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Diagnostic Accuracy of Novel Urinary Biomarker Tests in Non–muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-analysis

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Abstract

Context: During the past decade, several urinary biomarker tests (UBTs) for bladder cancer have been developed and made commercially available. However, none of these is recommended by international guidelines so far.

Objective: To assess the diagnostic estimates of novel commercially available UBTs for diagnosis and surveillance of non–muscle-invasive bladder cancer (NMIBC) using diagnostic test accuracy (DTA) and network meta-analysis (NMA).

Evidence acquisition: PubMed, Web of Science, and Scopus were searched up to April 2021 to identify studies addressing the diagnostic values of UBTs: Xpert bladder cancer, Adxbladder, Bladder EpiCheck, Uromonitor and Cxbladder Monitor, and Triage and Detect. The primary endpoint was to assess the pooled diagnostic values for disease recurrence in NMIBC patients using a DTA meta-analysis and to compare them with

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cytology using an NMA. The secondary endpoints were the diagnostic values for high-grade (HG) recurrence as well as for the initial detection of bladder cancer.

Evidence synthesis: Twenty-one studies, comprising 7330 patients, were included in the quantitative synthesis. In most of the studies, there was an unclear risk of bias. For NMIBC surveillance, novel UBTs demonstrated promising pooled diagnostic values with sensitivities up to 93%, specificities up to 84%, positive predictive values up to 67%, and negative predictive value up to 99%. Pooled estimates for the diagnosis of HG recurrence were similar to those for the diagnosis of any-grade recurrence. The analysis of the number of cystoscopies potentially avoided during the follow-up of 1000 patients showed that UBTs might be efficient in reducing the number of avoidable interventions with up to 740 cystoscopies. The NMA revealed that diagnostic values (except specificity) of the novel UBTs were significantly higher than those of cytology for the detection of NMIBC recurrence. There were too little data on UBTs in the primary diagnosis setting to allow a statistical analysis.

Conclusions: Our analyses support high diagnostic accuracy of the studied novel UBTs, supporting their utility in the NMIBC surveillance setting. All of these might potentially help prevent unnecessary cystoscopies safely. There are not enough data to reliably assess their use in the primary diagnostic setting. These results have to be confirmed in a larger cohort as well as in head-to-head comparative studies. Nevertheless, our study might help policymakers and stakeholders evaluate the clinical and social impact of the implementation of these tests into daily practice.

Patient summary: Novel urinary biomarker tests outperform cytology with the potential of improving routine clinical practice by preventing unnecessary cystoscopic examinations during the surveillance of non–muscle-invasive bladder cancer.

1. Introduction

Cystoscopy is the standard examination for the initial detection and follow-up of non–muscle-invasive bladder cancer (NMIBC) [1]. Urine cytology is the only widely used urinary biomarker; however, despite high sensitivity in high-grade (HG) tumors and carcinoma in situ (CIS), its sensitivity remains poor in low-grade (LG) tumors and related to the pathologist analysis [2]. In the past decades, several diagnostic urinary biomarkers have been developed with the aim to detect recurrences while avoiding unnecessary cystoscopies. Repeated cystoscopies are uncomfortable for the patient and are one of the reasons for the high cost associated with bladder cancer, especially NMIBC [3]. Some of these urinary biomarkers, such as nuclear matrix protein 22 (NMP22), bladder tumor antigen (BTA), UroVysion (fluorescence in situ hybridization), and ImmunoCyt/uCyt+ [4], have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA); these are commercially available as urinary biomarker tests (UBTs). However, none of these UBTs are commonly used in daily practice; these are rarely reimbursed by payors, and have not been implemented in guidelines due to poor specificity and a lack of demonstrable clinical benefits, with some exceptions such as atypical cytology and cystoscopic findings [1,5].

Recently, several novel UBTs, such as Xpert bladder cancer (Cepheid; Sunnyvale, California, USA), adxbladder (Arquer Diagnostics; Sunderland, UK), Bladder EpiCheck (Nucleix; Rehovot, Israel), Uromonitor (U-Monitor; Porto, Portugal), Cxbladder Monitor, and Triage and Detect (Pacific Edge; Dunedin, New Zealand), have become commercially available for surveillance and detection of bladder cancer [6]. However, data on their diagnostic accuracy are still immature to allow implementation in clinical practice. Moreover, these have not yet been approved by either the FDA or the EMA. In this context, the use of a diagnostic test accuracy (DTA) analysis associated with a meta-analysis and a network meta-analysis (NMA) is a new interesting approach to give an overall assessment of the test accuracy and to compare these tests giving better evidence in this field [7].

A specific pooled DTA analysis would expand upon the current evidence and deliver useful information to stakeholders and policymakers of health care agencies to facilitate the decision-making process on the value of the tests in the different NMIBC disease settings followed by their implementation into clinical practice [8].

To fill this gap in knowledge, we conducted a systematic review, DTA, and NMA to assess the estimates of the novel commercially available UBTs for diagnosis and surveillance of NMIBC.

2. Evidence acquisition

2.1. Protocol

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) of DTA studies [9]. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration ID CRD42021248896).

2.2. Literature search

PubMed, Web of Science, and Scopus were searched to identify reports published up to April 2021 and addressing the diagnostic value of select UBTs in NMIBC (Xpert bladder cancer, Adxbladder, Bladder EpiCheck, Uromonitor,

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Cxbladder Monitor, and Triage and Detect). The keywords used in our search strategy are reported in the Supplementary material. Initial screening was performed independently by three investigators based on the titles and abstracts of the article to identify ineligible reports. Reasons for exclusions were noted. Potentially relevant reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process. Any discrepancies during the primary and secondary literature screening were resolved by referring to the senior author. The primary endpoint was to assess pooled diagnostic values of the novel UBTs for recurrence during follow-up of NMIBC using a DTA meta-analysis and to compare these UBTs with cytology using an NMA. The secondary endpoints were to assess their diagnostic values in the detection of HG recurrence as well as for the primary diagnosis of bladder cancer.

