# ADXBLADDER for detecting bladder cancer

Medtech innovation briefing

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# Summary

- The **technology** described in this briefing is ADXBLADDER. It is used to detect bladder cancer in people with symptoms associated with malignancy and to monitor for recurrence within the urogenital tract during follow-up after transurethral resection of a bladder tumour.

- The **innovative aspect** is that it detects bladder cancer based on the novel biomarker, minichromosome maintenance complex component 5 (MCM5).

- The intended **place in therapy** would be alongside cystoscopy but as an alternative to other urine-based tests.

- The **main points from the evidence** summarised in this briefing are from 1 multicentre prospective study including a total of 577 people presenting with haematuria or lower urinary tract symptoms, with suspected malignancy. It shows that ADXBLADDER can detect bladder cancer with 76% sensitivity and 69% specificity.

- **Key uncertainties** around the evidence are that it is limited to 1 study, with data published in abstract form only. Further studies are needed to validate results when the test is used to help initial diagnosis and provide evidence for the test when it is used to monitor for recurrence. Longer-term data and comparative data to other urinary biomarker tests would be helpful.

- The **cost** of ADXBLADDER is £52 (excluding VAT) per test.

# The technology

ADXBLADDER (Arquer Diagnostics) is a urine test for detecting bladder cancer in people with symptoms associated with malignancy, including blood in the urine or lower urinary tract symptoms. It is also indicated for detecting bladder cancer recurrence in the urogenital tract during follow-up after surgical treatment of non-muscle-invasive bladder cancer (such as transurethral resection of a bladder tumour [TURBT]). It is unsuitable for use after radical cystectomy. It is intended to be used with cystoscopy. ADXBLADDER is a urine-based lab test, which uses enzyme-linked immunosorbent assay (ELISA) technology to detect minichromosome maintenance complex component 5 (MCM5) protein in full-void urine. MCM5 is expressed by proliferating cells and can act as a biomarker for cancer. Because MCM5-positive cells are shed from tumours on the inner surface of the bladder, the presence of MCM5 in the urine can suggest that cancer is present. The volume of a urine sample can range from 10 ml to 200 ml, and the patient is advised to give a sample at least 2 hours after their last urination.

# Innovations

ADXBLADDER is an in vitro diagnostic test based on a novel biomarker for bladder cancer, MCM5. Compared with urinary cytology, which is a subjective test because it relies on microscopic evaluation, ADXBLADDER acts as an objective method of detecting the presence of bladder cancer. The company claims that the test will be able to detect more cases of bladder cancer compared with cytology. It may also help indicate the presence of upper urinary tract transitional cell carcinoma, which is often difficult to diagnose. Also, because MCM5 is not expressed by red blood cells, inflammatory cells or bacteria, the test result is unlikely to be affected by their presence. This means the test can be done in people with urinary tract infections and haematuria.

# Current care pathway

## Diagnosis

Diagnosing bladder cancer is mainly based on cystoscopic investigation of the bladder, biopsy and cytology. NICE's guideline on the bladder cancer does not recommend substituting cystoscopy for urinary biomarkers to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study. White-light-guided TURBT is recommended for people with suspected bladder cancer if abnormalities are found during cystoscopy. CT or MRI staging should be considered before TURBT if muscle-invasive bladder cancer is suspected at cystoscopy. According to the guideline, TURBT should be done or supervised by a urologist experienced in the procedure. It should be done with either:

- photodynamic diagnosis

- narrow band imaging

- cytology or

- a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridisation, ImmunoCyt or a nuclear matrix protein 22 test).

The guideline also states that random biopsies of normal-looking urothelium during TURBT should not be taken unless there is a specific clinical indication (for example, investigation of positive cytology not otherwise explained). Also, the size and number of tumours found during TURBT should be recorded.

Recommendations for the diagnosis and management of non-muscle-invasive bladder cancer are also made by the European Association of Urology (EAU) and are largely in agreement with those made by NICE.

## Monitoring after treatment

NICE's guideline on bladder cancer describes patient follow-up after treatment for bladder cancer. Periodic cystoscopy should be offered to patients after treatment for non-muscle-invasive bladder cancer. It should also be offered to patients after radical radiotherapy for the treatment of muscle-invasive bladder cancer. The recommended frequency of cystoscopic follow-up varies and should be adjusted according to the severity and risk of

bladder cancer (see the guideline for further details).

