Appraisal of screening for bladder cancer

A report for the
UK National Screening Committee

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Introduction

1. This report reviews screening for bladder cancer against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search conducted by the NSC in June 2014 (Garrett 2014). Full details of the search strategy are set out in Appendix A.

2. Screening adults for bladder cancer was last assessed against the UK NSC criteria in December 2010 (Allaby 2010). The current NSC policy states that "screening for bladder cancer should not be offered. This has been reviewed as part of the Cancer Reform Strategy for England. Screening by urine dip stick testing for protein and blood is not recommended and should no longer take place".[1]

3. In 2011 the United States Preventative Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults (USPSTF 2011).

4. The 2010 NSC review (Allaby 2010) identified the lack of a reliable screening test for bladder cancer as a significant obstacle to screening, concluding that:

   "No test or combination of tests for bladder cancer has yet been shown to be simple, safe, precise and validated in the context of population screening. Urine dipstick testing for haematuria can offer reasonable sensitivity, but only if many repeat specimens are obtained, and only at the cost of many false positives. Few cancers have been detected in published studies of the performance of the newer urine-based bladder tumour markers in populations that are relevant to the NSC, but the limited data available suggests that none of them achieve an acceptable trade-off between sensitivity and specificity."

5. As the absence of a good test was the major barrier to a screening programme this current review focuses on issues related to testing for bladder cancer with the following key questions:

   a) Is there any evidence to suggest the reliability of microscopic haematuria as a screening marker has improved since the previous review?
   b) Have the trials mentioned in the recommendation of the previous review reported and, if so, what impact do they have on the current recommendation? The trials being Svatek and Lotan (2008) and Roobol et al (2009).
   c) At the time of the previous review a number of urine-based bladder tumour markers were being developed. Do any of these, either alone or in combination, meet the UK NSC criteria in offering a simple, safe, precise and valid test?

6. The population of interest in this review of screening for bladder cancer is apparently healthy people who do not have any urinary symptoms such as visible blood in the urine (macroscopic haematuria) or discomfort associated with urination (dysuria) and who have no previous history of bladder cancer. Studies considering screening for bladder cancer in a general population, a high risk population or a low risk population are considered.

[1] http://www.screening.nhs.uk/bladdercancer

The Condition

The condition should be an important health problem

7. In 2011, more than 10,000 people were diagnosed with bladder cancer in the UK, making it the seventh most common cancer in the UK (Cancer Research UK 2014), however it is the fourth most common cancer in men (Pang & Cotto 2013). The five-year survival rate for bladder cancer is 56% (2005 to 2009). About half of patients diagnosed with bladder cancer survive for at least ten years (Cancer Research UK 2014).

8. The European age-standardised incidence of bladder cancer is 10.9 per 100,000 population. The incidence is higher in males (17.7/ 100,000) than females (5.4/100,000) (Cancer Research UK 2014).

9. This criterion is met.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

10. More than half of all new cases of bladder cancer occur in people aged 75 and over (Cancer Research UK 2014), with an average age at diagnosis of 71 years (Shephard 2012).

11. The main preventable risk factor for bladder cancer is smoking, which causes about one third of the cases of bladder cancer each year in the UK. About 7% of male bladder cancer cases and 2% of female cases in the UK are linked to occupational exposure to certain chemicals and about 2.5% of cases are linked to radiation exposure (Cancer Research UK 2014).

12. The most common type of bladder cancer in the UK is urothelial cell carcinoma (previously known as transitional cell carcinoma), which accounts for 90% of bladder tumours (Pang & Cotto 2013). The tumour/ node/ metastasis (TNM) classification of bladder cancer is based on the depth of tissue invasion and involvement of lymph nodes or metastases. Tumour grade and stage is a strong predictor of future disease progression and prognosis (Pang & Cotto 2013). In about 20% of cases the cancer has invaded the muscle wall at presentation, and in these cases the cancer can spread rapidly and, even with optimal treatment, five-year survival is only 50% (NICE 2012).

13. The current classification system for bladder cancer is presented in the appendix. High-grade muscle invasive bladder cancers (T2 and above) are aggressive and carry the worst prognosis. The 2010 NSC review noted that for a bladder cancer screening programme to be effective in reducing mortality, any screening test must be able to detect cancers that are destined to become muscle-invading, but before they have done so (Madeb and Messing 2008, cited in Allaby 2010).

