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Caption: **Oncology**

Title: **A urine test for bladder cancer: available soon in primary care?**

Author: **Erica di Martino**, Research Fellow, Division of Primary Care, Public Health & Palliative Care, University of Leeds; **Anam Ayaz-Shah**, PhD student, Division of Primary Care, Public Health & Palliative Care, University of Leeds; **Bethany Shinkins**, Associate Professor of Health Economics, Test Evaluation Group, Leeds Institute of Health Sciences, University of Leeds; **Sunjay Jain**, Consultant Urologist, Department of Urology, St James's Hospital, Leeds Teaching Hospitals Trust; **Richard D. Neal**, General Practitioner and Professor of Primary Care Oncology, Division of Primary Care, Public Health & Palliative Care, University of Leeds

Haematuria: a problematic symptom

In the UK, bladder cancer (BC) kills around 5600 people per year. The majority of these cases are men, as the disease is 2.5 times more frequent in males than females.

Blood in the urine (haematuria) is the most common symptom, occurring in around 85% of cases. Patients may consult their GPs after noticing a change in the colour of their urine (occasionally referred to as 'visible', 'gross' or 'macroscopic' haematuria [VH]), while less obvious blood traces may be picked up by a routine urine test ('non-visible' or 'microscopic' haematuria [NVH]). Both types are associated with a small but not insignificant risk of bladder cancer, with NVH being more significant in older patients.[1]

NICE guidelines (https://cks.nice.org.uk/urological-cancers-recognition-and-referral) currently recommend that all patients aged over 45 years with unexplained or recurrent VH are referred to the haematuria clinic or urology department via the urgent two-week pathway for suspected cancer. Patients over 60 should also be referred if they have NVH combined with other clinical signs such dysuria or a raised white cell count. However, in the UK only around 34% of BC patients are diagnosed through this urgent referral pathway. Patients who do not fall within the urgent referral guidelines or with vague symptoms may end up being diagnosed through a standard GP referral (28% of all BC cases) or as an emergency presentation (18%). (http://www.ncin.org.uk/publications/routes_to_diagnosis).

Once a case of BC is suspected, the gold standard diagnostic test is visualisation of the bladder by cystoscopy. This procedure is reasonably sensitive and specific;(2) however, it is labour intensive, expensive (£243, code LB14E, NHS National Tariff 2018/19), can be embarrassing and painful, and carries risks such as infections, bleeding, damage to the bladder wall or to the urethra.

Urine cytology, which looks for abnormalities in bladder cells exfoliated in urine, is a very specific test but with little added diagnostic value due to its low sensitivity.[2] In practice, it is often limited to selected patients; for example, those with persistent haematuria but negative cystoscopy. Further imaging, such as an abdominal and pelvic ultrasound or CT scan, may also be performed in these patients to exclude upper urinary tract cancers (kidney and ureter).

Overall, only around 1 in 10 patients referred and investigated for haematuria are found to have BC, and very few have other urinary malignancies.[3] New tests to help identify haematuria patients who are at a higher risk of cancer would help improve the diagnostic pathway, reduce the number diagnosed by emergency presentation, lessen the burden on urology services and spare an invasive and costly examination, such as cystoscopy, to those who do not have cancer.

Bladder cancer urinary tests: from lab to clinic

Cancer is a multistep process during which cells accumulate a number of abnormalities, including changes in their DNA and in the type and amount of mRNA and proteins they produce. Overall bladder cancer cells may show hundreds of aberrations, some very common, others only found in a few cases. Because bladder cancer cells are in contact with urine and are shed into it, some of these alterations can be detected in urine samples from BC patients. A great effort is going into translating knowledge of these cancer-specific molecular changes into urinary tests for BC diagnosis (see Figure 1). The challenge, however, is narrowing them down to a few key markers that can identify most cancers while ruling out most non-cancers.

