Review

Current Urology

OPEN

Comparison of the clinical usefulness of different urinary tests for the initial detection of bladder cancer: a systematic review

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Abstract

Objectives: The standard initial approach in patients with hematuria or other symptoms suggestive of bladder cancer (BC) is a combination of cystoscopy and urine cytology (UC); however, UC has low sensitivity particularly in low-grade tumors. The aim of the present review was to critically analyze and compare results in the literature of promising molecular urinary tests for the initial diagnosis of BC.

Methods: We searched in the Medline and Cochrane Library databases for literature from January 2009 to January 2019, following the PRISMAguidelines.

Results: In terms of sensitivity, ImmunoCyt showed the highest mean and median value, higher than UC. All tests analyses showed higher mean and median sensitivity when compared with UC. In terms of specificity, only UroVysion and Microsatellite analyses showed mean and median values similar to those of UC, whereas for all other tests, the specificity was lower than UC. It is evident that the sensitivity of UC is particularly low in low grade BC. Urinary tests mainly had improved sensitivity when compared to UC, and ImmunoCyt and UroVysion had the highest improvement in low grade tumors.

Conclusions: Most of the proposed molecular markers were able to improve the sensitivity with similar or lower specificity when compared to UC. However, variability of results among the different studies was strong. Thus, as of now, none of these markers presented evidences so as to be accepted by international guidelines for diagnosis of BC.

Keywords: Bladder cancer; Cytology; Hematuria; MCM5; Urinary markers

1. Introduction

Bladder cancer (BC) represents the 4th most common neoplasia in men with a significant morbidity and mortality.[1] The standard initial approach in patients with hematuria or other symptoms suggestive of BC is a combination of cystoscopy and urine cytology (UC).[2] Cystoscopy is an invasive method whereas UC exhibits low sensitivity in detecting BC.[3,4] UC has high sensitivity in high-grade tumors (84%), but low sensitivity in low-grade tumors (16%).[5] A positive UC can indicate a urothelial tumor in the urinary tract; however, a negative cytology does not exclude the presence of a tumor. Cytological interpretation is user-dependent, and evaluation can be hampered by low cellular yield, urinary tract infections, and stones. However, in experienced hands the specificity exceeds 90%.[6]

Several non-invasive molecular tumor tests have been developed to improve the sensitivity of UC. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines.[2]

The following conclusions have been drawn by EAU guidelines regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity, compared to UC.
- Benign conditions may influence the results of many urinary marker tests.
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and the complicated laboratory methods required.
- UroVysion fluorescent in situ hybridization (FISH), ImmunoCyt/uCyt, NMP-22, BTA, and microsatellite analysis are interesting tests. However, a variable range of sensitivity and specificity in different clinical trials is reported in the literature.

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Supplementary Digital Content is available for this article.

Current Urology, (2021) 15, 22-32

Received December 27, 2019; Accepted January 7, 2020.

http://dx.doi.org/10.1097/CU9.0000000000000012

Different mechanisms of action are used by these tests. NMP-22 is a nuclear matrix protein involved in the proper distribution of chromatin during replication. It is a quantitative ELISA test using 2 antibodies.[7,8] Microsatellite analysis is carried out by polymerase chain reaction using DNA primers on polymorphic short tandem DNA repeats in the genome.[9]

ImmunoCyt is an immunocytological test using fluorescence that combines 3 monoclonal antibodies to detect tumor-associated cellular antigens.[10] The UroVysion test is a multitarget multicolour FISH assay, taking advantage of the high occurrence of chromosomal abnormalities in BC.[11,12] The BTA stat quantitative assay detects the human complement factor H-related protein and the complement factor H by immunochromatography.[13,14] MCM5 is a minichromosome maintenance protein examined by immunofluorometric assay using monoclonal antibodies.[15]

There is still a need for defining a useful urine biomarker that may help in the initial diagnosis and follow-up of BC, thus replacing UC.

2. Materials and methods

2.1. Objective

The aim of the present review was to critically analyze and compare results in the literature with promising molecular urinary tests for the initial diagnosis of BC. We limited our analysis to urine tests such as UroVysion, NMP-22, ImmunoCyt/uCyt, the BTA stat test, microsatellite analysis, and the MCM5 test. We compared sensitivity, specificity, and performance of these tests and that of UC in detecting BC.

2.2. Search strategy

We searched in the Medline and Cochrane Library databases (primary fields: bladder neoplasm AND initial diagnosis AND urinary test OR UroVysion OR NMP-22 OR BTA OR microsatellite analysis OR ImmunoCyt/uCyt OR the MCM5 test).

Our search was performed without language restriction in the literature from January 2000 to August 2019 following PRISMA guidelines (Fig. 1). Original and review articles were included and critically evaluated. Additional references were identified from reference lists of these articles. We did not include abstracts and reports from meetings.

2.3. Selection of the studies and inclusion criteria

Entry into the analysis was restricted to data collected from original studies on clinical trials including subjects with hematuria or other symptoms suggestive of an initial diagnosis of BC and verified by cystoscopy, transurethral biopsy, or resection of the bladder.

