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 PRISMA guidelines.

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.[7]

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.
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 multi-colour 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

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**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,15,8,32–37 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.5,17–20,22–31,33,34,37–40,42,44–47,49 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/CURRUR/ 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,44,45,48 4 catheter,32,34,36,38 and 5 bladder washing.32,34,36,38

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 cases17–19; UroVysion (uPISH) in 12 studies on 5033 cases20,21,23,32–39,45,49; NMP-22 in 19 studies on 8988 cases5,8,18,20,23–25,28–31,33,41–43,46–49; microsatellite analysis in 3 studies on 592 cases23,26,44; BTA stat in 6 studies on 999 cases5,20,23,27,40; and ImmunoCyt/uCyt in 7 studies on 4976 cases.5,17–20,22–24,26,27,30

Twenty-five studies also included UC as a diagnostic tool in comparison with the new tests (14,375 cases) (Table 1).5,8,17–19,21–24,26–33,37–42,44–47,49

3.5. Confirmatory 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
| Author, year, location | Study design | Sample size, n | Median participant age, y | Sampling method | Biomarker | Confirmatory test | Statistical results, % |
|------------------------|-------------|----------------|---------------------------|----------------|-----------|------------------|------------------------|
| Stober et al., 2002, UK | Monocenter prospective | 353 | 70 (62–78) | Voided urine | MCM5 | Cystoscopy, Bladder resection, Biopsy | Sens: 87, Spec: 87, NPV: 96, PPV: 64 |
| | | | | | | | |
| Kelly et al., 2012, UK | Monocenter prospective | 1677 | 63 (49–73) | Voided urine | MCM5, NMP-22 | Cystoscopy, Bladder resection, Biopsy | Sens: 69, Spec: 69, NPV: 93, PPV: 26 |
| | | | | | | | |
| Brems-Eskildsen et al., 2010, Denmark | Monocenter prospective | 117 | 71 | Voided urine | MCM5 | Cystoscopy, Bladder resection, Biopsy | Sens: 62.5, Spec: 65.9, NPV: 60, PPV: 68.2 |
| | | | | | | | |
| Vilk et al., 2017, USA | Monocenter retrospective | 377 | 67 | Voided, catheterized, bladder catheter washing, Bladder resection, Biopsy | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 44.6, Spec: 81.8, NPV: 80.3, PPV: 47.2 |
| | | | | | | | |
| Schomler et al., 2010, USA | Monocenter prospective | 108 | 65.7 (30–95) | Voided, bladder catheter washing, Bladder resection, Biopsy | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 57.1, Spec: 100, NPV: 25, PPV: 100 |
| | | | | | | | |
| Lotan et al., 2008, USA | Monocenter prospective | 50 | 65 (14.4) | Voided, bladder catheter washing, Bladder resection, Biopsy | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 77.8, Spec: 100, NPV: 60, PPV: 100 |
| | | | | | | | |
| Kehinde et al., 2011, Kuwait | Monocenter prospective | 43 | 53 (16–77) | Voided urine | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 80, Spec: 48, NPV: 71.2, PPV: 61 |
| | | | | | | | |
| Gopalakrishna et al., 2017, USA | Monocenter retrospective | 1022 | 66 (56–75) | Voided urine | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 70, Spec: 84, NPV: 40, PPV: 20 |
| | | | | | | | |
| Dimasthian et al., 2013, USA | Monocenter retrospective | 652 | NS | Voided, catheterized and bladder washing | UroVysion | Cystoscopy, Bladder resection, Biopsy | Sens: 37, Spec: 41, NPV: 37, PPV: 23.4 |

(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 | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Yafi et al. [39] 2015, Canada | Monocenter prospective | 109 | 69 (33–96) | Voided, washing, catheterized | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Toma et al. [39] 2004, Germany | Monocenter prospective | 126 | NS | Voided and bladder washing | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Soyuer et al. [40] 2009, Turkey | Monocenter prospective | 90 | 66 (46–80) | Voided | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Deininger et al. [21] 2017, Germany | Monocenter retrospective | 444 | 67 (18–90) | Midstream voided, catheter | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Comploj et al. [22] 2013, Italy | Monocenter prospective | 2217 | 69.5 (15–91) | Voided urine | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Todenhöfer et al. [24] 2013, Germany | Monocenter prospective | 898 | 67 (20–92) | Voided urine | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Sankhwar et al. [41] 2013, India | Monocenter retrospective | 1331 | 58.7 (14.3–65.2) | Voided urine | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |
| Ritter et al. [24] 2014, Germany | Monocenter prospective | 198 | 70 (20–90) | Midstream voided urine | UroVysion | Cytology | Sens: 61.9, Spec: 100, PPV: 42, NPV: 85 |