Many BC urinary tests require specialist laboratory expertise and complex, time-consuming, and costly methodologies. However, a few easy to use bladder cancer point-of-care (BC-POC) tests have reached the market (see Table 1). Most BC-POC tests are lateral flow immunochromatographic assays, based on the principle of a liquid (urine) running along a surface lined with antibodies against a certain marker. They look and function similarly to home pregnancy tests, with results displayed as the presence/absence of a result line in the test window shortly (5–30 minutes) after the addition of a few drops of urine. In contrast to the others, Xpert® Bladder Cancer Detect is a polymerase chain reaction-based assay. A small volume (4.5 ml) of urine is added to a cartridge that is then loaded into a processing unit, with results available within 90 minutes.

As BC-POC tests provide quick information on cancer risk without requiring specialist technical expertise, they would be ideal to use in primary care for triaging patients presenting with haematuria. However, implementation would first require meeting a number of essential requirements, detailed in Table 2.

Disappointingly, initial trials indicate that the sensitivity of some BC-POC tests is too low to be clinically useful as a stand-alone test. For example, pooled data from thousands of patients showed an overall sensitivity of 56% (hazard ratio [HR] 95%; confidence interval [CI] 52–59%) for the BladderChek®[4], and 59% (HR 95%; CI 55–62%) for UBC-Rapid®[5], which suggests that these tests would miss around 1 in 2 cancers.

In a similar pooled study,[6] BTAStat® fared better, with a 67% (HR 95%; CI 64–69%) sensitivity, while an initial assessment of Xpert® Bladder Cancer Detect showed a sensitivity in the 65–83% range. For comparison, the sensitivity of white light cystoscopy is around 87% for papillary lesions, although it is lower (around 67%) for flat carcinoma-in-situ (CIS).[7] As the performance of BC-POC tests is not superior to the gold standard test, they are generally considered as an add-on to cystoscopy rather than a stand-alone test (for example, they could be useful to help identify CIS lesions missed by cystoscopy). Notably, extreme variability in test performance is observed between studies (see the large sensitivity range in Table 1) due to differences in design and patient selection, showing the need for a more systematic comparative evaluation of these or upcoming BC-POC tests in future.

Evaluating BC-POC tests in the 'real world'

Funded by Cancer Research UK, the CanTest collaborative has recently developed a framework for the evaluation of cancer diagnostic tests, involving a five-phase iterative process.[8] This progresses from single tests, assessed in isolation in selected populations with high disease incidence, to direct comparisons of clinical and cost-effectiveness of several tests in a 'real world' clinically relevant population, where cancer prevalence is lower and confounding factors may be present.

Most studies of BC-POC tests map to the earlier steps in this process, as they have looked at single test performance in patients with BC or under surveillance for a previous BC compared to

healthy controls. These results are difficult to extrapolate to a primary care population for a number of reasons. Firstly, the performance of diagnostic tests is affected by disease prevalence, with a lower sensitivity and higher specificity more likely in low-prevalence populations (eg, primary care haematuria patients) compared to high-prevalence groups (eg, BC cases monitored for recurrence).[9]

Secondly, numerous studies have shown that BC-POC tests are much better at spotting high grade and stage tumours rather than low grade superficial ones. Therefore, sensitivity in primary care haematuria patients and patients under surveillance for a previous BC may not be comparable if the cancer stage and grade composition differs in the two groups (for example, due to cancers being picked up at an earlier stage in patients monitored for recurrences).

The specificity of BC-POC tests in primary care may also be lower than expected, based on studies using urine samples from healthy controls, because the presence of conditions that are common in primary care patients (eg, infection, inflammation, benign prostate disease and kidney stones) has been shown to increase the number of false positives [10, 11]. In addition, the rate of false positives of some BC-POC tests is increased by the presence of blood in the urine (see Table 1), which means that their specificity in patients presenting to their GP with severe haematuria may be worse than in patients under BC surveillance without haematuria.

Overall, this complexity illustrates the crucial importance of conducting future research on BC-POC tests in a 'real world' primary care setting, using the CanTest framework as guidance.

How good does a BC-POC test need to be?

It is evident that any test for triaging patients with potential cancer symptoms needs to be highly accurate, but there is little consensus on what is an acceptable value of sensitivity and specificity. By mapping the full clinical pathway and modelling the downstream clinical and cost effectiveness of different test results (eg, false positives and false negatives), acceptable levels of accuracy and test costs in different clinical settings could be explored. This information would be extremely useful for guiding the development of future tests, and avoid wasting resources in trialling tests that are unlikely to achieve clinical and cost-effectiveness.