14. The commonest presenting complaint for bladder cancer is intermittent, painless, visible (macroscopic) haematuria (blood in urine) (40%), followed by non-visible (microscopic) haematuria (30%) and other urinary symptoms such as recurrent urinary tract infections (30%) (Pang & Cotto 2013). In one UK primary care study, 363 patients with visible or non-visible haematuria were investigated for bladder cancer. Three of 186 patients with non-visible haematuria were found to have urological cancer (1.6%) and 32 of 172

patients with visible haematuria were found to have urological cancer (19%) (Shephard et al 2012).

15. Non-visible (microscopic) haematuria (detected by urine dipstick testing) represents one possible early disease marker for screening for bladder cancer. A number of urinary molecular markers have also been investigated as potential early disease markers.

16. There are defined criteria for the classification of bladder cancer tumours, the prognosis of different grade tumours has been described and there are known risk factors. There are a number of potential early disease markers, although their effectiveness in screening for bladder cancer is not yet established (see 'The Test' section). This criterion is partially met.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

17. About one third of cases of bladder cancer in the UK are caused by smoking (Cancer Research UK 2014). In 2012, 20% of UK adults (aged ≥16 years) were cigarette smokers, a rate which remained largely unchanged in the preceding five years (ONS 2013). Exposure to certain chemicals and radiation are also risk factors for bladder cancer.

18. A range of free services are available in the UK to support people to give up smoking. However, there may be scope for more primary prevention to reduce exposure to risk factors for bladder cancer.

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

19. Not applicable to screening for bladder cancer.

The Test

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

20. Three key questions relating to testing for bladder cancer were set out in the introduction to this review. These are addressed in turn.

    - **Have the trials mentioned in the recommendation of the previous review reported and, if so, what impact do they have on the current recommendation? The trials being Svatek and Lotan (2008) and Roobol et al (2009).**

21. In their 2008 paper, Svatek and Lotan mentioned a screening study that was to be carried out by MD Anderson Specialised Programmes of Research Excellence (SPORE) in which the study participants would undergo multiple dipstick testing for haematuria using Hemastix tests and everyone with a positive test would undergo cystoscopy and testing with three urine-based bladder tumour markers. The lead authors of this study were not specified. The SPORE programme for bladder cancer has a website that lists current

projects and publications[2]. None of the publications listed match the description of the study mentioned by Svatek and Lotan, and none of them consider screening for bladder cancer. No abstracts in the literature search for this review describe a study that matches the study mentioned by Svatek and Lotan. Therefore no publications from the study mentioned by Svatek and Lotan were identified.

22. The 2010 review commented on the early results of Roobel et al (2009), in which men aged 50-75 years underwent daily urine dipstick testing for 14 days and men with at least one sample positive for haematuria were tested for four urine-based bladder tumour markers. Data on sensitivity and specificity were not available but the 2010 NSC review noted that "a large proportion of participants (24.8%) tested positive for haematuria, which raises questions about the feasibility of this approach for population screening" (Allaby 2010). Further results from this study have now been published (Bangma et al 2013) and are discussed below as part of the evidence identified for this review.

    - **Is there any evidence to suggest the reliability of microscopic haematuria as a screening marker has improved since the previous review?**
    - **At the time of the previous review a number of urine-based bladder tumour markers were being developed, do any of these, either alone or in combination, meet the NSC criteria in offering a simple, safe, precise and valid test?**

23. The 2010 NSC review concluded that "no test or combination of tests for bladder cancer has yet been shown to be simple, safe, precise and validated in the context of population screening" (Allaby 2010). The 2010 review also stated that the "ideal screening tool(s) for bladder cancer would have excellent sensitivity for high-grade cancer, and good sensitivity for lower grade cancer … [but need not] necessarily discriminate between higher and lower grade tumours in routine use" (Allaby 2010).

24. The literature search conducted for this current review identified multiple studies assessing potential new tests for the diagnosis and monitoring of bladder cancer, however many of these are still in the developmental stage and have not yet been tested in screening-relevant populations. In this review we have only included studies testing the effectiveness of tests for bladder cancer using a population relevant to screening.

