UK National Screening Committee

Evidence map: Screening for bladder cancer

A literature search to outline the volume and type of evidence related to screening for bladder cancer for the UK National Screening Committee

Version: Final

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Date: September 2020

The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Published September 2020

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Summary

This document discusses the findings of an evidence map on screening for bladder cancer.

Evidence maps are a way of scanning published literature to gauge the volume, type and direction of the evidence base in relation to a specific topic. They inform whether there is sufficient evidence to commission an external rapid review on the topic under consideration.

Based on the findings of this evidence map, a rapid review on screening for bladder cancer should not be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to screening for bladder cancer in 3-years' time.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for bladder cancer is a topic currently due for an update review.

The UK NSC currently recommends against screening for bladder cancer. The Committee based this recommendation on the evidence provided by the 2014 review carried out by Solutions for Public Health. The 2014 review found that there were no reliable screening markers that met the UK NSC criteria for a safe, precise and validated screening test.

Preliminary work was undertaken to gauge whether this situation had changed. This took the form of an evidence map. Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. This approach has been used for this topic to support decision making on whether or not the evidence is sufficient to justify commissioning a more sustained review of the evidence.

This document discusses the findings and focuses on 2 key questions: the diagnostic accuracy of screening tests for bladder cancer and the existence of any national or international guidelines or recommendations on population screening for bladder cancer.

The aim of this document is to present the information necessary for the UK NSC to consider whether an evidence summary on screening for bladder cancer should be commissioned.

Previous review on screening for bladder cancer

The UK NSC previously reviewed screening for bladder cancer in 2014 (1). The 2014 UK NSC review only considered issues relating to screening tests. Evidence for the treatment for bladder cancer and screening programmes were not considered.

The 2014 review identified studies assessing test performance in a screening context or in a population relevant to screening. The tests identified included the dipstick test for haematuria, urinary biomarkers and urine cytology. However, these studies reported low positive predictive values (PPV) (ranging from 0% to 17.4%) suggesting that screening might identify a high number of false positive test results. This would lead to unnecessary follow-up tests.

The search for the 2014 review also identified numerous studies on potential screening tests for bladder cancer. These studies investigated the ability of these tests to distinguish between known cancer patients and healthy controls but had not been tested in screening populations.

The 2014 review concluded that the body of evidence identified by the literature search was insufficient to change the existing recommendation not to offer screening for bladder cancer.

Outcomes

On the basis of the 2019 evidence map, it is recommended that an evidence summary on screening for bladder cancer should not be commissioned at the present time.

The Committee will return to screening for bladder cancer in 3-years' time.

Evidence map

This evidence map has been developed as part of a process to assess whether an update review on screening for bladder cancer should be commissioned and to establish the volume and type of evidence on key issues related to this topic.

The evidence map aims to address the following questions:

1. What are the diagnostic accuracies of screening tests for bladder cancer?
2. Are there any national or international guidelines or recommendations on population screening for bladder cancer?

This evidence map will provide the basis for discussion on whether an evidence summary is justified.

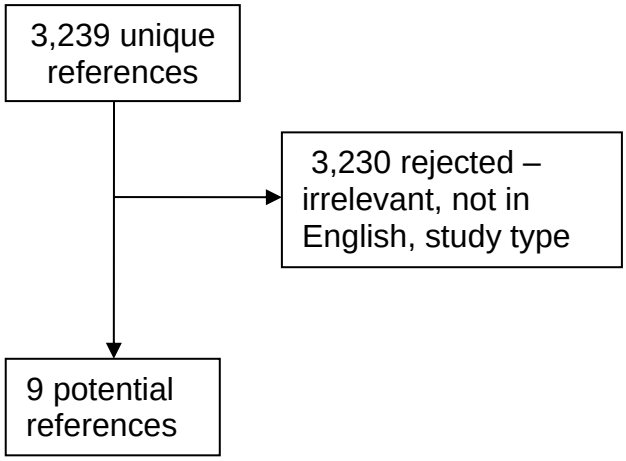
Summary of the evidence map findings

The search for the evidence map was conducted on 5th September 2019 in 3 databases: Medline, Embase, and the Cochrane Library. Since the search for the previous review was conducted in June 2014, the time period was restricted to 1st January 2014 to 5th September 2019. A detailed search strategy including exclusion and inclusion criteria is available in Appendix 1. The search returned a total of 3,239 unique references which were initially sifted by an information scientist for potential relevance. An SPH reviewer assessed 444 titles and abstracts for further appraisal and possible inclusion in the evidence map. A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

An additional search for guidelines was conducted on the TRIPdatabase, NICE Evidence Search and using an internet search engine. Returns were sifted by an SPH reviewer for potential relevance.