2.3. Inclusion and exclusion criteria

The population, intervention, control, and outcomes (PICO) in this study were decided by the coauthors as follows: patients who were included in detection (primary detection) or were undergoing follow-up for recurrent disease and with detected urothelial carcinoma recurrence at the cystoscopy or histopathology compared with patients without NMIBC. We analyzed diagnostic differences for the value of NMIBC detection in initial diagnosis or diagnosis of recurrence during follow-up. Studies were eligible if these reported data on the following: true positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity (Se), specificity (Sp), accuracy, positive predictive value (PPV), or negative predictive value (NPV). In case of not reporting NPV, PPV, TP, TN, FP, or FN, these were calculated from known variables (Se and Sp).

We excluded every study that did not evaluate the diagnostic accuracy of UBTs compared with reference methods (cystoscopy and/or histopathology). We also excluded studies reporting data on laboratory developing tests (eg, MCM5) as well as reviews, letters to editors, editorials, study protocols, case reports, brief correspondence, and articles not published in English. References of all papers included were scanned for additional studies of interest.

2.4. Data extraction

Three investigators independently extracted the following information from included articles: author's name, publication year, number of the patients, tumor stage and grade, presence of CIS, previous intravesical therapy, cutoff value of biomarker, recurrence rates, as well as Se, Sp, and the numbers of TP, FP, FN, and TN for the main outcomes (the value of NMIBC detection in initial diagnosis or diagnosis of recurrence during follow-up). All discrepancies regarding data extraction were resolved by consensus with the coauthors.

2.5. Risk of bias assessment

The risk of bias of included studies was evaluated according to the risk of bias using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [10]. The index test was defined as the value of NMIBC detection with the novel UBTs. NMIBC detection with cystoscopy and histopathology was used as a reference. Discrepancies were resolved through discussion and consensus.

2.6. Statistical analyses

2.6.1. Meta-analysis of diagnostic test accuracy

Pooled Se, Sp, PPV and NPV, and diagnostic odds ratio (DOR) were calculated for each UBT. The pooled DOR is a single indicator of test performance that pooled measure of the performance of a diagnostic test. It is defined as the ratio of the odds of the TP relative to the odds of the FP. We also performed subgroup analyses for the detection of HG recurrence of NMIBC. We used the bivariate random-effect model for analysis and pooling of the diagnostic performance measures across studies, as well as comparisons between different index tests. The bivariate model estimates pairs of logit-transformed Se and Sp from studies, incorporating the correlation that might exist between specificity from studies [7,11]. Forest plots with 95% confidence interval (CI) were calculated and depicted. We developed a hierarchical summary receiver operating curve and calculated the area under the curve (AUC) to examine the diagnostic accuracy of each UBT. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using the Cochrane's Q test and the I^2 statistic. Significant heterogeneity was indicated by $p < 0.05$ in the Cochrane's Q tests and a ratio of >50% in I^2 statistics. All statistical analyses were performed using R version 4.0.3 (2020; R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at $p < 0.05$.

2.6.2. Network meta-analysis

The NMA was performed for the diagnostic values of the five UBTs that were used for the detection of NMIBC recurrence and compared with cytology. For the assessment of the diagnostic values, arm-based analyses were performed to estimate the odds ratio (OR) of the recurrence detection and 95% credible interval (CrI) from Se, Sp, PPV, and NPV in the included manuscripts.

As described previously, first, a prior distribution (prior probability) was selected [12–14]. Second, the likelihood was calculated from the present data, and a Bayesian hierarchical model was created in NMA. Third, prior distribution and likelihood were entered as input to the Markov chain Monte Carlo (MCMC) simulation, and a distribution that best converges the posterior distribution was set. The probability of stable distribution and the area under the posterior distribution function could be determined through the MCMC simulation. Finally, statistical reasoning for the treatment effect was performed with the determined posterior distribution. For the MCMC simulation, we selected the random-effect model that had four chains, 5000 burn-ins, 50 000 iterations, and an interval of 5 to sufficiently remove the effect of initial values, increase the iterations and extraction interval, and minimize the MCMC error and the deviance information criterion variation with almost no variations and stability of various plots [12–14]. For the consistency test, we performed node-splitting assessments to determine the association between the direct and indirect evidence.

To assist in the interpretation of diagnostic performance, the surface under the cumulative ranking curve (SUCRA) was used to calculate the probability of each UBT, being the most effective diagnostic method based on a Bayesian

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approach using probability values, and the larger was the SUCRA value, the better was the rank of the intervention [15,16]. Publication bias was assessed with funnel plots.

3. Evidence synthesis

3.1. Study selection and characteristics

The literature search identified 2231 unique references. Among them, 190 records were removed due to duplication and 1763 articles were excluded due to unrelated outcomes during the screening process (Supplementary Fig. 1). Of the 278 full-text articles assessed for eligibility, 252 were excluded based on the selection criteria.

Twenty-seven studies were included in the qualitative synthesis (Table 1). Twenty-one studies, comprising 7330 patients, were included in the quantitative synthesis. All the studies included in the quantitative synthesis reported on the diagnostic value of UBTs for the detection of recurrence during surveillance: ten studies on Xpert bladder cancer [17–26], five studies on Bladder EpiCheck [26–30], three on Adxbladder [31–33], two on Uromonitor [34,35], and two on Cxbladder Monitor [36,37].

The summary of the risk of bias and applicability concerns is presented in Supplementary Figure 2. Overall quality of the included studies was deemed satisfactory. In most of the studies, there was an unclear risk of bias as to reference standards because included studies did not specify whether, during cystoscopy and/or histopathological assessment, urologists and/or pathologists were blinded to UBT results.

The prevalence of disease for each UBT is reported in Table 1. The pooled recurrence rate was calculated at 18%, with significant heterogeneity across studies with rates ranging from 6% [36] up to 70% [32].