There were 2 authors (G.D.L. and F.D.G.) who independently screened the titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were independently examined by 3 authors (G.D.L., M.M., and F.D.G.) to determine

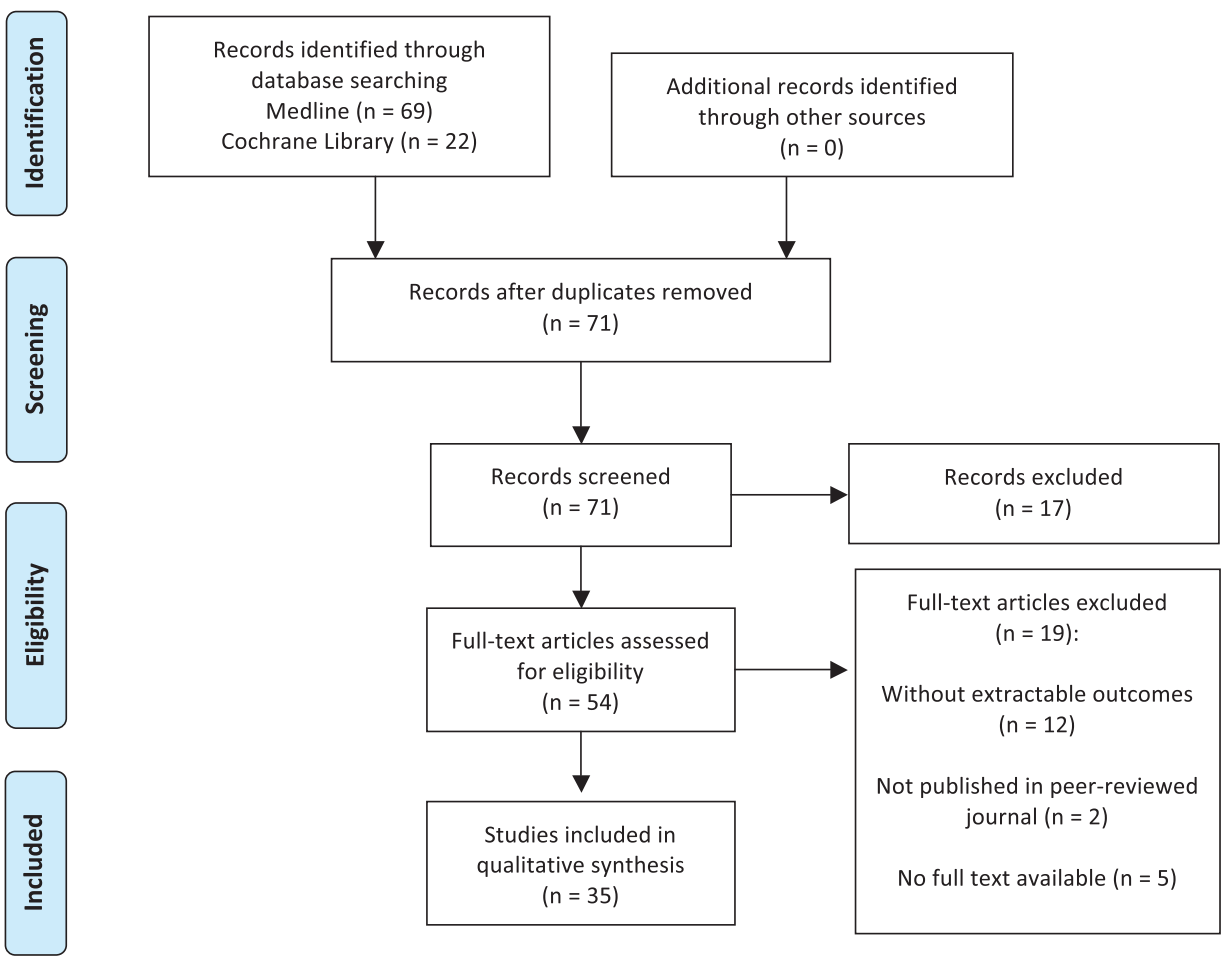

Figure 1. PRISMA flow diagram.

whether or not they met the inclusion criteria. Then, 3 authors (G. D.L., M.M., and F.D.G.) extracted data from the selected articles. Final inclusion was determined by all investigators' evaluation discussion.

The studies selected for inclusion met the following criteria: (1) analysis for initial diagnosis of BC; (2) UroVysion, NMP-22, BTA, microsatellite analysis, ImmunoCyt/uCyt, MCM5 tests compared with UC; (3) cystoscopy or transurethral biopsy or resection of the bladder methods used to confirm results and diagnosis of BC; and (4) results expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Articles were excluded if: (1) multiple reports were published on the same population; (2) data provided were insufficient for the outcomes; or (3) confirmation from at least cystoscopy was not reported. Risk of bias for all included reports was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies.[16]

3. Results

3.1. Search results

The database searches initially yielded 91 journal article references. Of these 20 were subsequently removed due to either duplication or a failure to meet the inclusion criteria. Full-text articles were then re-evaluated and critically analyzed for the remaining 71 journal references. Of these, 36 did not meet the inclusion criteria. The remaining 35 studies were considered for our critical review (Fig. 1) (Table 1).