Nine references were included in the final evidence map. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertainty.

Figure 1. Summary of publications included and excluded



Question 1: What are the diagnostic accuracies of screening tests for bladder cancer?

Of the 9 potential references identified from the search, 2 met the criteria for inclusion for this question (2, 3). The inclusion and exclusion criteria are summarised in Appendix 1. These were about the diagnostic accuracy of screening tests in asymptomatic populations, tested in a screening context and in countries comparable to the UK. Two further references that partially met the criteria for inclusion were systematic reviews that discussed screening tests for bladder cancer (4, 5).

The 2 studies that met the inclusion criteria were published in 2014 and 2015 and reported the results of tests for bladder cancer conducted as part of screening programmes (2, 3). These studies were set in Germany and the US and included 1,609 male participants and 7,826 (95% male) participants respectively. They reported test performance in high risk populations such as chemical workers with exposure to aromatic amines and people with a history of working in areas where they might be exposed to coal tar pitch. The urine screening tests used included the NMP22 assay, UroVysionTM, ImmunoCyt/ uCYT+ and cytology. Both studies reported measures of test performance including sensitivity, specificity, positive predictive value and negative predictive value. The positive predictive values (PPV) reported were low ranging from 2.96% to 26.7% for different tests or combinations of tests.

These studies were conducted in high risk populations where the prevalence of bladder cancer may be higher than in the general population. Both studies concluded that continued screening of their cohort with the tests used was not supported. This was because the high number of false positive tests had led to people undergoing unnecessary and expensive tests.

One systematic review assessed microscopic haematuria as a biomarker to screen for urologic malignancy in women. This review included studies published up to June 2018 and identified 8 studies including 110,179 women with microscopic haematuria. The PPV range reported was low at approximately 0.6% to 2.8%. This systematic review was recently published online and the full text was not readily accessible. The abstract states that the detection of microscopic haematuria was used to screen for urologic malignancy but does not provide any specific details on the included study designs

or populations, the tests used or if testing for microscopic haematuria was offered in combination with other markers (4).

A second systematic review assessed the accuracy of the urine test NMP22 BladderChek to detect bladder cancer in patients with high bladder cancer risk. This review included 19 studies published up to June 2017 in a meta-analysis. Sample sizes of the included studies ranged from 53 to 1,328. The design of the included studies was not stated. The included patients were described as being at high risk of bladder cancer but no further details were provided. The authors reported sensitivity, specificity, positive likelihood ratio and negative likelihood ratio but did not report PPV. The review included studies published in both English and Chinese. It is not clear how applicable the results are to a UK screening population (5).

The UK NSC's current position is that a test which is suitable for population screening is not available. The limited number of relevant studies identified restricts the conclusions that could be drawn and what could be expected from an evidence summary. At present there is insufficient new evidence in this key area to justify commissioning an evidence summary. The volume and type of evidence identified is unlikely to lead to a change in the UK NSC's current position.

Question 2: Are there any national or international guidelines or recommendations on population screening for bladder cancer?

Five guidelines/ consensus documents that mentioned screening for bladder cancer were identified. None of these recommended general population screening of asymptomatic adults.

The recommendations or statements on screening for bladder cancer in the identified documents are summarised briefly below.

The United States Preventative Services Task Force (USPSTF) last reviewed screening for bladder cancer in adults in 2011 (6). This concluded that there was insufficient evidence to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults. The USPSTF also conducted literature searches in April 2019 and found a lack of new evidence to support an updated systematic review.

A 2019 guideline on bladder cancer from the European Association of Urology included the statement: “The low incidence of bladder cancer in the general population and the short lead-time impair feasibility and cost-effectiveness. Routine screening for bladder cancer is not recommended” (7).

The Société Internationale d’Urologie (SIU) - International Consultation on Urologic Diseases (ICUD) Joint Consultation in 2017 included recommendations on screening and early detection. These stated that “bladder cancer screening, if undertaken, should be confined to high-risk patients” and that “bladder cancer screening cannot be recommended for [the] general population” (8).

A 2015 report from the World Health Organization/ ICUD consensus group considered if molecular markers could support the screening of patients at risk of having or developing bladder cancer. The resulting recommendation was that “bladder cancer screening using urine for testing is promising but cannot be recommended at present” (9).

A 2014 clinical practice guideline on bladder cancer from the European Society for Medical Oncology included the statement that “current evidence suggests that screening for bladder cancer on a population level is not helpful for improving survival” (10).