Urinary biomarkers and cytology can be offered with cystoscopy, except for the follow-up of patients with low-risk bladder cancer, when their use is not recommended. Patients who have had treatment for muscle-invasive bladder cancer (radical cystectomy or radical radiotherapy) should also be offered annual upper-tract imaging and CT of the abdomen, pelvis and chest 6, 12 and 24 months after treatment to monitor for local and distant recurrence. The guideline recommends urgently referring any patient to urological services if they have haematuria or other urinary symptoms and a history of non-muscle-invasive bladder cancer.

# Population, setting and intended user

The intended use for ADXBLADDER would be as a diagnostic test in people presenting with haematuria or lower urinary tract symptoms with a suspicion of malignancy. It is also intended to be used to monitor for recurrence within the urogenital tract during the follow-up of patients after surgical treatment of non-muscle-invasive bladder cancer (for example, TURBT). It is unsuitable for use after radical cystectomy. The test is intended to be used in secondary care with cystoscopy, but instead of urine cytology or other urine biomarker tests that are currently used with cystoscopy for the detection of bladder cancer and recurrence within the urogenital tract. Urine samples would be collected by nurses in a hospital clinic and processed and analysed in a laboratory. The test results would then be sent to the patients' urologist.

# Costs

## Technology costs

The cost of ADXBLADDER is £52 per test (excluding VAT). This does not include the costs of consumables or healthcare professionals' time. The company estimates the cost of consumables (consisting of 1 urine collection pot, 1 centrifuge tube, 1 Eppendorf tube and pipette tips) to be £0.37 per person.

## Costs of standard care

Per test costs (excluding VAT), including the cost of consumables and the healthcare professionals' time, are based on 2018/19 hospital resource group (HRG) tariffs and 2017/

18 national schedule of reference costs, and are as follows:

- Cystoscopy: £244 (HRG code LB72A, Diagnostic Flexible Cystoscopy, 19 years and over).

- Cytology: £12 (currency code DAPS01, cytology).

## Resource consequences

The technology is being introduced into the NHS but is not yet widely used. If adopted, ADXBLADDER has the potential to be resource releasing if its use results in earlier diagnoses and subsequent treatment by more accurately detecting cases of bladder cancer. However, false-positive results could have cost and resource consequences because they could lead to further testing. Using the test to monitor patients during follow-up may lead to an initial increase in resource use in this setting. There is minimal to no training, and no changes to facilities or infrastructure are needed to adopt the technology because urinalysis and ELISA technology are already used routinely.

# Regulatory information

ADXBLADDER was CE marked as a self-certificated in vitro diagnostic on 10 October 2017.

# Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Bladder cancer is more common in men than women; 72% of cases in the UK are in men, and 28% are in women. Despite a lower incidence of bladder cancer in women, rates of survival are considerably lower for women than for men. It mainly affects older people with the highest incidence rates seen in people aged 90 years and over (Cancer Research UK,

2015). People of European family origin have a much higher risk of developing bladder cancer compared with those of African American, Hispanic or Asian family origin. People with cancer are protected under the Equality Act 2010 from the point of diagnosis.

# Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

# Published evidence

One multicentre, prospective study involving 577 people presenting with haematuria or lower urinary tract symptoms with a suspicion of malignancy is summarised in this briefing. Results from this study were published in the form of a conference abstract only.

Two other studies evaluating the use of minichromosome maintenance complex component 5 (MCM5) as a biomarker in the detection of bladder cancer were identified (Stoeber et al. 2002; Kelly et al. 2012). Overall, they showed that immunofluorometric detection of MCM5 in urine sediment is a sensitive and specific diagnostic test for bladder cancer (with a sensitivity of 92% and specificity of 78%), with similar diagnostic accuracy to the nuclear matrix protein number 22 (NMP22) enzyme-linked immunosorbent assay (ELISA) test. These studies are not discussed further in this briefing because they are preliminary and do not fully reflect the technology in its current ELISA-based form.