25. Bangma et al (2013) was a Dutch cohort study evaluating the feasibility and usefulness of screening for bladder cancer. A total of 1,747 men aged 50 to 75 years identified from a population register underwent home haematuria testing using 14 dipsticks over 14 consecutive days, with molecular testing using four biomarkers for those that screened positive. Cystoscopy was recommended for selected individuals based on the results of the haematuria and molecular testing. The results of this study are presented in Table 1.

[2] MD Anderson Cancer Center. Bladder Cancer Spore. News and Publications: http://www.mdanderson.org/education-and-research/research-at-md-anderson/early-detection-and-treatment/research-programs/spores/bladder-cancer-spore/index.html (Accessed September 2014)

Table 1: Summary of the key results from Bangma et al 2013

Study	Population	First stage-testing	Second-stage testing	Cystoscopy	Follow-up (registry data)	Sensitivity and Specificity (including registry data)
Bangma et al 2013 Cohort study The 'Bladder Cancer Urine Marker Project' evaluating the feasibility of bladder cancer screening Netherlands	Men aged 50 to 75 years, identified from a population register N=1,747 Men with a previous history of bladder cancer were excluded	**Process** Home haematuria testing using 14 dipsticks over 14 consecutive days **Results** Positive[3]: 409 (23.4%)[4]	N= 385 **Process** Molecular testing of 4 urine samples for 4 biomarkers[5] (NMP22, MA, FGFR3, MSA) **Results** • One or more positive molecular tests: 75 (4.3%) • Cystoscopy recommended for 75 individuals	N= 71 **Results** • Bladder cancer: 4 (0.23%) • Kidney tumour: 1 (0.06%) 3 of the bladder cancer cases were Ta grade 2 tumours, 1 case was Ta grade 1[6]	Linkages to the Dutch cancer registry and PALGA[7] were used to follow-up participants for two-years **Cancer identified within 1 year of screening, but not through screening** From participants who were compliant with screening: • Bladder cancer: 1 • Kidney cancer: 1 From participants who agreed to participate but did not complete haematuria testing: • Bladder cancer: 2	**For any microhaematuria** **Sensitivity:** 80.0% (95%CI 28.4 to 99.5) **Specificity:** 76.7% (95%CI 74.7 to 78.7) **PPV:** 0.98% (95%CI 0.3 to 2.5) **NPV:** 99.9% (95%CI 99.6 to 100) **For any positive molecular marker[8]** **Sensitivity:** 80.0% (95%CI 28.4 to 99.5) **Specificity:** 95.9% (95%CI 94.9 to 96.8) **PPV:** 5.3% (95%CI 1.5 to 13.1) **NPV:** 99.9% (95%CI 99.7 to 100)

FGFR3 - Fibroblast growth factor receptor; MA - Microsatellite analysis ; MSA - Mutation snapshot assay; NMP22 - Nuclear matrix protein 22; NPV – negative predictive value; PPV – positive predictive value; Ta - Non-invasive papillary carcinoma

[3] A positive test = one or more positive home haematuria tests
[4] In the 2010 review 24.8% of men were reported to have a positive result, but this figure from Roobol et al 2009 was a preliminary result at a point when only 395 men had completed the home haematuria testing
[5] Samples were tested for leukocytes to avoid urinary tract infections confounding the results
[6] There are 3 grades of tumour, with grade 3 having the greatest potential for spread
[7] The nationwide network and registry of histo- and cytopathology (PALGA)
[8] Molecular testing only performed in 385 patients with positive microhaematuria testing

26. The number of cancers cases detected in Bangma et al's study was small, and the authors concluded that a mass screening programme was not useful in an unselected asymptomatic European male population. Bangma et al (2013) reported a sensitivity of 80% for both testing for any microhaematuria and any positive molecular marker, however the 95% confidence intervals are very wide, reducing confidence in the clinical significance of the result. The positive predictive value (indicating the probability that a patient with a positive result does have the condition) is very low at 0.98% for any microhaemturia and 5.3% for any positive molecular marker. Bangma et al (2013) was a feasibility study and only the men who were screen positive received the gold standard test of cystoscopy to determine whether they did or did not have cancer. Participants were followed up for two years through examination of registry data, and further cancer cases were identified within a year of the screening programme. The sensitivity and specificity results cited include cases detected through the registry data that were not detected through the screening programme, however it is possible that additional cases of bladder cancer were not detected, because screen-negative individuals were not cystoscoped.