Table 1 (continued)
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| 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 | Cytoscopy | 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 | Sens: 70 Spec: 80 NPV: 68 PPV: 82 |
| Grossman et al.,[44] 2005, USA | Monocenter retrospective | 1331 | 58.7 (14.3) | Voided urine | NMP-22 | Cytoscopy | Sens: 55.7 Spec: 85.7 NPV: 96.8 PPV: 19.7 |
| Dogan et al.[45] 2013, Turkey | Monocenter prospective | 87 | 60 (21–98) | Voided urine | NMP-22 | Cytology | Sens: 70 Spec: 80 NPV: 68 PPV: 82 |
| Grossman et al.,[46] 2005, USA | Monocenter retrospective | 1331 | 58.7 (14.3) | Voided urine | NMP-22 | Cytoscopy | Sens: 55.7 Spec: 85.7 NPV: 96.8 PPV: 19.7 |
| Breen et al.,[47] 2015, New Zealand | Multicenter retrospective | 939 | NS | Voided urine | NMP-22 | UroVysion | Sens: 44.9 Spec: 89 NPV: NS PPV: NS |
| Bangma et al.[48] 2013, The Netherlands | Prospective multicenter | 409 | 50–75 | Voided urine | NMP-22 | Microsatellite analysis | Sens: 25 Spec: 96.6 NPV: 99.2 PPV: 7.1 |
| Liang et al.,[49] 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 |
| Wiik et al.[50] 2009, Switzerland | Monocenter prospective | 119 | NS | Voided urine | Microsatellite analysis | Cytology | Sens: 2.5 Spec: 99.2 NPV: 99.2 PPV: 7.1 |
| Cha et al.[51] 2012, Germany | Multicenter prospective | 1182 | 65 (18–93) | Midstream voided urine | ImmunoCyt | Cytology | Sens: 82.4 Spec: 86.6 NPV: 95 PPV: 61.6 |
| Friedrich et al.[52] 2002, Germany | Monocenter prospective | 115 | NS | Voided, bladder washing | NMP-22 | Cytoscopy | Sens: 70.3 Spec: 70.6 NPV: 80.2 PPV: 58.4 |

(continued)
| Author, year, location | Study design | Sample size, n | Median participant age, y | Sampling method | Biomarker | Confirmatory test | Statistical results, % |
|------------------------|-------------|----------------|--------------------------|----------------|-----------|-----------------|------------------------|
| Giannopoulos et al., 2001, Greece | Monocenter prospective | 234 | 66 (25–90) | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 72.9 – Spec: 73.1 – NPV: 70.1 – PPV: 67.7 |
| | | | | | – NMP-22 | – Biopsy | NMP-22 – Sens: 63.5 – Spec: 75 – NPV: 66.9 – PPV: 72.1 |
| Gutierrez Banos et al., 2001, Spain | Monocenter prospective | 150 | 67.8 (11.3) | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 72.4 – Spec: 89.1 – NPV: 75.9 – PPV: 87.3 |
| | | | | | – NMP-22 | – Bladder resection | NMP-22 – Sens: 76.3 – Spec: 90.5 – NPV: 78.8 – PPV: 89.2 |
| | | | | | – Cytology | Cystoscopy – Bladder resection | – Sens: 69.7 – Spec: 93.2 – NPV: 75 – PPV: 91.4 |
| Halling et al., 2002, USA | Monocenter prospective | 265 | 71 | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Bladder resection/biopsy | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| | | | | | – Cytology | Cystoscopy – Bladder resection/biopsy | – Sens: 23.9 – Spec: 99 – NPV: 91 – PPV: 91 |
| O’Sullivan et al., 2012, New Zealand | Multicenter prospective | 485 | 69 (59–77) | Midstream voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Cytology | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| Song et al., 2010, South Korea | Monocenter prospective | 602 | 62 | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Biopt | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| | | | | | – Cytology | Cystoscopy – Biopt | – Sens: 23.9 – Spec: 99 – NPV: 91 – PPV: 91 |
| Smrkolj et al., 2011, Slovenia | Monocenter prospective | 109 | 68.3 (9.3) | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Bladder resection | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| | | | | | – Cytology | Cystoscopy – Bladder resection | – Sens: 23.9 – Spec: 99 – NPV: 91 – PPV: 91 |
| Hwang et al., 2011, Korea | Monocenter prospective | 424 | 65 | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Bladder resection | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| | | | | | – Cytology | Cystoscopy – Bladder resection | – Sens: 23.9 – Spec: 99 – NPV: 91 – PPV: 91 |
| Song et al., 2011, Turkey | Monocenter prospective | 164 | 30.8 (6.4) | Voided urine | – BAT stat | – Cystoscopy | BAT stat – Sens: 78 – Spec: 74 – NPV: 65 – PPV: 47.9 |
| | | | | | – NMP-22 | – Cytology | NMP-22 – Sens: 50 – Spec: 88 – NPV: 51 – PPV: 47.9 |
| | | | | | – Cytology | Cystoscopy – Bladder resection | – Sens: 23.9 – Spec: 99 – NPV: 91 – PPV: 91 |