ADXBLADDER can also be used for diagnosing bladder cancer recurrence within the urogenital tract during follow-up after transurethral resection of a bladder tumour but there are no published data to support this use.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

# Overall assessment of the evidence

Evidence from a multicentre prospective study showed that overall ADXBLADDER was able to detect bladder cancer with a sensitivity and specificity of 76% (95% confidence interval

[CI]: 61% to 87%) and 69% (95% CI: 65% to 73%) respectively (using a diagnosis based on cystoscopy, imaging and biopsy as a reference standard). This contributed to a negative predictive value of 97% (95% CI: 95% to 98%). Despite reporting a high negative predictive value, based on the reported sensitivity around 24% of people with cancer would be classed as not having cancer by the test. Sensitivity of the test for the combined high-risk and muscle-invasive groups was 95% (95% CI: 75% to100%), suggesting the test may be better at detecting these tumour types over low-grade tumours. Results from the study also showed that ADXBLADDER was able to detect more cases of bladder cancer compared with cytology. However, this data came from a very small subset of patients (n=10).

The study was done in a relatively large number of patients across 6 UK centres, so the results are likely to be generalisable to NHS practice. Overall, the evidence for the technology is limited to 1 study which assessed the diagnostic ability of the test only. The study was funded by the company and data are available in abstract form only so additional details about the results could not be verified. The accuracy data are therefore subject to uncertainty and further studies will be needed to verify these results, as well as understand the effect that adopting this test will have on longer-term outcomes including the overall cost consequence for the healthcare system. Studies comparing the diagnostic accuracy of ADXBLADDER with that of cytology and other urinary biomarker tests (such as UroVysion fluorescence in-situ hybridisation, ImmunoCyt or NMP22 test) would also be helpful.

## Table 1 Summary of selected studies

| Dudderidge et al. (2018) | |
| --- | --- |
| Study size, design and location | Multicentre, prospective study involving 577 people presenting with haematuria or lower urinary tract symptoms between September 2016 and February 2017, with a suspicion of malignancy. The study was done across 6 UK sites. |
| Intervention and comparator(s) | Intervention: ADXBLADDER.<br>A diagnosis obtained by cystoscopy, imaging, and resection biopsy of suspect lesions was used as a reference standard. |

| Key outcomes | Out of the 577 enrolled patients, 46 were diagnosed with cancer (7.96% prevalence). ADXBLADDER was able to detect 35 out of 46 of all tumours and 19 out of 20 high-risk muscle-invasive tumours. ADXBLADDER sensitivity was 76% for all tumours and 95% for high-risk and muscle-invasive tumours. The specificity and NPV of ADXBLADDER for all tumours were 69% and 97.1%, respectively. The NPV reported for high-risk tumours was 99.7%. In a subgroup analysis with cytology comparison data (n=10), ADXBLADDER detected 8 out of 10 tumours while cytology detected 2 out 10 tumours. All tumours detected by cytology were detected by ADXBLADDER. |
|---|---|
| Strengths and limitations | This was multicentre study involving a relatively large number of people and was done across 6 UK centres. Therefore, results are likely to be generalisable to NHS practice. The study was funded by the company and results were only published in the form of a conference abstract, full study details including exclusion/inclusion criteria and patient demographics were not available. |
| Abbreviations: NPV, negative predictive value. | |

# Recent and ongoing studies

No ongoing or in-development trials were identified on any of the clinical trial registries searched. The company states that ADXBLADDER is currently being evaluated in 2 clinical studies. These are a prospective performance evaluation to determine the utility of ADXBLADDER in helping detect recurrent bladder cancer, and a single-centre Italian study looking at the optimisation of urine sample collection, processing and storage. The company also states that 5 additional clinical studies are planned, with the aim of providing further data on specific patient groups and to clarify product performance and specificity.

# Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

Two of the commentators said they were aware of ADXBLADDER, but none of the commentators had used the technology before.