27. UroScreen was a prospective study exploring the performance of several molecular tumour markers for the early diagnosis of bladder cancer in 1,772 workers with occupational exposure to aromatic amines. In this study active and retired workers of two chemical companies in Germany were invited to take part in an extended screening programme between 2003 and 2010 with annual testing with urine-based tumour markers in addition to an existing surveillance programme of annual dipstick urine analysis. Cystoscopy was recommended for positive or suspicious cases. The performance of the tests was assessed using the results of the last visit before diagnosis of bladder cancer or the results of the last visit for non-cancer cases (Banek et al 2013). It is important to note that this method of analysis will flatter the performance of the tests, because anyone who had a false positive result before their most recent test will be counted as having a true negative test result. However, such a test result should be considered as a partial false positive, because the individuals involved were told in that screening round that their test result was positive, though they did not have bladder cancer. For most of the participants samples were not available for each consecutive year (Johnen et al 2012).

28. Overall 16 new bladder cancer cases (13 primary bladder cancer and three papillary urothelial neoplasms of low malignant potential) and five recurrent tumours were identified in 20[9] study participants, which included six cases that were diagnosed elsewhere and were not identified through the screening process. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each of the urine based markers for detecting bladder cancer were published in a series of publications (Banek et al 2013; Huber et al 2012; Johnen et al 2012; Pesch et al 2012) and are summarised in Table 2 (NB. As explained above in paragraph 27, these figures are likely to exaggerate the true performance of the tests).

29. The number of participants receiving each test and the number of cancer cases identified varied in the UroScreen study (as indicated in Table 2). Tests were performed when sufficient material was available to provide a valid result.

[9] One participant had both recurrent bladder cancer and a new papillary urothelial neoplasm

Table 2: Summary of the key results from the UroScreen study

Test[10] and number of lesions detected	Threshold	All bladder lesions				High-grade bladder lesions				Publication
		Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	
FISH (n=1,538) All bladder lesions: n=21 High-grade bladder lesions: n=13	≤2 copy numbers at defined loci of chromosomes (3,7 or 17) in at least 4 cells; or at least 12 cells with no detectable signal for 9p21	45.00%	96.97%	16.36%	99.26%	53.85%	96.97%	13.21%	99.59%	Banek et al 2013
NMP22 (n=1,325) All bladder lesions: n=21 High-grade bladder lesions: n=13	<10 U/mL	28.57%	97.29%	12.24%	99.04%	23.08%	97.29%	6.52%	99.36%	Huber et al 2012
Survivin (n=1,522) All bladder lesions: n=18 High-grade bladder lesions: n=11	Three different assays used to detect survivin[11]. Manufacturers cut-off levels used.	21.05%	97.50%	9.52%	99.00%	36.36%	97.50%	9.52%	99.53%	Johnen et al 2012

[10] Tests were performed if sufficient material was available to obtain a valid result
[11] Due to issues regarding the reliability and availability of assay components during the seven year study period

Haematuria tested by dipstick and microscope (n=1,323) All bladder lesions: n=15 High-grade bladder lesions: n=9	Microscopic haematuria (µH): 5 -250 erythrocytes Gross haematuria (GH): ≥ 250 erythrocytes	Not reported	Not reported	µH: 1.24% GH: 11.43%	µH: 99.24% GH: 99.15%	Not reported	Not reported	µH: 0% GH: 11.43%	µH: 99.52% GH: 99.61%	Pesch et al 2012

FISH - fluorescence-in-situ-hybridization; GH – gross haematuria; NMP22 - nuclear matrix protein 22; NPV – negative predictive value; PPV – positive predictive value; µH – microscopic haematuria
*95% confidence intervals not reported

30. Separate results were presented for UroScreen for all bladder lesions and high grade lesions. The results varied for each test but only one test achieved a sensitivity of more than 50% (FISH test for high grade bladder lesions) and the positive predictive values for both haematuria and molecular testing were low (ranging from 0% to 16.36%). In contrast the specificity and negative predictive values were high for all tests and for both all and high grade lesions.