The pooled diagnostic values calculated for 1000 patients as well as net benefits, the number of cystoscopies avoided (TN + FN), and the risk of missing recurrences by avoiding cystoscopy (TN) for each UBT are presented in Figure 1 and Supplementary Table 1. The calculations were based on the pooled recurrence rate and on 5-yr recurrence rates according to risk classification [1,38]. UBTs might be efficient in reducing the number of avoidable interventions, with up to 740 cystoscopies avoided for 1000 patients. For the detection of HG recurrence, the number of the cystoscopies avoided was similar among UBTs, with up to 790 cystoscopies being potentially avoided. For the detection of recurrence at 5 yr in low-, intermediate-, and high-risk groups, the number of the cystoscopies avoided reduced to 510, 491, and 474, respectively. The number of cancers missed (FN) are also presented in Supplementary Table 1.

3.2. Meta-analysis of diagnostic test accuracy for NMIBC recurrence

3.2.1. Xpert bladder cancer

Ten studies provided data on the diagnostic values of the Xpert bladder cancer UBT for the diagnosis of recurrence during NMIBC follow-up [17–26]. The pooled Se, Sp, PPV, and NPV were 0.72 (95% CI 0.63–0.80), 0.76 (95% CI 0.72–0.81), 0.43 (95% CI 0.32–0.54), and 0.92 (95% CI 0.90–0.94), respectively (Fig. 2–5). The Cochrane's Q tests and

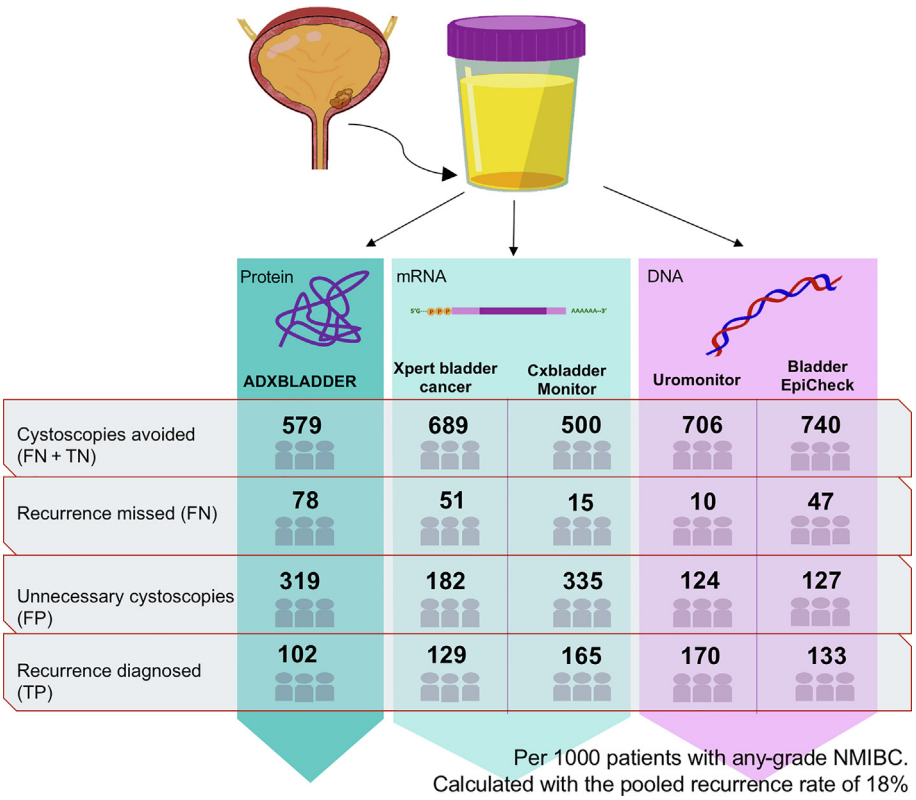

Fig. 1 – Net benefits and interventions avoided for the urinary biomarker tests for the detection of recurrence during the follow-up of 1000 patients with NMIBC based on the pooled recurrence rate. FP = false positive; FN = false negative; NMIBC = non–muscle-invasive bladder cancer; TN = true negative; TP = true positive.

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Table 1 – Characteristics of included studies reporting the diagnostic estimates of urinary biomarkers for diagnostics of NMIBC during the diagnosis of recurrence within follow-up