Interestingly, an investigation looking at what minimal sensitivity would be considered acceptable to patients has shown that, despite being an invasive procedure, cystoscopy was preferred by some as it provided greater peace of mind.[12] According to the study, for a urinary test to be considered acceptable to most patients as a replacement of cystoscopy, the minimal sensitivity would need to be at least 90%. This study, however, focussed on BC patients undergoing cystoscopy for monitoring recurrences. Primary care patients with haematuria but no prior cancer diagnosis or experience of cystoscopy may hold a different perspective.

Declaration of interests:

The authors do not have any conflict of interest to declare.

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References

1. Price SJ, Shephard EA, Stapley SA, Barraclough K, Hamilton WT. Non-visible versus visible haematuria and bladder cancer risk: a study of electronic records in primary care. Br J Gen Pract. 2014;64(626):e584-9.

2. Zhu CZ, Ting HN, Ng KH, Ong TA. A review on the accuracy of bladder cancer detection methods. J Cancer. 2019;10(17):4038-44.

3. Tan WS, Feber A, Sarpong R, Khetrapal P, Rodney S, Jalil R, et al. Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients. Eur Urol. 2018;74(1):10-4.

4. Wang Z, Que H, Suo C, Han Z, Tao J, Huang Z, et al. Evaluation of the NMP22 BladderChek test for detecting bladder cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(59):100648-56.

5. Lu P, Cui J, Chen K, Lu Q, Zhang J, Tao J, et al. Diagnostic accuracy of the UBC® Rapid Test for bladder cancer: A meta-analysis. Oncol Lett. 2018;16(3):3770-8.

6. Guo A, Wang X, Gao L, Shi J, Sun C, Wan Z. Bladder tumour antigen (BTA stat) test compared to the urine cytology in the diagnosis of bladder cancer: A meta-analysis. Can Urol Assoc J. 2014;8(5-6):E347-52.

7. Geavlete B, Jecu M, Multescu R, Geavlete P. Narrow-band imaging cystoscopy in non-muscle-invasive bladder cancer: a prospective comparison to the standard approach. Ther Adv Urol. 2012;4(5):211-7.

8. Walter FM, Thompson MJ, Wellwood I, Abel GA, Hamilton W, Johnson M, et al. Evaluating diagnostic strategies for early detection of cancer: the CanTest framework. BMC Cancer. 2019;19(1):586.

9. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. BMJ. 2016;353:i3139.

10. Sarosdy MF, Hudson MA, Ellis WJ, Soloway MS, deVere White R, Sheinfeld J, et al. Improved detection of recurrent bladder cancer using the Bard BTA stat Test. Urology. 1997;50(3):349-53.

11. Choi HS, Lee SI, Kim DJ, Jeong TY. Usefulness of the NMP22BladderChek Test for Screening and Follow-up of Bladder Cancer. Korean J Urol. 2010;51(2):88-93.

12. Tan WS, Teo CH, Chan D, Heinrich M, Feber A, Sarpong R, et al. Mixed-methods approach to exploring patients' perspectives on the acceptability of a urinary biomarker test in replacing cystoscopy for bladder cancer surveillance. BJU Int. 2019;124(3):408-17.