A number of guidelines and consensus documents have made recommendations relating to population screening for bladder cancer. No guidance was identified that recommends screening in a general population.

Conclusions

The findings of this evidence map are unlikely to impact on the current recommendation on screening for bladder cancer as no new evidence was identified that would change those conclusions.

Recommendations

- The volume and type of evidence related to screening for bladder cancer is insufficient to justify an update review at this stage and it should be re-considered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: 1st January 2014 to 5th September 2019

SEARCH STRATEGIES:

Medline Question 1: screening tests			**Embase Question 1: screening tests**		
1	Urinary Bladder Neoplasms/	52741	1	exp bladder cancer/ or bladder papilloma/	66274
2	Urologic Neoplasms/	4736	2	*urinary tract cancer/	3032
3	(Carcinoma, Transitional Cell/ or Carcinoma, Papillary/) and bladder*.mp.	15303	3	(transitional cell cancer/ or papilloma/) and bladder*.mp.	18414
4	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	66932	4	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	93260
5	((urinary tract or urologic) adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	7773	5	((urinary tract or urologic) adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	11106
6	((transitional cell or transitional cancer cell or tcc or papillary) and bladder*).mp.	18779	6	((transitional cell or transitional cancer cell or tcc or papillary) and bladder*).mp.	23501
7	1 or 2 or 3 or 4 or 5 or 6	72829	7	1 or 2 or 3 or 4 or 5 or 6	103621
8	Mass Screening/	98817	8	mass screening/ or cancer screening/ or screening/	295232
9	exp early diagnosis/	46731	9	screening test/	66968
10	Urinalysis/ or diagnostic techniques, urological/	8484	10	early diagnosis/ or early cancer diagnosis/	106874
11	Urine/an, bl, cy [Analysis, Blood, Cytology]	5567	11	urinalysis/	91509
12	Reagent Strips/	3299	12	urine cytology/	3882
13	Biomarkers/ur or exp biomarkers, tumor/ur	15119	13	test strip/ or urine test strip/	4306
14	Antibody-Coated Bacteria Test, Urinary/	148	14	(*marker/ or biological marker/ or exp tumor marker/) and urine/	8558
15	Hematuria/di	1953	15	hematuria/di [Diagnosis]	2832
16	Hematuria/ and Diagnostic Tests, Routine/	30	16	(screen* or (early adj3 (diagnos* or detect*))).ti,ab,kw.	1211452
17	(screen* or (early adj3 (diagnos* or detect*))).ti,ab,kw.	854686	17	(urinalysis or urinanalysis).ti,ab,kw.	13051

18	(urinalysis or urinanalysis).ti,ab,kw.	7653	18	(urin* adj5 (test* or screen* or analys* or cytolog*)).ti,ab,kw.	60255
19	(urin* adj5 (test* or screen* or analys* or cytolog*)).ti,ab,kw.	41064	19	(dipstick? or dip stick? or strip?).ti,ab,kw.	54010
20	(dipstick? or dip stick? or strip?).ti,ab,kw.	45505	20	((hematuria or haematuria) adj5 (microscopic or nonvisible or non-visible)).ti,ab,kw.	3413
21	((hematuria or haematuria) adj5 (microscopic or nonvisible or non-visible)).ti,ab,kw.	2204	21	(biomarker? or marker?).ti.	249383
22	(biomarker? or marker?).ti.	175558	22	(urin* adj5 (biomarker? or marker?)).ti,ab,kw.	14827
23	(urin* adj5 (biomarker? or marker?)).ti,ab,kw.	10282	23	(((cancer* or neoplas* or carcinoma* or tumo?r* or malignan*) adj5 (biomarker? or marker?)) and urin*).ti,ab,kw.	5346
24	(((cancer* or neoplas* or carcinoma* or tumo?r* or malignan*) adj5 (biomarker? or marker?)) and urin*).ti,ab,kw.	3452	24	(((cancer* or neoplas* or carcinoma* or tumo?r* or malignan*) adj5 (biomarker? or marker?)) and screen*).ti,ab,kw.	11236
25	(((cancer* or neoplas* or carcinoma* or tumo?r* or malignan*) adj5 (biomarker? or marker?)) and screen*).ti,ab,kw.	7048	25	(minichromosom* maintenance complex or mini-chromosom* maintenance complex or mmc5 or mmc-5).ti,ab,kw.	347
26	(minichromosom* maintenance complex or mini-chromosom* maintenance complex or mmc5 or mmc-5).ti,ab,kw.	294	26	(nuclear matrix protein* or nmp22 or nmp-22).ti,ab,kw.	1286
27	(nuclear matrix protein* or nmp22 or nmp-22).ti,ab,kw.	1057	27	(adxbladder or adx bladder or immunocyt or immuno cyt or urovysion or cxbladder or cx bladder or urna2 or urna-2).ti,ab,kw.	458
28	(adxbladder or adx bladder or immunocyt or immuno cyt or urovysion or cxbladder or cx bladder or urna2 or urna-2).ti,ab,kw.	261	28	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	1692946
29	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	1151754	29	7 and 28	14571
30	7 and 29	8559	30	(editorial or letter or note or "review").pt. or case report.ti,ab.	5337924