Author (publication year)	Study design	Number of patients	T stage, *n* (%)	Grade, *n* (%)	CIS, *n* (%)	Previous intravesical therapy, *n* (%)	Cutoff of biomarker	Sensitivity (%)	Specificity (%)	Recurrence rate, *n* (%)	Follow-up, median (range)
Xpert bladder cancer											
Cancel-Tassin (2021) [17]	P	500	Ta: 360 (72%)	LG: 287 (57.4%)	47 (9.4%)	No BCG 6 wk before	0.5	All: 72.7	73.7	All: 44 (8%)	NR
			T1: 88 (17.6%)	HG: 194 (38.8 %)				HG: 92.3		HG: 13 (29.5%)	
								LG: 64.5		LG: 31 (70.5%)	
Cowan (2021) [18]	P	429	Ta: 324 (75.5%)	LG: 178 (41.5%)	37 (8.6%)	BCG: 149 (34.7%)	NR	All: 60.3	76.5	All: 58 (13.5%)	In case of positive test: 12 mo (±90 d)
			T1/T2: 46 (10.7%)	HG: 230 (53.6%)		chemo: 63 (14.7%)		HG: 87.0		HG: 23	
										LG: 35	
D'Elia (2021) [21]	P	416 (1015 samples)	NR	LG: 126 (75%)	NR	NR	0.5	All: 52.38	78.39	168 samples (16.5%)	3–48 mo
				HG: 42 (25%)				LG: 42.86			
								HG: 80.95			
Elsawy (2021) [19]	P	181	Ta: 25 (13.8%)	LG: 33 (18.2%)	Exclusion	BCG or chemo (epirubicin)	NR	73.7	79.6	19 (10.4%)	In cystoscopy-negative patients:9 (5–19) mo
			T1: 156 (86.2)	HG: 148 (81.8%)							
Elsawy (2021) [20]	P	254	Ta: 8 (3.1%)	LG: 51 (20.1%)	Exclusion	BCG: 21 (8.3%)	NR	85.9	72.3	84 (35%)	12 (3–25) mo
			T1: 53 (20.9%)	HG: 10 (3.9%)		Chemo (epirubicin): 40 (15.7%)					
Hurle (2020) [22]	P	106	Only Ta, T1a	LG: 106 (100%)	Exclusion	NR	0.4	29.85	94.12	NR	18.8 (0–56.5) mo
				HG: exclusion			0.5	30	90.24		
Pichler (2018) [23]	P	140	Ta: 110 (78.6%)	LG: 97 (69.3%)	8 (5.7%)	BCG: 33 (23.6%)	NR	All: 84	All: 91	43 (30.7%)	NR
			T1: 22 (15.7%)	HG: 43 (30.7%)		MMC: 26 (18.6%)		Previous intravesical therapy: 100	Previous intravesical therapy: 92		
								No previous intravesical therapy: 79	No previous intravesical therapy: 90		
Smrkolj (2020) [24]	P	54	NR	NR	NR	No BCG or chemo 3 mo before	0.5	66.7	95.2	NR	NR
							0.4923	75	95.2		
Van Valenberg (2018) [25]	P	239	NR	NR	NR	BCG: 83 (35%)	NR	All: 74	All: 80	All: 43 (18%)	NR
						Chemo: 69 (29%)		HG: 83.3	HG: 75.8	HG: 24	
										LG: 19	
Trenti (2020) [26]	P	487	Ta: 341 (70%)	LG: 336 (69%)	59 (12%)	BCG: 122 (25.1%)	0.5	All: 66.30	76.47	All: 92 (21.3%)	NR
			T1: 87 (18%)	HG: 151 (31%)		MMC: 37 (7.6%)		HG: 78.95		HG: 38 (8.8%)	
								LG: 57.41		LG: 54 (12.5%)	
Bladder EpiCheck											
D'Andrea (2019) [27]	P	357	Ta: 219 (61.3%)	LG: 182 (51%)	36 (10%)	BCG: 70 (20.2%)	60	All: 67.3	All: 88	All: 49 (13.7%)	NR
			T1: 97 (27.2%)	HG: 170 (47.6%)		MMC: 111(31.1%)		HG: 88.9	HG: 84.1	HG: 18 (5.1%)	
						Both: 59 (16.5%)		LG: 40	LG: 81.6	LG: 20 (5.6%)	
Pierconti (2021) [28]	R	375	T1: 269 (71.7%)	HG: 269 (71.7%)	106 (28.3%)	BCG: 305 (81.3%)	60	HG: 73	HG: 70.1	111 (29.6%)	In case of negative cytology: 12 mo
						MMC: 70 (18.7%)					
Trenti (2019) [29]	P	243	Ta: 165 (68%)	LG: 154 (63.4%)	49 (20.2%)	BCG: 83 (34.2%)	60	All: 62.3	All: 86.3	All: 69 (32.1%)	NR
			T1: 29 (12%)	HG: 89 (36.6%)		MMC: 11 (4.5%)		HG: 83.3	HG: 79.5	HG: 30 (14.0%)	
								LG: 46.1	LG: 74.4	LG: 39 (18.1%)	
Trenti (2020) [26]	P	487	Ta: 341 (70%)	LG: 336 (69%)	59 (12%)	BCG: 122 (25.1%)	60	All: 64.13	82.06	All: 92 (21.3%)	NR
			T1: 87 (18%)	HG: 151 (31%)		MMC: 37 (7.6%)		HG: 78.95		HG: 38 (8.8%)	
								LG: 53.70		LG: 54 (12.5%)	
Wasserstrom (2016) [30]	R	222	NR	NR	NR	NR	60	All: 90	All: 83	All: 40 (18%)	NR
								HG: 95		HG: 19 (8.6%)	
								LG: 84		LG: 19 (8.6%)	

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Table 1 (*continued*)