Figures/tables

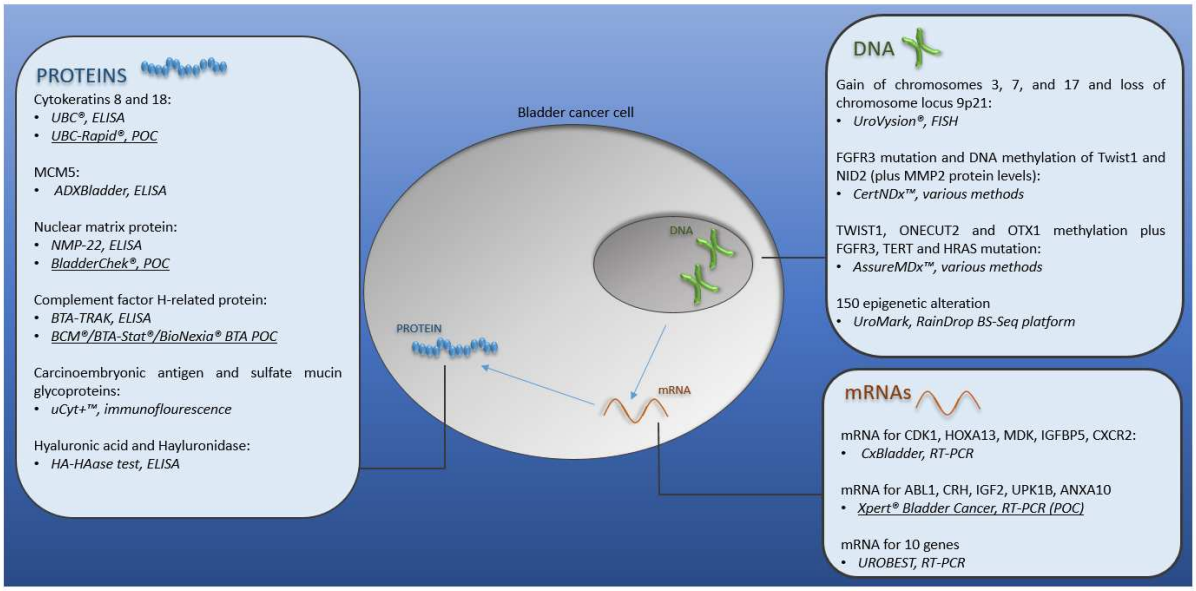

Figure 1. Types of bladder cancer markers (protein, DNA or mRNA-based) and examples of corresponding urinary tests and methodologies required. Key: FISH = fluorescence in situ hybridisation; RT-PCR = real time reverse transcription polymerase chain reaction; ELISA = enzyme-linked immunosorbent assay; POC = point-of-care (POC options are underlined)

Name of test	Time to result	Sensitivity	Specificity	Does presence of blood in urine affect test performance?
BTAStat®	5 min	53–78	50–95	Yes
BladderChek®	30 min	16–88	67–100	Yes/No
UBC-Rapid®	10 min	38–78	58–97	No
Xpert® Bladder Cancer Detect	90 min	65–83	77–90	No
BioNexia® BTA	5 min	-	-	Yes
BCM/PreventID®	10 min	57–89	-	Yes

Table 1. Bladder cancer point-of-care tests, specificity and sensitivity and effect of haematuria on test performance. For BTAStat®, BladderCheck®, UBC-Rapid® and Xpert® Bladder Cancer the range of sensitivity and specificity is based on reviewing 29 references. For BioNexia® BTA and BCM/PreventID®, no published data are currently available on sensitivity and specificity; figures for BCM/PreventID® are from the company website

Test characteristic	Rationale
High sensitivity	Low sensitivity would lead to cancers being missed
High specificity	Low specificity would cause unnecessary referrals

Minimal training required	To be performed by healthcare workers without specialist skills
Minimal equipment required	Small, practical to use, easy to maintain and service
Easy and quick to perform	To fit within the time constrains of primary care
Quick results	Ideally immediately or, if not, within a few days, to avoid delaying cancer diagnosis
Outcome easily interpretable	Clear positive or negative result to support clinical decision making
Cost-effective	To be economically viable from an NHS perspective
Non invasive and acceptable to patients and clinicians	To ensure a high up-take rate
Overall patients benefit	Taking into account harms of false negatives and additional procedures triggered by the test results

Table 2. Essential characteristics of novel point of care tests to be used in primary care for triaging of patients with bladder cancer symptoms

Key points

- The management of patients presenting to their GP with unexplained haematuria is problematic;
- A number of simple and quick bladder cancer point-of-care tests are available but it is unclear whether they are sensitive enough to be used as triage tests for haematuria patients;
- Robust primary-care based trials to evaluate clinical and cost effectiveness in the relevant 'real world' population are needed to underpin implementation.