Quality of studies: of the 35 studies entered into the review, 15 were conducted in Europe,[17–31] 8 in America,[5,8,32–37] 10 in Asia,[38–47] and 2 in Oceania.[48,49] Of the 35 studies, 2 were randomized studies,[18,38] 7 were retrospective mono- or multicenter,[8,21,32,35,36,41,48] and 28 were prospective mono- or multicenter.[5,17–20,22–31,33,34,37–40,42–47,49] Each study comparatively considered one or more recognized biomarkers for BC diagnosis, and compared them with one or more confirmatory tests such as cystoscopy, transurethral bladder biopsy, or resection (Table 1). Risk of bias for all included reports was evaluated using the QUADAS-2 tool for diagnostic accuracy studies (fig. S1, supplementary material, http://links.lww.com/CURRUROL/A0). The major bias within the studies focused upon "patient selection" and "index test." In general, 21 out of the 35 studies were of upper middle quality.

3.2. Study sample size, mean age, and inclusion/exclusion criteria

In the 35 studies, the sample size of cases strongly varied from 41 to 2217 cases analyzed (total sample 16,691 cases). The range of mean age across the studies varied from 30.8 to 72.4 years. No study had as exclusion criteria data such as age, race, or other registries. All studies had as inclusion criteria hematuria or other symptoms requiring initial investigation for BC.

3.3. Sampling methods

All 35 studies used voided urine as the main method for sample collection. Some studies used in association others collecting methods. In particular, 3 trials used bladder barbotage,[32–34] 4 catheter,[5,21,32,36] and 5 bladder washing.[5,20,28,32,36]

3.4. Biomarker used

Most of the analyzed studies considered one or more recognized biomarker for the initial diagnosis of BC.

MCM5 was used in 3 studies on 2147 cases[17–19]; UroVysion (uFISH) in 12 studies on 5033 cases[20,23,32–39,45,48]; NMP-22 in 19 studies on 8988 cases [5,8,18,20,23–25,28–31,38,41–43,46–49]; microsatellite analysis in 3 studies on 592 cases[25,26,44]; BTA stat in 6 studies on 999 cases[5,20,28–30,37]; and ImmunoCyt/uCyt in 7 studies on 4976 cases.[5,20–23,27,40] Twenty-five studies also included UC as a diagnostic tool in comparison with the new tests (14,375 cases) (Table 1).[5,8,17–20,22–24,26,27,30,31,35,36,38–41,43,45–49]

3.5. Comfirmatory test

In all analyzed studies, at least cystoscopy was used as the confirmatory test to verify biomarker results. In addition to cystoscopy, 28 studies also performed transurethral bladder biopsy or resection.[5,8,17–19,21–24,26–33,37–42,44–47,49]

3.6. Diagnostic accuracy analysis of the different biomarkers

Table 2 summarizes sensitivity, specificity, PPV, and NPV of each test analyzed in the studies in terms of prediction for initial diagnosis of BC. Results were analyzed across all grades and risk categories of BC.

In the 25 studies that analyzed UC in comparison with the new tests, sensitivity, specificity, PPV, and NPV ranges were 9.0%–88.2%, 41.0%–100%, 10.0%–94.9%, and 34.0%–98.7%, respectively.

Values for MCM5 and microsatellites analysis were only reported in 3 studies.

All 6 urinary tests analyzed, showed a strong variability of results in terms of diagnostic accuracy among studies (Table 2) (Fig. 2).

Microsatellite analysis, UroVysion, and NMP-22 tests showed a higher mean and median specificity than sensitivity whereas for all the other tests sensitivity and specificity showed similar mean and median values.

In terms of sensitivity, ImmunoCyt showed the highest mean and median values, higher than UC. All 6 tests showed higher mean and median sensitivity when compared with UC.

In terms of specificity, only UroVysion and microsatellite analysis showed mean and median values similar to those of UC, whereas for all other tests, specificity was lower than UC. Mean and median values of false negatives where particularly low using microsatellite, ImmunoCyt, and MCM5 tests (NPV).

3.7. Sensitivity in relation to BC grade

Table 3 shows sensitivity, specificity, NPV, and PPV for each urinary test in relation to the BC histological grade (Table 3) (Fig. 3). No data were found for microsatellite and MCM5 tests.

It is evident that sensitivity of UC is particularly low in low grade BC. The urinary tests mainly improved sensitivity compared to UC, and ImmunoCyt and UroVysion had the highest improvement in low grade tumors (ImmunoCyt G1 vs. UC G1: mean difference 42.9, 95%CI 3.67–82.13, $p=0.0186$; UroVysion G1 vs. UC G1: mean difference 42.2, 95%CI 2.83–81.39, $p=0.0229$).

4. Critical analysis and conclusion

A number of noninvasive tests to detect BC have been developed. It is interesting to note that none of these urinary markers have a better sensitivity than cytology but have similar or mainly lower specificity (Table 2) (Fig. 2). These markers can be divided into 2 categories based on whether urine (soluble urine markers: BTA

Table 1

Main data from the 35 studies considered in the review.