31	(comment or editorial or letter or news or "review").pt. or case report.ti,ab.	4709981	31	29 not 30	11680
32	30 not 31	6795	32	limit 31 to "reviews (maximizes specificity)"	176
33	limit 30 to ("systematic review" or "reviews (maximizes specificity)")	236	33	31 or 32	11680
34	32 or 33	6938	34	conference*.pt.	4330120
35	limit 34 to (english language and yr="2014 - Current")	1855	35	33 not 34	8213
			36	limit 35 to (english language and yr="2014 -Current")	2423
			37	(exp animals/ or nonhuman/) not human/	6341805
			38	36 not 37	2362

Medline: Question 2 guidelines			**Embase: Question 2 guidelines**		
1	Urinary Bladder Neoplasms/	52741	1	exp bladder cancer/ or bladder papilloma/	66274
2	Urologic Neoplasms/	4736	2	*urinary tract cancer/	3032
3	(Carcinoma, Transitional Cell/ or Carcinoma, Papillary/) and bladder*.mp.	15303	3	(transitional cell cancer/ or papilloma/) and bladder*.mp.	18414
4	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	66932	4	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	93260
5	((urinary tract or urologic) adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	7773	5	((urinary tract or urologic) adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).mp.	11106
6	((transitional cell or transitional cancer cell or tcc or papillary) and bladder*).mp.	18779	6	((transitional cell or transitional cancer cell or tcc or papillary) and bladder*).mp.	23501
7	1 or 2 or 3 or 4 or 5 or 6	72829	7	1 or 2 or 3 or 4 or 5 or 6	103621
8	Mass Screening/	98817	8	mass screening/ or cancer screening/ or screening/	295232
9	exp early diagnosis/	46731	9	screening test/	66968
10	(screen* or (early adj3 (diagnos* or detect*))).ti,ab,kw.	854686	10	early diagnosis/ or early cancer diagnosis/	106874
11	diagnos*.ti.	569978	11	(screen* or (early adj3 (diagnos* or detect*))).ti,ab,kw.	1211452
12	8 or 9 or 10 or 11	1402362	12	diagnos*.ti.	649209
13	7 and 12	5803	13	8 or 9 or 10 or 11 or 12	1865760
14	exp guideline/	32447	14	7 and 13	9435
15	Societies, Medical/	64835	15	practice guideline/ or consensus development/	411030
16	(guideline or consensus statement or consensus	65135	16	medical society/	171340

	development conference or delphi).ti,ab,kw.				
17	recommendation*.ti. or ((screen* or practice) adj5 recommendation*).ti,ab,kw.	47550	17	(guideline or consensus statement or consensus development conference or delphi).ti,ab,kw.	104107
18	14 or 15 or 16 or 17	190898	18	recommendation*.ti. or ((screen* or practice) adj5 recommendation*).ti,ab,kw.	62492
19	13 and 18	90	19	15 or 16 or 17 or 18	655852
20	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).ti.	32196	20	14 and 19	359
21	(guideline or consensus statement or consensus development conference or delphi or recommendation*).ti.	54491	21	(bladder* adj3 (cancer* or neoplas* or carcinoma* or tumo?r* or malignan*)).ti.	41358
22	20 and 21	84	22	(guideline or consensus statement or consensus development conference or delphi or recommendation*).ti.	70504
23	19 or 22	160	23	21 and 22	112
24	limit 23 to (english language and yr="2014 - Current")	65	24	20 or 23	453
			25	limit 24 to (english language and yr="2014 - Current")	221
			26	conference*.pt.	4330120
			27	25 not 26	157