Author (publication year)	Study design	Number of patients	T stage, *n* (%)	Grade, *n* (%)	CIS, *n* (%)	Previous intravesical therapy, *n* (%)	Cutoff of biomarker	Sensitivity (%)	Specificity (%)	Recurrence rate, *n* (%)	Follow-up, median (range)
ADXBLADDER											
Biaûçûçlek (2021) [32]	P	119	pTaLG: 80 (67%)	NR	NR	0.985	All: 73.5	33.3	83 (69.7%)	In recurrence patients: 46 (18–117) mo; in nonrecurrence patients: 41 (22–72) mo	
			pTaHG: 14 (12%)				HG: 81.8				
			pT1LG: 2 (2%)				LG: 72.2				
			pT1HG: 23 (19%)				CIS: 50				
							Ta: 72.6				
							T1-T2: 100				
Gontero (2021) [33]	P	503	TaLG: 203 (40%)	CIS all: 63 (13%)	BCG: 288 (57%)	NR	All: 51.9	66.4	54 (10%)	NR	
			TaHG: 143 (28%)	CIS alone: 7 (1%)	Chemo: 105 (21%)		HG: 58.8				
			T1: 136 (27%)				LG: 44.1				
							CIS all: 60				
							CIS alone: 100				
							Ta: 45.2				
							T1: 75				
							LG pTa: 44.1				
							Solitary: 44.8				
							Multiple: 52.4				
Roupret (2020) [31]	P	1431	TaLG: 738 (51.6%)	145 (10.1%)	BCG: 534 (37.3%)	NR	All: 44.9	71.1	127 (8.9%)	NR	
			TaHG: 376 (26.3%)		Chemo: 424 (29.6%)		HG: 73				
			T1: 267 (18.7%)				LG: 30.2				
							pTa: 38.3				
							pT1: 75				
							pT2: 100				
							CIS all: 71.4				
							pTaLG: 30.2				
							Non-pTaLG: 75.6				
							Solitary: 45.9				
							Multiple: 42.1				
Uromonitor											
Batista (2019) [34]	P	185 (122 follow-up)	Ta: 32 (62.7%)	LG: 25 (51%)	5 (9.8%)	NR	NR	Uromonitor:	93.2	34/122 (28%)	NR
			T1: 12 (23.5%)	HG: 24 (49%)				All: 73.5			
			T2: 1 (2%)					HG: 75			
								LG: 62.5			
								CIS: 100			
								Ta: 53.8			
								T1: 71.4			
								Uromonitor-V2: 100	83.3		
Sieverink (2020) [35]	P	77	Ta: 44 (57%)	LG: 32 (42%)	20 (26%)	BCG: 16 (21%)	NR	Uromonitor-V2: 93.1	85.4	29 (37.7%)	6 mo
			T1: 11 (14%)	HG: 45 (58%)		MMC: 34 (44%)					
			PUNLMP: 2 (3%)			Synergo: 21 (27%)					
Cxbladder Monitor											
Koya (2020) [36]	R	309	Ta LG: 257 (83%)	NR	NR	100	79.7	13 (6.2%)	35 mo		
			Tis or HG: 52 (17%)								
Lotan (2017) [37]	P	803	Ta: 675 (80%)	LG: 508 (50%)	101 (10%)	NR	NR	90.7	38.8	151 (14.9%)	NR
			T1: 161 (20%)	HG: 453 (45%)							

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high grade; LG = low grade; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; NPV = negative predictive value; NR = not reported; P = prospective; PPV = positive predictive value; PUNLMP = papillary urothelial neoplasm of low malignant potential; R = retrospective.Additionally, PPV and NPV can be found in Supplementary Table 1.

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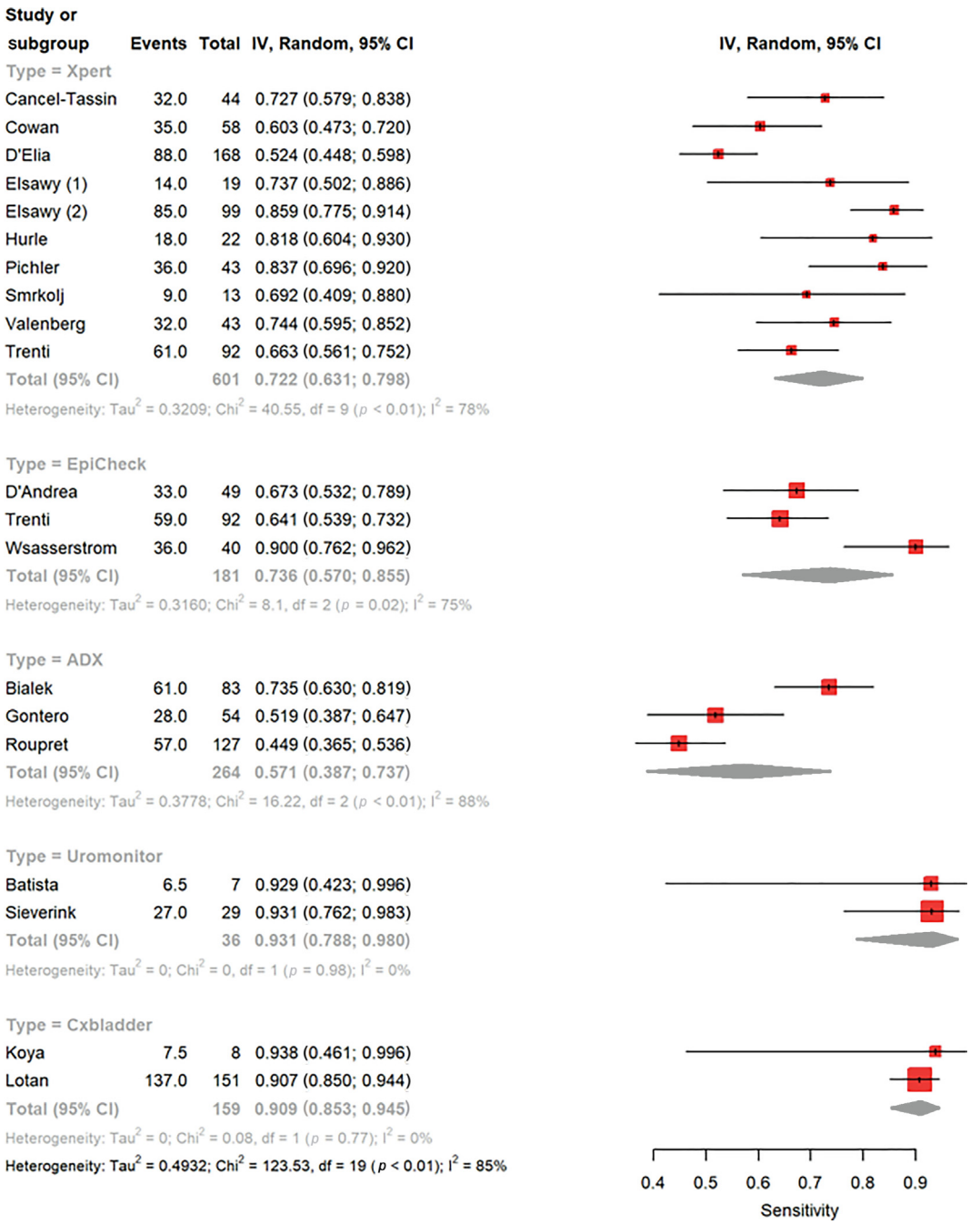

Fig. 2 – Forest plot for pooled sensitivity of five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for diagnostics of NMIBC recurrence during follow-up. CI = confidence interval; df = degree of freedom; IV = inverse variance; NMIBC = non–muscle-invasive bladder cancer.