Author, year, location	Study design	Sample size, n	Median participant age, y	Sampling method	Biomarker	Confirmatory test	Statistical results, %			
Stober et al.,[17] 2002, UK	Monocenter prospective	353	70 (62–78)	Voided urine	– MCM5 – Cytology	– Cystoscopy – Biopsy	MCM5 – Sens: 87 – Spec: 87 – NPV: 96 – PPV: 64		Cytology – Sens: 48 – Spec: 97 – NPV: 88 – PPV: 82	
Kelly et al.,[18] 2012, UK	Monocenter prospective blinded randomized	1677	63 (49–73)	Voided urine	– MCM5 – NMP-22 – Cytology	– Cystoscopy – Bladder resection	MCM5 – Sens: 69 – Spec: 69 – NPV: 93 – PPV: 26	NMP-22 – Sens: 53 – Spec: 84 – NPV: 92 – PPV: 36		Cytology – Sens: 9 – Spec: 88 – NPV: 87 – PPV: 10
Brems-Eskildsen et al.,[19] 2010, Denmark	Monocenter prospective	117	71	Voided urine	– MCM5 – Cytology	– Cstoscopy – Biopsy	MCM5 – Sens: 62.5 – Spec: 65.9 – NPV: 60 – PPV: 68.2		Cytology – Sens: 41.7 – Spec: 87.9 – NPV: 59.3 – PPV: 78.1	
Virk et al.,[32] 2017, USA	Monocenter retrospective	377	67	Voided, catheterized, bladder borbotage washing	– UroVysion	– Cystoscopy – Bladder resection/ biopsy	UroVysion – Sens: 44.6 – Spec: 81.8 – NPV: 80.3 – PPV: 47.2			
Schomler et al.,[33] 2010, USA	Monocenter prospective	108	65.7 (30–99)*	Voided/borbotage	– UroVysion	– Cystoscopy – Bladder resection	UroVysion – Sens: 57.1 – Spec: 100 – NPV: 25 – PPV: 100			
Lotan et al.,[34] 2008, USA	Monocenter prospective	50	65 (14.4)+	Voided/borbotage	– UroVysion	– Cystoscopy	UroVysion – Sens: 77.8 – Spec: 100 – NPV: 60 – PPV: 100			
Kehinde et al.,[38] 2011, Kuwait	Monocenter Prospective blinded randomized	43	53 (16–77)*	Voided urine	– UroVysion – NMP-22 – Cytology	– Cystoscopy – Biopsy	UroVysion – Sens: 80 – Spec: 48 – NPV: 71.2 – PPV: 61	NMP-22 – Sens: 82 – Spec: 66 – NPV: 78.8 – PPV: 71.3		Cytology – Sens: 28 – Spec: 95 – NPV: 84.1 – PPV: 84.9
Gopalakrishna et al.,[35] 2017, USA	Monocenter retrospective	1022	66 (56–75)	Voided urine	– UroVysion – Cytology	– Cystoscopy	UroVysion – Sens: 37 – Spec: 84 – NPV: NS – PPV: NS		Cytology – Sens: 63 – Spec: 41 – NPV: NS – PPV: NS	
Dimashkien et al.,[36] 2013, USA	Monocenter retrospective	652	NS	Voided, catheterized and bladder washing	– UroVysion – Cytology	– Cystoscopy	UroVysion – Sens: 60 – Spec: 93.4 – NPV: 97.5 – PPV: 35.5		Cytology – Sens: 57.8 – Spec: 88.6 – NPV: 97.2 – PPV: 23.4	

(*continued*)

Table 1
(continued).