	Cochrane
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
#2	MeSH descriptor: [Urologic Neoplasms] this term only
#3	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
#4	MeSH descriptor: [Carcinoma, Papillary] explode all trees
#5	(bladder*):ti,ab,kw
#6	(#3 or #4) AND #5
#7	((bladder* NEAR/3 (cancer* or neoplas* or carcinoma* or tumo* or malignan*)).mp.):ti,ab,kw OR (((urinary tract or urologic) NEAR/3 (cancer* or neoplas* or carcinoma* or tumo* or malignan*)).mp.):ti,ab,kw OR ((("transitional cell" or "transitional cancer cell" or tcc or papillary) and bladder*)):ti,ab,kw
#8	#1 or #2 or #6 or #7
#9	MeSH descriptor: [Mass Screening] this term only
#10	MeSH descriptor: [Early Diagnosis] explode all trees
#11	MeSH descriptor: [Urinalysis] explode all trees
#12	MeSH descriptor: [Urine] explode all trees
#13	MeSH descriptor: [Reagent Strips] explode all trees
#14	MeSH descriptor: [Biomarkers] this term only
#15	MeSH descriptor: [Biomarkers, Tumor] explode all trees
#16	MeSH descriptor: [Hematuria] explode all trees
#17	MeSH descriptor: [Diagnostic Tests, Routine] explode all trees

#18	((screen* or (early NEAR/3 (diagnos* or detect*))):ti,ab,kw OR (urinalysis or urinanalysis):ti,ab,kw OR ((urin* NEAR (test* or screen* or analys* or cytolog*))):ti,ab,kw OR (dipstick* or "dip stick*"or strip*):ti,ab,kw
#19	(((hematuria or haematuria) NEAR (microscopic or nonvisible or nonvisible))):ti,ab,kw
#20	(biomarker* or marker*):ti OR ((urin* NEAR (biomarker* or marker*))):ti,ab,kw OR ((((cancer* or neoplas* or carcinoma* or tumo* or malignan*) NEAR (biomarker* or marker*)) and urin*)):ti,ab,kw OR ((((cancer* or neoplas* or carcinoma* or tumo* or malignan*) NEAR (biomarker* or marker*)) and screen*)):ti,ab,kw
#21	((minichromosom* maintenance complex or mini-chromosom* maintenance complex or mmc5 or mmc-5)):ti,ab,kw OR (("nuclear matrix protein*" or nmp22 or nmp-22)):ti,ab,kw OR ((adxbladder or "adx bladder" or immunocyt or "immuno cyt" or urovysion or cxbladder or "cx bladder" or urna2 or urna-2)):ti,ab,kw
#22	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23	#8 and #22

Results by database

Medline	**1,920**
Embase	**2,519**
Cochrane Library	**227**
Total	**4,666**

After the exclusion of duplicates, 3,239 references remained.

An additional search for guidelines was conducted on TRIPdatabase, NICE Evidence Search and an internet search engine (Google). Key terms searched for included combinations of bladder cancer, screening and guidance.

Inclusions and exclusion criteria

Publications not in the English language, case studies, conference reports and comment/letters were excluded.

Eligibility for inclusion in the map
Question 1

- population: asymptomatic adults aged ≥18 years (studies from the UK should be prioritised but, in the absence of such studies, those from comparable countries could be reported)
- index tests:
    - dipstick markers for microscopic haematuria, if offered in combination with other markers
    - urinary biomarkers such as
        - protein- and cell-based biomarkers: BTAstat® (BTA), Nuclear matrix protein (NMP22), ImmunoCyt™, MCM5
        - gene-based biomarkers, UroVysion® (FISH) and Cxbladder (uRNA-2)
        - urinary cytology
- comparator: any or none
- reference standard: cystoscopy and biopsy

- outcomes: sensitivity, specificity, positive predictive value, negative predictive value
- study design: diagnostic accuracy studies in consecutively enrolled or randomly assigned populations should be prioritised. Other study designs should be reported if no studies of this type are available

Question 2

- population: asymptomatic adults aged ≥18 years (guidelines and recommendations for population screening programmes should be prioritised. Followed by any other type of formal screening)
- intervention: guidelines or recommendations for any type of formal screening programme
- comparator: n/a
- outcomes: n/a
- study design: national or international guidelines, recommendations or consensus statements from professional organisations, royal colleges or equivalent, national departments of health or national screening organisations

References

Introduction

1. Solutions for Public Health. Screening for bladder cancer: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC), 2014

Question 1: screening tests for bladder cancer (4)

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3. Taiwo OA. Slade MD. Cantley LF. Tessier-Sherman B. Galusha D. et al. Bladder cancer screening in aluminium smelter workers. Journal of Occupational & Environmental Medicine 2015, 57(4): 421-427
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Question 2: Guidelines for population screening (5)

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7. EAU Guidelines. Edn. presented at the EAU Annual Congress Barcelona 2019. https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/
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