31. The participants in UroScreen underwent a range of tests but there was no consistent reference standard and the methodology did not include the gold standard test of cystoscopy in all participants. It should also be noted that participants who had previously had bladder cancer were not excluded and that five of the 21 total bladder cancer cases identified were recurrence. A high-risk population was used in this study so the results may not be generalisable to a general screening population. In particular, the positive predictive values may well be lower in a general screening population because the incidence of bladder cancer amongst people with microscopic haematuria is probably lower when they are drawn from the general population than when they are drawn from a population known to have occupational risk factors for bladder cancer, or a personal history of bladder cancer.

32. Two additional studies were identified assessing the utility of Nuclear Matrix Protein 22 (NMP22) and cytology in low risk patients with microscopic haematuria.

33. A Turkish study (Sagnak et al 2011) evaluated the use of NMP22 as an initial test in comparison to voided urine cytology for screening 164 low risk male and female patients with asymptomatic microscopic haematuria detected incidentally. All participants were aged 40 years or under and had a low risk of bladder cancer based on a non-smoking history. The results are summarised in Table 3.

34. A Canadian study (Feifer et al 2010) evaluated the performance of voided urine cytology in 200 low-risk male and female patients referred to a urology clinic with asymptomatic microscopic haematuria. The median age was 64 years and all were non-smokers and did not have any risk factors for bladder cancer[12]. The results are summarised in Table 3.

Table 3: Summary of the key results from Sagnak et al (2011) and Feifer et al (2010)

Study	Population	Test[13]	Results
Sagnak et al 2011	People with microscopic haematuria[14] detected incidentally with low risk of bladder cancer[15] ages<40 years	Urine cytology NMP22 Ultrasonography Cystoscopy Biopsy performed	**Cytology** • Sensitivity: 0% (95%CI 0% to 80.2%) • Specificity: 96.9% (95%CI 92.6% to 98.8%) • PPV: 0% (95%CI 0% to 53.7%) • NPV: 98.7% (95%CI 95.1% to

[12] All patients were non-smokers, had no previous malignancies, had no cyclophosphomaide exposure, no previous radiation therapy and no documented occupational exposure
[13] Cut-off thresholds not reported
[14] Microscopic haematuria was defined as ≥ 3 red blood cells per high-power field on at least two occasions with a minimum time gap of two weeks. Urine cultures were obtained where there was high suspicion of a urinary tract infection
[15] Patients with risk factors for bladder cancer were excluded from the study i.e. smoking history, occupational exposure to chemicals or dyes, history of gross haematuria, age >40 years, history of urologic disorder or disease, history of urinary tract infection, analgesic abuse, history of pelvic irradiation

	N=164 Two TaG1 (non-invasive) lesions were detected	for suspicious lesions or positive cytology CT scan performed for positive NMP22 and atypical cytology and absence of lesion and negative biopsy	99.9%) **NMP22** • Sensitivity: 100% (95%CI 19.8% to 100%) • Specificity: 85.2% (95%CI 78.6% to 90.1%) • PPV: 7.7% (95%CI 1.3% to 26.6%) • NPV: 100% (95% CI 96.6% to 100%)
Feifer et al (2010)	People referred to a urology clinic with asymptomatic microscopic haematuria[16] with low risk of bladder cancer N=200 Median age: 64 (range 44 to 80) Eight low grade Ta and T1 bladder tumours were detected	Urine cytology (3 samples)[17] Cystoscopy Upper tract imaging	**If atypical cytology was considered positive:** • Sensitivity: 50% (95%CI 15.7% to 84.3%) • Specificity: 90.1% (95%CI 85.0% to 93.9%) • PPV: 17.4% (95%CI 4.95% to 38.8%) • NPV: 97.7% (95%CI 94.3% to 99.4%) **If atypical cytology was considered negative:** • Sensitivity: 0% (95%CI 0% to 36.0%) • Specificity: 100% (95%CI 98.1% to 100%) • PPV: 0% (95%CI n/a) • NPV: 96.0% (95%CI 92.27% to 98.26%)

35. In Sagnak et al (2011) the results were interpreted by observers blinded to the results of the other tests and all participants received cystoscopy. Two cases of non-invasive bladder cancer were identified. In both of these cases the results of the NMP22 test were positive and the result of the cytology test was negative. For both tests the positive predictive value was less than 10% which suggests that a high number of false positive results would be obtained. The patient group in this study were young (adults aged <40 years) and were at low risk of bladder cancer and may not be generalisable to a general screening population.