Author, year, location	Study design	Sample size, n	Median participant age, y	Sampling method	Biomarker	Confirmatory test	Statistical results, %
Daniely et al.,[39] 2005, Israel	Monocenter prospective	41	72.4 (12.2)	Voided urine	– UroVysion – Cytology	– Cystoscopy – Bladder resection/ biopsy	UroVysion – Sens: 100 – Spec: 100 – NPV: NS – PPV: NS Cytology – Sens: 61.9 – Spec: 100 – NPV: NS – PPV: NS
Yafi et al.,[5] 2015, Canada	Monocenter prospective	109	69 (33–96)§	Voided, washing, catheterized	– NMP-22 – BTA stat – ImmunoCyt – Cytology	– Cystoscopy – Biopsy	NMP-22 – Sens: 58 – Spec: 85 – NPV: 39 – PPV: 92 BTA stat – Sens: 61 – Spec: 78 – NPV: 38 – PPV: 89 ImmunoCyt – Sens: 62 – Spec: 79 – NPV: 37 – PPV: 91 Cytology – Sens: 48 – Spec: 86 – NPV: 34 – PPV: 90
Toma et al.,[20] 2004, Germany	Monocenter prospective	126	NS	Voided and bladder washing	– ImmunoCyt – BTA stat – NMP-22 – UroVysion – Cytology	– Cystoscopy	ImmunoCyt – Sens: 78.3 – Spec: 73.8 – NPV: 85.5 – PPV: 63.2 BTA stat – Sens: 66.6 –Spec: 78.2 – NPV: 75.4 – PPV: 71.4 NMP-22 – Sens: 68.5 – Spec: 65.2 – NPV: 77.9 – PPV: 53.6 UroVysion – Sens: 68.8 – Spec: 89.1 – NPV: 77.8 – PPV: 83.8 cytology – Sens 84.6 – Spec: 80 – NPV: 88 – PPV: 75
Soyuer et al.,[40] 2009, Turkey	Monocenter prospective	90	66 (46–80)*	Voided	– ImmunoCyt – Cytology	– Cystoscopy – Bladder resection/ biopsy	ImmunoCyt – Sens: 83.3 – Spec: 86.1 – NPV: 79.5 – PPV: 90 Cytology – Sens: 75.9 – Spec: 66.7 – NPV: 88.9 – PPV: 77.3
Deininger et al.,[21] 2017, Germany	Monocenter retrospective	444	67 (18–93)§	Midstream voided, catheter	– ImmunoCyt	– Cystoscopy – Bladder resection	ImmunoCyt – Sens: 86.8 – Spec: 78.7 – NPV: 97 – PPV: 42
Comploj et al.,[22] 2013, Italy	Monocenter prospective	2217	69.5 (15–99)*	Voided urine	– ImmunoCyt – Cytology	– Cystoscopy – Bladder resection/ biopsy	ImmunoCyt – Sens: 68.1 – Spec: 72.3 – NPV: 95.2 – PPV: 22 Cytology – Sens: 34.5 – Spec: 97.9 – NPV: 92.9 – PPV: 65.2
Todenhofer et al.,[23] 2013, Germany	Monocenter prospective	808	67 (20–92)§	Voided urine	– NMP-22 – UroVysion – ImmunoCyt – Cytology	– Cystoscopy – Bladder resection/ biopsy	NMP-22 – Sens: 84.4 – Spec: 41.3 – NPV: 94.1 – PPV: 19.2 UroVysion – Sens: 71.3 – Spec: 86.3 – NPV: 94.8 – PPV: 46.3 ImmunoCyt – Sens: 73.9 – Spec: 76.6 – NPV: 94.7 – PPV: 34.4 Cytology – Sens: 67.8 – Spec: 87.5 – NPV: 94.3 – PPV: 47.3
Sankhwar et al.,[41] 2013, India	Monocenter retrospective	1331	58.7 (14.3)# (18–96)¶	Voided urine	– NMP-22 – Cytology	– Cystoscopy – Bladder resection	NMP-22 – Sens: 55.7 – Spec: 85.7 – NPV: 96.8 – PPV: 19.7 Cytology – Sens: 15.8 – Spec: 99.2 – NPV: 94.9 – PPV: 94.9
Ritter et al.,[24] 2014, Germany	Monocenter prospective	198	70 (20–90)§	Midstream voided urine	– NMP-22 – Cytology	– Cystoscopy – Bladder resection	NMP-22 – Sens: 16.4 – Spec: 95.3 – NPV: 70.5 – PPV: 62.5 Cytology – Sens: 51.7 – Spec: 78.1 – NPV: 78.1 – PPV: 51.7

(*continued*)

Table 1
(continued).

Author, year, location	Study design	Sample size, n	Median participant age, y	Sampling method	Biomarker	Confirmatory test	Statistical results, %			
Jeong et al.,[42] 2012, Korea	Monocenter prospective	250	57 (50–65)	Midstream voided urine	– NMP-22	– Cystoscopy – Bladder resection/ biopsy	NMP-22 – Sens: 84.9 – Spec: 82.8 – NPV: NS – PPV: NS			
Dogan et al.,[43] 2013, Turkey	Monocenter prospective	87	60 (21–98)*	Voided urine	– NMP-22 – Cytology	– Cystoscopy	NMP-22 – Sens: 70 – Spec: 80 – NPV: 81 – PPV: 68		Cytology – Sens: 27 – Spec: 96 – NPV: 68 – PPV: 82	
Grossman et al.,[8] 2005, USA	Monocenter retrospective	1331	58.7 (14.3)# (18–96)¶	Voided urine	– NMP-22 – Cytology	– Cystoscopy – Bladder resection/ biopsy	NMP-22 – Sens: 55.7 – Spec: 85.7 – NPV: 96.8 – PPV: 19.7		cytology – Sens: 15.8 – Spec: 99.2 – NPV: 94.9 – PPV: 54.6	
Breen et al.,[48] 2015, New Zealand	Multicenter retrospective	939	NS	Voided urine	– NMP-22 – UroVysion – Cytology	– Cystoscopy	NMP-22 – Sens: 44.9 – Spec: 89 – NPV: NS – PPV: NS	UroVysion – Sens: 40 – Spec: 87.3 – NPV: NS – PPV: NS	Cytology – Sens: 45.5 – Spec: 96.3 – NPV: NS – PPV: NS	
Bangma et al.,[25] 2013, The Netherlands	Prospective multicenter	409	50–75 ¶	Voided urine	– NMP-22 – Microsatellite analysis	– Cystoscopy	NMP-22 – Sens: 25 – Spec: 96.6 – NPV: 99.2 – PPV: 7.1			Microsatellite analysis – Sens: 50 – Spec: 91.9 – NPV: 99.4 – PPV: 6.1
Liang et al.,[44] 2010, China	Monocenter prospective	64	NS	Voided urine	– Microsatellite analysis	– Bladder resection	Microsatellite analysis – Sens: 62.5 – Spec: n.s. – NPV: 100 – PPV: 62.5			
Wild et al.,[26] 2009, Switzerland	Monocenter prospective	119	NS	Voided urine	– Microsatellite analysis – Cytology	– Cystoscopy – Biopsy	Microsatellite analysis – Sens: 72.1 – Spec: 88.2 – NPV: 61.2 – PPV: 92.5			Cytology – Sens: 88.2 – Spec: 79.4 – NPV: 77.1 – PPV: 89.6
Cha et al.,[27] 2012, Germany	Multicenter prospective	1182	65 (18–93)§	Midstream voided urine	– ImmunoCyt – Cytology	– Cystoscopy – Biopsy	ImmunoCyt – Sens: 82.4 – Spec: 86.6 – NPV: 95 – PPV: 61.6			Cytology – Sens: 46.5 – Spec: 94.9 – NPV: 87.2 – PPV: 70.4
Friedrich et al.,[28] 2002, Germany	Monocenter prospective	115	NS	Voided, bladder washing	– BAT stat – NMP-22	– Cystoscopy – Bladder resection/ biopsy	BAT stat – Sens: 70.3 – Spec: 70.6 – NPV: 80.2 – PPV: 58.4			NMP-22 – Sens: 68.5 – Spec: 65.2 – NPV: 77.9 – PPV: 53.6