# Level of innovation

One commentator did not think that ADXBLADDER was innovative, adding that there are many other urine-based tests used in the diagnosis of bladder cancer, with similar diagnostic performance to ADXBLADDER. Another commentator said that the technology is a minor variation because it uses a different biomarker to other urine-based tests. The remaining commentator agreed that it is a minor variation to standard care but added that it wasn't a unique test or product. All commentators highlighted the relatively large number of competing technologies. Among those identified, urine cytology was regarded as the most common urine test for diagnosing bladder cancer. Nuclear matrix protein-22 test, UroVysion fluorescence in-situ hybridisation, ImmunoCyst and narrow band imaging during cystoscopy were also identified as competing technologies by commentators.

# Potential patient impact

The benefits identified by the experts included: better triaging of high-risk patients based on its high negative predictive value; avoiding unnecessary invasive cystoscopy; improving the ease of sample collection and processing. One expert was not convinced by the claimed benefits of the technology over standard care, adding that initial cystoscopy would still be needed to assess other causes of haematuria, and that there is currently a lack of data to support the use of the ADXBLADDER test in the follow-up of people with bladder cancer. Commentators believed that the test could potentially be used in all patients with suspected bladder cancer, although 1 commentator said that in clinical practice the test is likely to only be used when cystoscopy does not offer diagnostic certainty. Patients needing monitoring after a diagnosis of bladder cancer were also identified by 1 of the commentators as those who could benefit from the technology. One commentator thought it was too early to say whether adopting the technology would change the current care pathway, while 1 commentator thought that it may be added as a follow-up option for patients but would not replace cystoscopy.

# Potential system impact

The main system benefits identified by commentators were better triaging for some patients, potentially leading to a release of resource because of reduced cystoscopy, as well as the potential to improve follow-up in patients already diagnosed with bladder cancer. One commentator felt it was too early to say what the system benefits would be. All commentators agreed that ADXBLADDER would be an addition to standard care. Two of

the commentators did not think ADXBLADDER would replace cytology in clinical practice; 1 said that the test is not sensitive or specific enough and 1 said that it did not provide more information than cytology which is a cheaper test. One commentator said it has the possibility to replace cytology if future studies can validate the findings from Dudderidge et al. (2018); that ADXBLADDER detects more cases of bladder cancers than cytology. One commentator said that use of ADXBLADDER would be cost-incurring because it would not replace cystoscopy, which is the costliest test. Two commentators said the technology would result in a minor increase in running costs but has the potential to be cost-saving overall if it is used in more selective cases and if it leads a reduction in the number of cystoscopies needed. One commentator thought that it would be cost-saving in the follow-up of patients with bladder cancer but only if it replaced the use of flexible cystoscopy in these patients.

Most commentators did not believe adopting the technology would have a substantial resource impact. Some commentators said that, because it is not a point-of-care test, it could potentially lead to more follow-up appointments or increase the time needed for processing or sending samples to a third party. No substantial changes to infrastructure or facilities were identified by any of the commentators, given that enzyme-linked immunosorbent assay testing is commonplace. One commentator thought that the test would be relatively easy to adopt with a simple learning curve, but would need further long-term and comparative data before a national rollout of the technology can be considered. None of the commentators were aware of any safety concerns or regulatory issues surrounding the technology.

# General comments

One commentator noted that, although available, urine biomarker tests are not widely used across the NHS because of the marginal benefit they are thought to have over standard care such as cystoscopy and imaging. Apart from not being a point-of-care test, no substantial practical or usability issues were identified by the commentators. One commentator said that the data supporting the technology needs to be validated by independent studies assessing clinical utility and also highlighted the need for data comparing the clinical and cost effectiveness of ADXBLADDER to other competing technologies. One commentator said that the proposed patient population needs to be better defined. Another commentator highlighted their concern about the sensitivity of the product (76%), despite its high negative predictive value (97%).

# Specialist commentators

The following clinicians contributed to this briefing:

- Rakesh Heer, consultant urologist, Newcastle upon Tyne Hospitals NHS Foundation Trust, chief investigator of the National Institute for Health Research (NIHR)-funded PHOTO trial.

- Rami Issa, consultant urological surgeon, St George's Hospital, London, was a specialist adviser to NICE on interventional procedures guidance for intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer.

- Mr Nikhil Vasdev, consultant urological surgeon and clinical senior lecturer, East and North Herts NHS Trust, did not declare any interests.

# Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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