36. In Feifer et al (2010) all participants were assessed by two urological oncologists and received cystoscopy. Eight cases of low grade, non-muscle invasive cancers were detected, four of which had negative cytology and four of which had atypical cytology. When an atypical cytology result was counted as positive a positive predictive value of 17.4% was achieved. The population of this study were older than that of Sagnak et al (2011) but were also at low risk of bladder cancer.

[16] Microscopic haematuria was defined as ≥ 3 red blood cells per high-power field
[17] Cytology samples were classified as suspicious or high grade, atypical or negative

Summary

37. The literature search for this review identified four studies that have assessed the performance of haematuria and several urine based tumour markers in a screening context or in a population relevant to screening.

38. In all four studies the precision of the results was limited by the small number of bladder cancer cases detected. In Bangma et al (2013) and the UroScreen study not all participants received the gold standard of cystoscopy as a reference test. Ideally all participants would receive the gold standard test of cystoscopy to confirm or rule-out bladder cancer in all participants. However, cystoscopy is an invasive procedure which may limit the number of studies that would seek to perform the procedure in participants who had not received a positive haematuria or molecular test result. Whilst there are limitations in all of these studies, the positive predictive values obtained were low for all tests in studies that either used a general population, a high risk population or a low risk population, which suggests that a high number of false positive results would be obtained in screening for bladder cancer.

39. Considering the key questions posed at the outset of this section:

    - The current review did not identify studies published since the 2010 NSC review which have evaluated the performance of microscopic haematuria alone as a screening marker for bladder cancer.
    - Of the two trials mentioned in the 2010 NSC review, one of them (mentioned in Svatek and Lotan 2008) does not appear to have published; the other (Roobol et al 2009) has been published as Bangma et al (2013) and is considered in the context of three other relevant studies which have been published since the 2010 review.
    - The evidence identified for this report does not suggest that urine-based tumour markers, either alone or in combination, meet the NSC criteria in offering a simple, safe, precise and valid test.
    - In the current review the positive predictive values achieved in the studies included ranged from 0% to 17.4%.This compares with a range from 0.3% to 48% in the studies included in the 2010 NSC review.
    - In the current review the **sensitivity** figures achieved in the studies included ranged from 0% to 100%. This compares with a range from 5% to 100% in the 2010 NSC review (though the quality of these estimates was limited by the lack of cystoscopy and imaging for screen-negative individuals in all but one of the studies).

40. Numerous studies were identified within the literature search testing other potential screening tests for bladder cancer. These studies reported the sensitivity and specificity of these tests for distinguishing between known cancer patients and healthy controls but no studies were identified in which they were tested in a screening population.

41. A recent review of the current state of urinary biomarkers for bladder cancer (Sapre et al 2014) concluded that four protein and cell-based markers (cytology, ImmunoCyt, BTA stat/TRAK, NMP22) and two gene-based markers (FISH (UroVysion), Cxbladder (uRNA-2)) were established and commercialised for the detection and surveillance of bladder cancer. The performance of protein and cell-based markers was described as being too inadequate to incorporate into routine clinical practice, primarily because they are affected by other bladder conditions, such as infection, inflammation and intravesical therapy. The overall conclusion for gene-based biomarkers was that the majority of these studies remain in the discovery phase and that multicentre prospective validation studies are needed for clinical translation. This review did not specifically consider the use of these tests in a screening context.

The test should be acceptable to the population

42. In a Dutch study evaluating the feasibility and usefulness of bladder cancer screening, 6,500 men were invited to participate in the study and 1,984 (30.5%) agreed to take part. Of these, 1,747 (88.1%) completed the 14 day home-based haematuria testing and 385 of the 409 (94.1%) who tested positive completed the second phase of molecular testing. Cystoscopy was completed for 71 of the 75 (94.6%) men for whom it was recommended (Bangma et al 2013).

43. No studies assessing the acceptability of bladder cancer in women, or in a UK population were identified. This criterion is not met as the acceptability of bladder cancer screening tests to a UK general population is unknown.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

44. The National Institute for Health and Care Excellence (NICE) is currently in the process of developing a clinical guideline for the diagnosis and management of bladder cancer in adults. The expected publication date is February 2015. Screening is not mentioned within the scoping document for this clinical guideline (NICE 2012).