(*continued*)

Table 1
(continued).

Author, year, location	Study design	Sample size, n	Median participant age, y	Sampling method	Biomarker	Confirmatory test	Statistical results, %			
Giannopoulos et al.,[29] 2001, Greece	Monocenter prospective	234	66 (25–93)*	Voided urine	– BAT stat – NMP-22	– Cystoscopy – Biopsy	BAT stat – Sens: 72.9 – Spec: 73.1 – NPV: 70.1 – PPV: 67.7		NMP-22 – Sens: 63.5 – Spec: 75 – NPV: 66.9 – PPV: 72.1	
Gutierrez Banos et al.,[30] 2001, Spain	Monocenter prospective	150	67.8 (11.3)# (20–91)¶	Voided urine	– BAT stat – NMP-22 – Cytology	– Cystoscopy – Bladder resection	BAT stat – Sens: 72.4 – Spec: 89.1 – NPV: 75.9 – PPV: 87.3	NMP-22 – Sens: 76.3 – Spec: 90.5 – NPV: 78.8 – PPV: 89.2		Cytology – Sens: 69.7 – Spec: 93.2 – NPV: 75 – PPV: 91.4
Halling et al.,[37] 2002, USA	Monocenter prospective	265	71	Voided urine	– BAT stat – UroVysion	– Cystoscopy – Bladder resection/ biopsy	BAT stat – Sens: 78 – Spec: 74 – NPV: NS – PPV: NS		UroVysion – Sens: 81 – Spec: 96 – NPV: NS – PPV: NS	
O'Sullivan et al.,[49] 2012, New Zealand	Multicenter prospective	485	69 (59–77)	Midstream voided urine	– NMP-22 – Cytology	– Cystoscopy – Biopsy	NMP-22 – Sens: 50 – Spec: 88 – NPV: NS – PPV: NS		Cytology – Sens: 56.1 – Spec: 94.5 – NPV: NS – PPV: NS	
Song et al.,[45] 2010, South Korea	Monocenter prospective	602	62∞	Voided urine	– UroVysion – Cytology	– Cystoscopy – Bladder resection	UroVysion – Sens: 53.5 – Spec: 94.9 – NPV: NS – PPV: NS		Cytology – Sens: 23.9 – Spec: 99 – NPV: NS – PPV: NS	
Smrkolj et al.,[31] 2011, Slovenia	Monocenter prospective	108	68.3 (9.9)	Voided urine	– NMP-22 – Cytology	– Cystoscopy – Bladder resection	NMP-22 – Sens: 45.2 – Spec: 75 – NPV: NS – PPV: NS		Cytology – Sens: 37 – Spec: 100 – NPV: NS – PPV: NS	
Hwang et al.,[46] 2011, Korea	Monocenter prospective	424	65∞	Voided urine	– NMP-22 – Cytology	– Cystoscopy – Bladder resection	NMP-22 – Sens: 40.6 – Spec: 96.3 – NPV: NS – PPV: NS		Cytology – Sens: 40.6 – Spec: 99.7 – NPV: NS – PPV: NS	
Sagnak et al.,[47] 2011, Turkey	Monocenter prospective	164	30.8 (6.4)	Voided urine	– NMP-22 – Cytology	– Cystoscopy – Biopsy	NMP-22 – Sens: 100 – Spec: 85.2 – NPV: 100 – PPV: 7.7		Cytology – Sens: 0 – Spec: 96.9 – NPV: 98.7 – PPV: 0	

IQR = interquartile range; NS = not specified; Sens = sensitivity; Spec = specificity.
+ = Median (SD); § = median (range); * = mean (range); # = mean (SD); ¶ = range; ∞ = mean.

