-related protein and complement factor H | Immunoassay or point-of-care               | For diagnosis & follow-up |
| BTA TRAK® (Polymedco)| Complement factor H-related protein and complement factor H | Sandwich ELISA                                | For diagnosis & follow-up |
| CYFRA 21-1 (Bio International; Roche Diagnostics) | Cytoskeletal protein (cytokeratin 19) | Immunoradiometric assay or ELISA | – |
| DD23 (UroCor Labs) | 185-kDa tumor associated antigen                     | Immunocytochemistry                            | –            |
| NMP22/BladderChek® (Alere) | Nuclear mitotic apparatus protein                  | Sandwich ELISA or point-of-care               | For diagnosis & follow-up |
| Survivin            | Inhibitor of apoptosis gene                          | Bio-dot test (rabbit polyclonal antibody)      | –            |
| UBC™ (IDL Biotech)  | Cytoskeletal proteins (cytokeratin 8 and 18)         | Sandwich ELISA or point-of-care               | –            |
| ImmunoCyt™/uCyt™ (Scimedx) | Carcinoembryonic antigen, two bladder tumor cell-associated mucins | Immunocytochemistry                           | For follow-up |
| UroVysion™ (Abbott, Vysis) | Alterations in chromosomes 3, 7, 17, and 9p21 | FISH                                           | For diagnosis & follow-up |

ELISA, enzyme-linked immunosorbent assay; FISH, fluorescence in-situ hybridization
incidence of 0.64%. Given this low prevalence, screening of both the general population and high-risk populations has been called into question.

In similar fashion, final results of a screening program using home hematuria testing and molecular markers were recently published [19]. 1747 asymptomatic men completed home hematuria testing and, if positive, were screened with a variety of molecular markers and underwent subsequent cystoscopy if warranted. Of this cohort, four patients were diagnosed with bladder cancer and one with a kidney tumor. Screening missed one patient with bladder cancer and one with a kidney tumor. The authors concluded that a sequential screening approach may help minimize unnecessary invasive testing with very few missed cancers. However, this mass screening program had a very low diagnostic yield.

Innumerable assays have been developed over the last few decades, with many of them claiming good performance initially, only to have this fade with long-term follow-up. We have focused on some of the more common, and more promising, urinary markers to date. This includes urine-based assays (BLCA-4, BTA stat®, BTA TRAK®, CYFRA 21-1, NMP22, Survivin, UBC™) and cell-based assays (DD23, ImmunoCyt™/uCyt+™, UroVysion™). To date, the only urinary markers that have Food and Drug Administration (FDA) approval for diagnosis and follow-up of bladder cancer are BTA stat®, BTA TRAK®, NMP22, and UroVysion™, with ImmunoCyt™/uCyt+™ only being approved for follow-up of bladder cancer. The molecular targets of each assay differ widely and are summarized in Table 1.

One of the few markers to gain widespread clinical use is the UroVysion™ test, which utilizes fluorescence in-situ hybridization (FISH) to identify chromosomal abnormalities. This test seems to be more sensitive, but less specific, than urinary cytology across all tumor grades. A recent meta-analysis showed that the overall performance of UroVysion™ was better than that of cytology (area under the curve: 87% vs 63%) [20]. However, the difference was almost entirely attributable to the ability of FISH to diagnose stage Ta patients better than cytology, as the value decreased when these patients were excluded from the analysis (area under the curve: 94% vs 91%). Another reason for the popularity of FISH is in its usefulness for monitoring patients with superficial bladder cancer after treatment with intravesical bacillus Calmette-Guérin (BCG). In this group, FISH has shown superiority to cytology and is beneficial when cytology results are equivocal [21-23].

Another marker with promise is nuclear mitotic apparatus protein (NMP22), a member of the nuclear matrix protein family. NMP22 is quite prevalent in malignant urothelial cells, but not in their normal counterpart. A recent study compared NMP22, cytology, and cystoscopy by performing both urine tests during 351 consecutive cystoscopies [24]. NMP22, cytology, and cystoscopy demonstrated sensitivity/specificity of 51%/96%, 35%/97%, and 92%/88%, respectively. Importantly, the cost of NMP22 and cytology were $8,750 and $52,500, respectively, showing that not all new markers will be more expensive than the current gold standard. However, because this protein is released from apoptotic urothelial cells, many benign conditions of the urinary tract contribute to a significant false-positive rate. One study found that greater than 80% of the false-positive results were categorized as benign inflammatory or infectious conditions, stone disease, recent foreign body in the urinary tract, bowel interposition segment, another genitourinary cancer, or an instrumented urine sample [25]. In fact, the presence of ureteral stents or any bowel interposition segment had a 100% false-positive rate.

| Table 2. Sensitivity and specificity of urinary markers for bladder cancer |
|-----------------|-----------------|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Test             | Surveillance*   |          |                  |                  |                  |                  |                  |                  |                  |
|                 | Sensitivity (%) | Specificity (%) | References       |                  |                  |                  |                  |                  |                  |
| Cytology         | 22-52           | 96-98    | [14,28,29]       |                  |                  |                  |                  |                  |                  |
| BLCA-4           | 89-96           | 100      | [32,33]          |                  |                  |                  |                  |                  |                  |
| BTA stat®        | 53-83           | 67-72    | [34,35,29,36]    |                  |                  |                  |                  |                  |                  |
| BTA TRAK®        | 66-72           | 51-75    | [37-39]          |                  |                  |                  |                  |                  |                  |
| CYFRA 21-1       | 67-97           | 67-89    | [40-42]          |                  |                  |                  |                  |                  |                  |
| DD23             | 70-81           | 60       |                  |                  |                  |                  |                  |                  |                  |
| NMP22/BladderChek® | 47-100     | 60-90    | [24,25,35,40,45-51] |                  |                  |                  |                  |                  |                  |
| Survivin         | 64-100          | 87-93    | [53-55]          |                  |                  |                  |                  |                  |                  |
| UBC™             | 66-82           | 83-90    | [34,56]          |                  |                  |                  |                  |                  |                  |
| ImmunoCyt™/uCyt+™ | 50-100     | 69-79    | [28,57-60]       |                  |                  |                  |                  |                  |                  |
| UroVysion™       | 36-100          | 89-98    | [61,62]          |                  |                  |                  |                  |                  |                  |
|                  |                  |          |                  |                  |                  |                  |                  |                  |                  |
|                  |                  |          |                  |                  |                  |                  |                  |                  |                  |

*Also includes mixed cohorts
Table 3. Summary of International Consultation on Urological Diseases recommendations regarding urinary markers for bladder cancer [27]

| Bladder cancer screening and early detection using urinary markers is promising but cannot be recommended at present. |
| Marker-guided follow-up of patients with low-grade NMIBC appears attractive; however, based on current levels of evidence, this procedure cannot be recommended at present. |
| A use of molecular markers in surveillance of patients with high-grade NMIBC cannot be recommended. |
| Reflex testing is considered experimental at present and should be evaluated in clinical studies. |

Abbreviations
ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug administration; FISH, fluorescence in situ hybridization; NMP22, nuclear mitotic apparatus protein; PSA, prostate-specific antigen.

Disclosures
The authors declare that they have no disclosures.

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