I^2 tests revealed significant heterogeneity among studies for each variable.

The pooled DOR was 9.09 (95% CI 5.67–14.57; Supplementary Fig. 3). The test reached an AUC of 80.7% for the detection of recurrence during follow-up (Supplementary Fig. 4).

In the subgroup analysis of patients with HG recurrence, the forest plots revealed that the pooled Se, Sp, PPV, and NPV were 0.88 (95% CI 0.79–0.96), 0.75 (95% CI 0.73–0.78), 0.18 (95% CI 0.08–0.28), and 0.99 (95% CI 0.98–1.00), respectively (Supplementary Fig 5–8). The Cochrane's Q tests and I^2 tests revealed significant heterogeneity among studies only for PPV. The pooled DOR was 19.80 (95% CI 9.18–42.72; Supplementary Fig. 9). Xpert bladder cancer for the detection of HG recurrence of NMIBC reached an AUC of 79.5% during follow-up.

3.2.2. Bladder EpiCheck

Five studies provided data on the diagnostic values of the Bladder EpiCheck UBT for the diagnosis of recurrence during NMIBC follow-up [26–30]. The forest plots revealed that the pooled Se, Sp, PPV, and NPV were 0.74 (95% CI 0.57–0.85), 0.84 (95% CI 0.80–0.88), 0.48 (95% CI 0.42–0.54), and 0.94 (95% CI 0.90–0.97), respectively (Fig. 2–5). The Cochrane's

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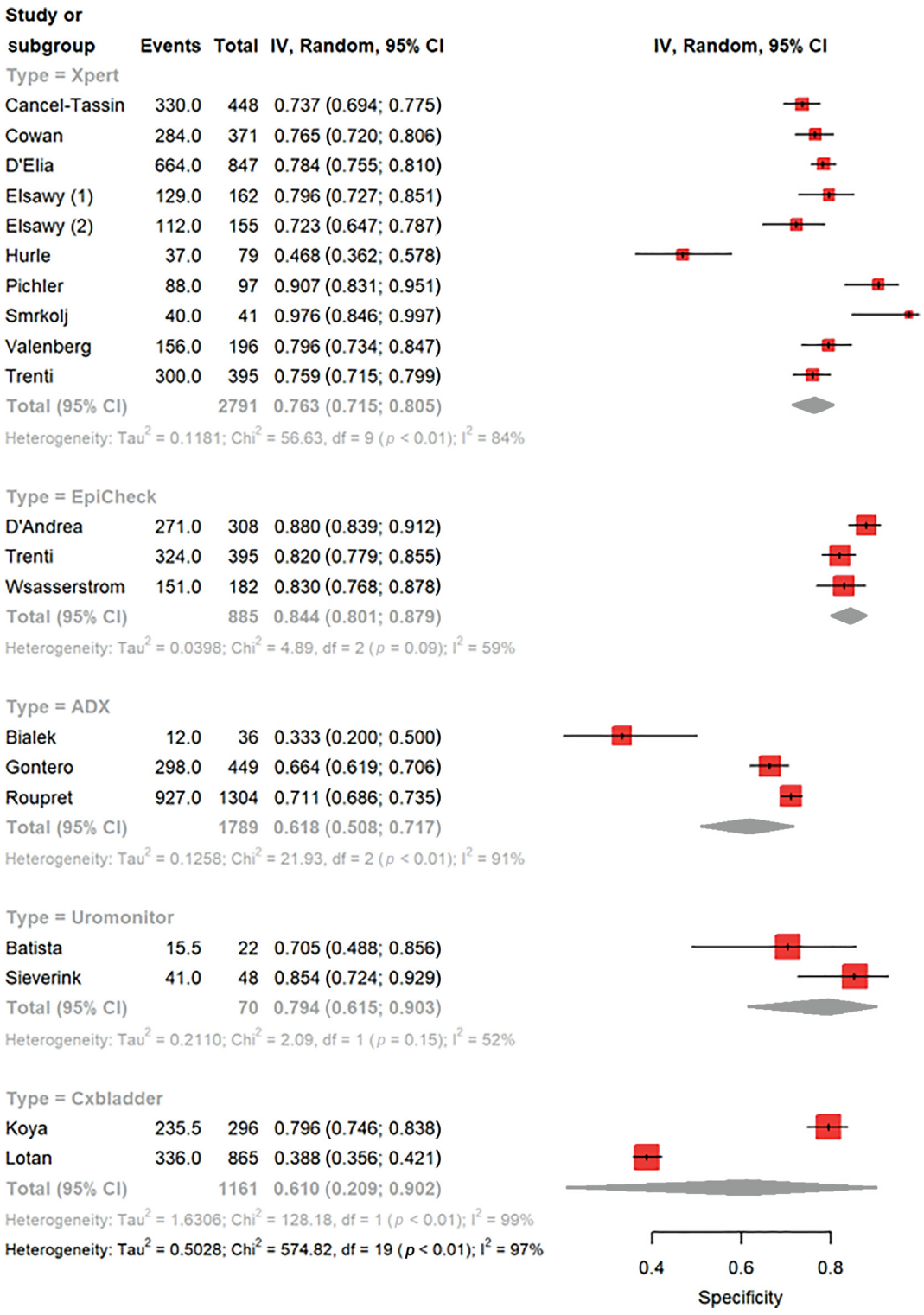

Fig. 3 – Forest plot for pooled specificity of five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for diagnostics of NMIBC recurrence during follow-up. CI = confidence interval; df = degree of freedom; IV = inverse variance; NMIBC = non–muscle-invasive bladder cancer.