45. The European Association of Urology published updated guidelines on the diagnosis and management of non-muscle-invasive urothelial carcinoma of the bladder in 2013 (Babjuk et al 2013).

46. A UK guideline from NICE is in development however this may not address the issue of the investigation of individuals detected through a screening programme. This criterion is not currently met.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

47. Not relevant to screening for bladder cancer

The focus of this report is on issues related to testing for bladder cancer. Therefore the remaining NSC criteria, covering treatment and the screening programme have not been considered at this time.

Implications for policy

It remains appropriate not to introduce a national screening programme for bladder cancer because there is no evidence that the reliability of haematuria as a screening marker has improved since the 2010 NSC review and no urine-based tumour markers, either alone or in combination have been shown to meet the NSC criteria in offering a simple, safe, precise and valid test.

The low positive predictive values achieved in all of the included studies suggest that a high number of false positive results would be obtained in screening for bladder cancer. This could result in people undergoing unnecessary diagnostic tests that might include imaging tests and cystoscopy with the potential for anxiety, discomfort or complications, in addition to the financial costs associated with further testing.

Implications for Research

The literature review for this report identified one study (Vickers et al 2013) which described the eligibility criteria for a potential clinical trial of screening for bladder cancer by modelling the likely benefit for different risk scores using data from a trial of screening for prostate, lung, colorectal and ovarian cancers. The authors concluded that testing for bladder cancer can be optimized by restricting the eligible population to a sub-group with an elevated risk score[18] (>6 or >8). For example, using a risk score of >6 would result in 23% of the population being tested to prevent 57 invasive or high grade bladder cancers per 100,000 population, whereas screening the entire population would prevent 95 such cancers (i.e. only an additional 38 cases detected, despite screening more than four times as many people than in the targeted approach). Given the low positive predictive values that have been found when currently available urine-based bladder tumour markers have been evaluated in general population screening studies, this sort of targeted approach may be considered advisable for any future studies evaluating approaches to large scale, test based, programmes for bladder cancer.

[18] The variables contributing to the risk score were age (2 points for ≥65), gender (4 points for male), smoking history (2 points for 10-19 pack years; 4 points for 20+ pack years) and family history of bladder cancer (1 point)

Appendix A

Literature search for bladder cancer screening
Elaine Garrett, Librarian, June 2014

BACKGROUND: A previous search for screening for bladder cancer using the urinalysis/ dipstick method was undertaken by Imperial College London in 2009.

SOURCES SEARCHED: Ovid Medline 2009 – April Week 5 2014, Embase 2009 to 2014 May 09, and Cochrane Library 2009 – May 2014

SEARCH STRATEGY:

Database: Ovid MEDLINE(R) <1946 to April Week 5 2014>
---
1 (bladder adj3 cancer$).mp. (21656)
2 (bladder adj3 neoplas$).mp. (43417)
3 (bladder adj tum$).mp. (8459)
4 (urinary adj tract adj malignan$).mp. (84)
5 utm.mp. (88)
6 (transitional adj cell adj cancer$).mp. (336)
7 (transitional adj cancer adj cell$).mp. (17)
8 (transitional adj cell adj carcinoma$).mp. (8359)
9 tcc.mp. (3564)
10 (papillary adj3 tum$).mp. (3338)
11 (urologic adj3 neoplas$).mp. (3312)
12 Urologic Neoplasms/ (3267)
13 Urinary Bladder Neoplasms/ (43287)
14 Carcinoma, Transitional Cell/ (15734)
15 Carcinoma, Papillary/ (12876)
16 or/1-15 (69232)
17 Mass Screening/ (81352)
18 "Early Detection of Cancer"/ (7554)
19 Diagnostic Tests, Routine/ (6910)
20 diagnostic techniques, urological/ or antibody-coated bacteria test, urinary/ or cystoscopy/ or urinalysis/ (11381)
21 urine.mp. (189870)
22 urinalysis.mp. (9175)
23 urine/ (33086)
24 Reagent Strips/ (2861)
25 (dipstick$ or (dip adj stick$)).mp. (2291)
26 (hematuria or haematuria).mp. (19284)
27 Hematuria/ (10319)
28 strip$.mp. (46033)
29 or/17-28 (351650)
30 16 and 29 (8084)
31 *Urologic Neoplasms/ep, mo or *Urinary Bladder Neoplasms/ep, mo or *Carcinoma, Transitional Cell/ep, mo (1829)
32 *Urologic Neoplasms/dh, dt, rt, su, th or *urinary bladder neoplasms/dh, dt, rt, su, th (13163)
33 *Urologic Neoplasms/di or *urinary bladder neoplasms/di (3636)
34 randomized controlled trial.pt. (372317)
35 controlled clinical trial.pt. (88255)
36 randomized.ab. (270962)
37 placebo.ab. (145586)
38 clinical trials as topic.sh. (169744)
39 randomly.ab. (192497)
40 trial.ti. (116980)
41 or/34-40 (854390)
42 exp animals/ not humans.sh. (3934706)