IQR = interquartile range; NS = not specified; Sens = sensitivity; Spec = specificity.

* = Median (SD); † = median (range); ‡ = mean (range); § = mean (SD); ¶ = range; □ = mean.
or exfoliated cells (cell-associated markers: microsatellite, ImmunoCyt, UroVysion, MCM5) are used for the assay.\cite{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.\cite{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,\cite{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.\cite{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

| Biomarker         | Cytology n = 25 (14,375) | MCM-5 n = 3 (2147) | Microsatellite n = 3 (992) | UroVysion n = 12 (5033) | BTA stat n = 6 (999) | ImmunoCyt n = 7 (4976) | NMP-22 n = 19 (8988) |
|-------------------|--------------------------|--------------------|---------------------------|------------------------|---------------------|-----------------------|----------------------|
| Sensitivity, %    | Mean ± SD                | Median             | Range                     | Mean ± SD              | Median              | Range                 | Mean ± SD            |
|                   | 45.5 ± 23.1              | 69.0               | 62.5                      | 64.3 ± 19.0            | 70.2 ± 5.8          | 61.0–78.0             | 60.1 ± 21.0          |
|                   | 46.5                     | 69.0               | 62.5                      | 64.4                   | 71.4                | 62.0–86.8             | 76.3                 |
|                   | 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                | Median             | Range                     | Mean ± SD              | Median              | Range                 | Mean ± SD            |
|                   | 89.7 ± 13.2              | 90.1 ± 2.6         | 88.2–91.9                 | 77.2 ± 6.5             | 70.6               | 72.3–89.1             | 80.6 ± 13.6          |
|                   | 94.9                     | 90.1               | 91.3                      | 76.0                   | 78.7                | 85.0                  |                      |
|                   | 41.0–100                 | 65.9–87.0          | 60.0–100.0                | 48.0–100.0             | 70.6–89.1           | 72.3–86.6             | 41.3–96.6            |
| NPV, %            | Mean ± SD                | Median             | Range                     | Mean ± SD              | Median              | Range                 | Mean ± SD            |
|                   | 82.6 ± 16.1              | 93.0               | 99.4                      | 72.4 ± 24.6            | 67.9 ± 17.1         | 83.4 ± 21.4           | 82.1 ± 16.6          |
|                   | 87.6                     | 94.4               | 77.8                      | 75.4                   | 74.7                | 94.7                  | 79.9                 |
|                   | 34.0–98.7                | 60.0–96.0          | 50.0–97.5                 | 38.0–80.2              | 37.0–97.0           | 39.0–100.0            |                      |
| PPV, %            | Mean ± SD                | Median             | Range                     | Mean ± SD              | Median              | Range                 | Mean ± SD            |
|                   | 64.9 ± 28.5              | 62.5               | 61.0                      | 67.7 ± 26.8            | 57.7 ± 26.7         | 48.0 ± 29.5           |                      |
|                   | 76.2                     | 61.0               | 53.7 ± 43.9               | 74.8 ± 13.1            | 57.7 ± 26.7         | 48.0 ± 29.5           |                      |
|                   | 10.0–94.9                | 26–68.2            | 6.1–92.5                  | 35.5–100.0             | 22.0–91.0           | 7.1–92.0              |                      |

\(\text{pts} = \text{patients; SD} = \text{standard deviation.}\)
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]

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### Statement of ethics

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

### Conflict of interest statement

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### 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: writing - review and editing; 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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