Q tests and I^2 tests revealed significant heterogeneity among studies only for Se and NPV. The pooled DOR was 15.57 (95% CI 6.71–36.13). Bladder EpiCheck for diagnostics of NMIBC recurrence reached an AUC of 86.7% during follow-up.

In the subgroup analysis of patients with HG recurrence, the forest plots revealed that the pooled Se, Sp, PPV, and NPV were 0.80 (95% CI 0.70–0.90), 0.78 (95% CI 0.69–0.86), 0.38 (95% CI 0.21–0.55), and 0.94 (95% CI 0.89–1.00), respectively (Supplementary Fig. 5–8). The Cochrane's Q tests and I^2 tests revealed significant heterogeneity among studies in terms of Sp, PPV, and NPV. The pooled DOR was 14.74 (95% CI 4.80–45.27). Bladder

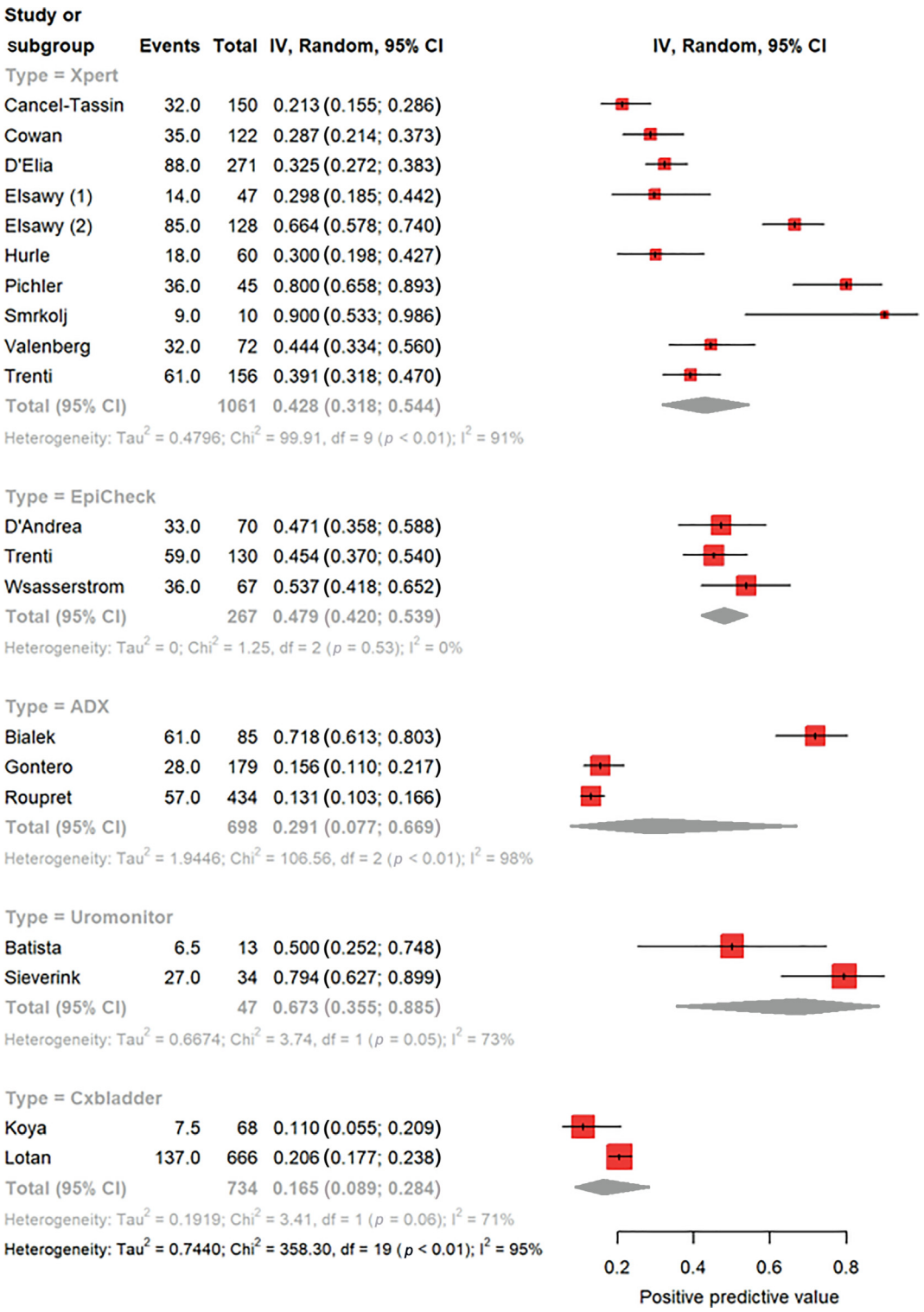

Fig. 4 – Forest plot for pooled positive predictive value of five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for diagnostics of NMIBC recurrence during follow-up. CI = confidence interval; df = degree of freedom; IV = inverse variance; NMIBC = non–muscle-invasive bladder cancer.

EpiCheck for diagnostics of HG recurrence reached an AUC of 86.6% during follow-up.