43 41 not 42 (784840)
44 32 and 43 (1680)
45 meta-analysis/ (47653)
46 review literature/ (1868507)
47 meta-analy$.tw. (54910)
48 metaanal$.tw. (1227)
49 (systematic$ adj4 (review$ or overview$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (51216)
50 meta-analysis.pt. (47653)
51 review.pt. (1868507)
52 review.ti. (231286)
53 or/45-52 (1988698)
54 case report/ (1677639)
55 letter.pt. (810962)
56 historical article.pt. (300730)
57 54 or 55 or 56 (2609291)
58 53 not 57 (1849136)
59 32 and 58 (1979)
60 30 or 31 or 33 or 44 or 59 (14524)
61 limit 60 to yr="2009 -Current" (3140)
62 limit 61 to (case reports or comment or editorial or news) (624)
63 61 not 62 (2516)
64 remove duplicates from 63 (2438)

Similar searches were also undertaken in Embase and the Cochrane Library.
All 6,055 results were downloaded into a spreadsheet and 1,711 duplicates removed.

Medline	2,428
Embase	1,737
Cochrane Library	179
Total	**4,344**

The title and abstracts of the remaining articles were scanned for relevance for bladder cancer screening by the NSC and 1,562 articles remained. These are categorised as follows:

Systematic reviews General (2) Test (13) Therapy (46)*	**61**
Non-systematic reviews General (82) Test (72) Therapy (357)*	**511**
Epidemiology **UK (5)** **Non-UK (56)**	**61**
Condition/ natural history	**90**
Test	**438**
Therapy*	**348**
Screening	**13**
Guidelines and guideline adherence	**40**
Total	**1,562**

***Systematic review, non systematic reviews and studies relating to therapy were not reviewed for this report.**

Appendix B

Tumour/node/metastasis classification of bladder cancer (Pang & Catto 2013)

Primary tumour (T)

- Tx – Primary tumour cannot be assessed
- T0 – No evidence of primary tumour
- Ta – Non-invasive papillary carcinoma
- Tis – Carcinoma in situ
- T1 – Invasion of sub-epithelial connective tissue
- T2 – Invasion of muscularis propria
- pT2a – Invasion of superficial (inner half) muscularis propria
- pT2b – Invasion of deep (outer half) muscularis propria
- T3 – Invasion of perivesical tissue
- T4 – Invasion of prostate and/or seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
- T4a – Invasion of prostate, uterus, vagina
- T4b – Invasion of pelvic wall, abdominal wall

Regional lymph nodes (N)

- Nx – Lymph nodes cannot be assessed
- N0 – No lymph node involvement
- N1 – Single regional lymph node metastasis in the pelvis (hypogastric, obturator, external iliac, presacral)
- N2 – Multiple regional lymph node metastates in the pelvis
- N3 – Common iliac lymph nodes metastases

Distant metastasis (M)

- Mx - Distant metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

Non-muscle invasive cancers are divided into low-risk tumours (pTAG1 and most pTaG2) and high-risk tumours (some pTaG2, pTis, pTaG3 and pT1) based on the risk of progression (NICE 2012). Most pTa tumours are not life-threatening and progression to more advanced disease from the pTa stage is uncommon. However, recurrence is common and may affect other areas of the urinary tract (NICE 2012). Progression from pT1 disease is more common, occurring in up to 50% of cases (NICE 2012).

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