Table 2

Performance of different urinary biomarkers to predict BC.

Biomarker *n° of studies (n° of pts)*	Cytology *n=25 (14,375)*	MCM-5 *n=3 (2147)*	Microsatellite *n=3 (592)*	UroVysion *n=12 (5033)*	BTA stat *n=6 (999)*	ImmunoCyt *n=7 (4976)*	NMP-22 *n=19 (8988)*
Sensitivity, %							
Mean ± SD	45.5±23.1	72.8±12.7	61.5±11.1	64.3±19.0	70.2±5.8	76.4±8.9	60.1±21.0
Median	46.5	69.0	62.5	64.4	71.4	78.3	58.0
Range	9.0–88.2	62.5–87.0	50.0–72.1	37.0–100.0	61.0–78.0	62.0–86.8	16.4–100.0
Specificity, %							
Mean ± SD	89.7±13.2	74.0±11.4	90.1±2.6	88.4±14.2	77.2±6.5	79.0±5.6	80.6±13.6
Median	94.9	69.0	90.1	91.3	76.0	78.7	85.0
Range	41.0–100	65.9–87.0	88.2–91.9	48.0–100.0	70.6–89.1	72.3–86.6	41.3–96.6
NPV, %							
Mean ± SD	82.6±16.1	83.0±20.0	86.9±22.2	72.4±24.6	67.9±17.1	83.4±21.4	82.1±16.6
Median	87.6	93.0	99.4	77.8	75.4	94.7	79.9
Range	34.0–98.7	60–96.0	61.2–100.0	25.0–97.5	38.0–80.2	37.0–97.0	39.0–100.0
PPV, %							
Mean ± SD	64.9±28.5	52.7±23.2	53.7±43.9	67.7±26.8	74.8±13.1	57.7±26.7	48.0±29.5
Median	76.2	64.0	62.5	61.0	71.4	61.6	53.6
Range	10.0–94.9	26–68.2	6.1–92.5	35.5–100.0	58.4–89.0	22.0–91.0	7.1–92.0

pts = patients; SD = standard deviation.

stat, NMP-22) or exfoliated cells (cell-associated markers: microsatellite, ImmunoCyt, UroVysion, MCM5) are used for the assay.[4]

Considering the high rates of variability of results in terms of sensitivity, specificity, NPV, and PPV for each test among the different studies, it is not possible to define a real advantage of one test over the others. A direct comparison among at least 3 different tests in the same study and on the same population was performed in only 3 studies and different tests were compared each time.[5,20,23]

The sensitivity and specificity of these urinary tests as predictors for an initial diagnosis of BC varied from 16.4–100% to 41.0–100%, respectively. As reported by guidelines,[2] this variability of results was in part related to patient selection and complicated laboratory methods.

The performance of these tests on the basis of BC grades was not clearly reported by most of the studies. Tetu et al.[4] underlined that whereas for BTA stat, NMP-22, and UroVysion tests, the improvement in sensitivity when compared to UC was lower for low grade tumors, ImmunoCyt was able to improve

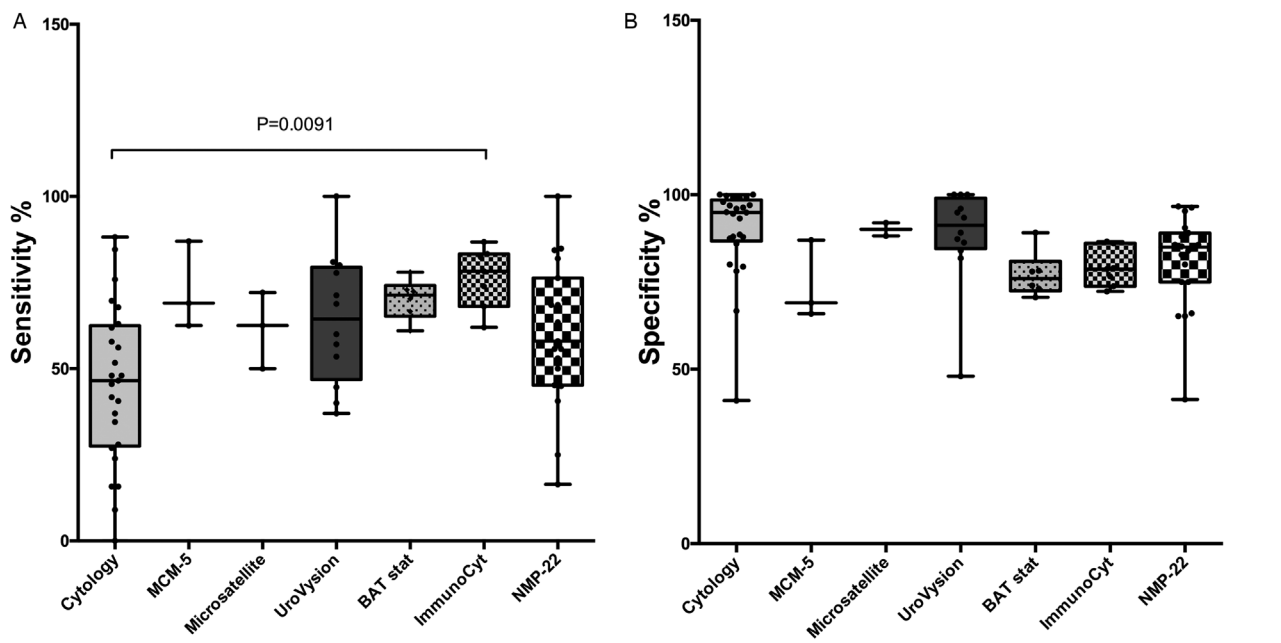

Figure 2. Sensitivity (A) and specificity (B) of different urinary biomarkers in predicting BC.

Table 3

Sensitivity of different urinary biomarkers to predict BC by histological grade.

Biomarker *n° of studies (n° of pts)*	Cytology *n=14 (7585)*	UroVysion *n=6 (1997)*	BTA stat *n=4 (584)*	ImmunoCyt *n=5 (3350)*	NMP-22 *n=11 (4867)*
G1					
Mean ± SD	24.4±22.2	66.5±34.2	42.9±5.7	67.3±15.5	48.0±25.7
Median	16.0	61.5	42.9	69.2	48.2
Range	0–67.7	20.0–100.0	36–50.0	47.0–85.7	5.1–100.0
G2					
Mean ± SD	41.9±25.5	75.2±23.1	61.9±17.4	69.7±13.3	54.8±26.5
Median	36.1	63.0	69.1	75.0	53.3
Range	16.0–87.0	51.4–100.0	36.0–73.3	47–79.9	5.1–100.0
G3					
Mean ± SD	69.6±19.2	95.5±7.3	89.7±2.0	85.2±5.0	76.9±16.2
Median	74.0	100.0	89.7	83.3	76.9
Range	37.5–100.0	83.3–100.0	87.5–91.7	79.0–91.3	36.4–100.0

pts = patients; SD = standard deviation.

sensitivity for low or high grade BC. In our analysis, Table 3 and Figure 3 show that either ImmunoCyt ($p=0.0186$) or UroVysion ($p=0.0229$) strongly improved sensitivity in low grade tumors when compared with UC.

In conclusion, the low sensitivity of UC drives interest in new urinary markers for the initial diagnosis of BC that can substitute or be used in combination with UC. Most of the proposed molecular markers are able to improve sensitivity with similar or lower specificity when compared to UC. As of now, none of these markers showed evidences so as to be accepted by international guidelines for the diagnosis of BC.[2]

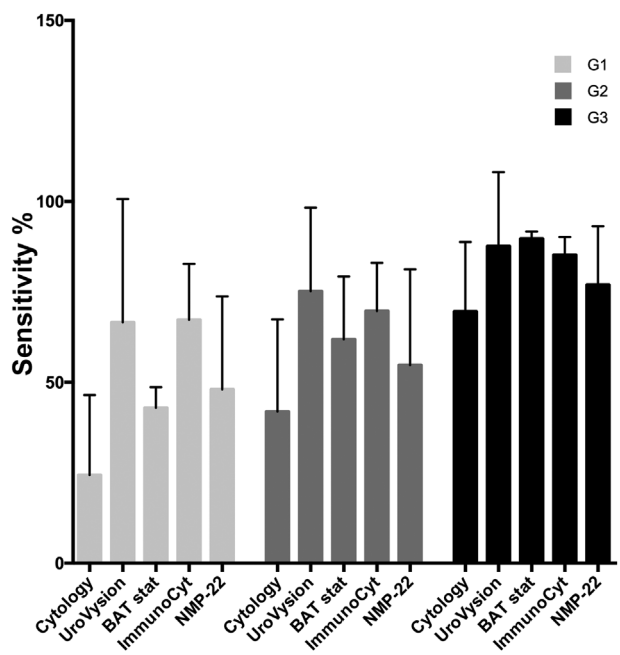

Figure 3. Sensitivity of different urinary biomarkers in predicting BC according to grade.

Acknowledgments

None.

Statement of ethics

This review has been carried out according to the internationally-accepted standards for research practice and reporting.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors listed gave a substantive contribution to this study and to this original article. A. Sciarra: conceptualization, writing - original draft preparation; G. Di Lascio: conceptualization, formal analysis and investigation; F. Del Giudice: formal analysis and investigation; P.P. Leoncini: statistical analysis; S. Salciccia: methodology;A. Gentilucci: methodology;A. Porreca: formal analysis and investigation; B.I. Chung: conceptualization; G. Di Pierro: writing - review and editing, G.M. Busetto: formal analysis and investigation; E. De Berardinis: writing - review and editing, M. Maggi: writing - original draft preparation, formal analysis and investigation.

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How to cite this article: Sciarra A, Di Lascio G, Del Giudice F, Leoncini PP, Salciccia S, Gentilucci A, Porreca A, Chung BI, Di Pierro G, Busetto GM, De Berardinis E, Maggi M. Comparison of the clinical usefulness of different urinary tests for the initial detection of bladder cancer: a systematic review. *Curr Urol*. 2021;15(1):22–32. doi: 10.1097/CU9.0000000000000012