3.2.3. ADXBLADDER

Three studies provided data on the diagnostic values of the ADXBLADDER test for the diagnosis of recurrence during NMIBC follow-up [31–33]. The forest plots revealed that the pooled Se, Sp, PPV, and NPV were 0.57 (95% CI 0.39–0.73), 0.62 (95% CI 0.51–0.72), 0.29 (95% CI 0.08–0.67), and 0.82 (95% CI 0.53–0.95), respectively (Fig. 2–5). The Cochrane's Q tests and I^2 tests revealed significant heterogeneity among studies in terms of Se, Sp, PPV, and NPV. The

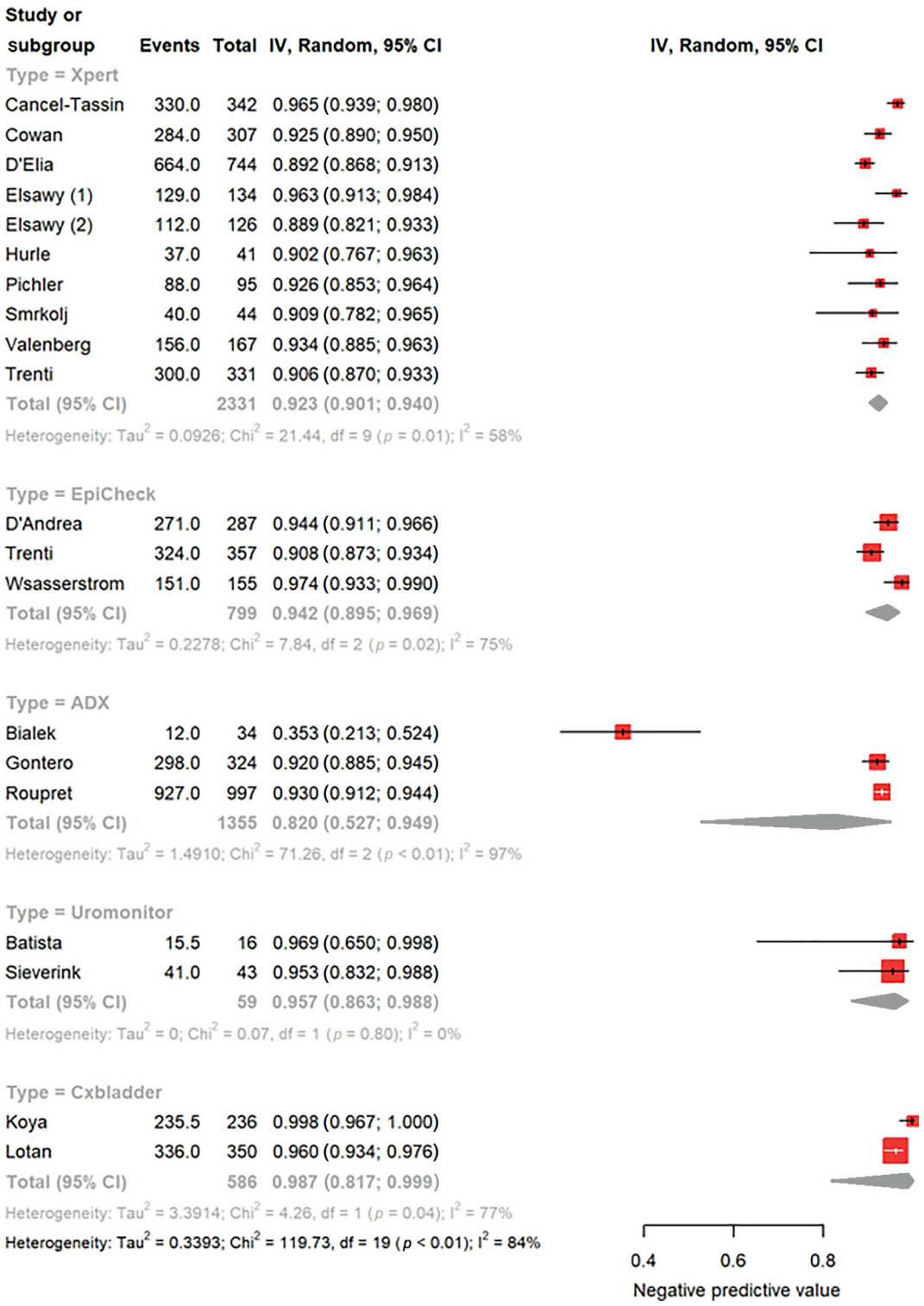

Fig. 5 – Forest plot for pooled negative predictive value of five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for diagnostics of NMIBC recurrence during follow-up. CI = confidence interval; df = degree of freedom; IV = inverse variance; NMIBC = non–muscle-invasive bladder cancer.

pooled DOR was 1.95 (95% CI 1.46–2.61). ADXBLADDER for diagnostics of NMIBC recurrence reached an AUC of 59.7%.

In the subgroup analysis of patients with HG recurrence, the pooled Se, Sp, PPV, and NPV were 0.71 (95% CI 0.63–0.79), 0.76 (95% CI 0.65–0.88), 0.37 (95% CI 0.26–0.99), and 0.93 (95% CI 0.87–0.99), respectively (Supplementary Fig. 5–8). There was significant heterogeneity among studies in terms of Sp, PPV, and NPV. The pooled DOR was 6.19 (95% CI 1.94–19.84). ADXBLADDER for diagnostics of HG recurrence reached an AUC of 74.5%.

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3.2.4. Uromonitor

Two studies provided data on the diagnostic values of the Uromonitor test for the diagnosis of recurrence during NMIBC follow-up [34,35]. The forest plots revealed that the pooled Se, Sp, PPV, and NPV were 0.93 (95% CI 0.79–0.98), 0.79 (95% CI 0.62–0.90), 0.67 (95% CI 0.36–0.89), and 0.96 (95% CI 0.86–0.99), respectively (Fig. 2–5). The Cochrane's Q tests and I^2 tests did not reveal significant heterogeneity among studies in terms of Se, Sp, PPV, or NPV. The pooled DOR was 63.82 (95% CI 15.05–270.52). Uromonitor reached an AUC of 92.4% for the detection of recurrence. A subgroup analysis for HG recurrence was not feasible due to the lack of data.

3.2.5. Cxbladder Monitor

Two studies provided data on the diagnostic values of Cxbladder Monitor for the diagnosis of recurrence [36,37]. The pooled Se, Sp, PPV, and NPV were 0.91 (95% CI 0.85–0.95), 0.61 (95% CI 0.21–0.90), 0.16 (95% CI 0.09–0.28), and 0.98 (95% CI 0.82–0.99), respectively (Fig. 2–5). There was significant heterogeneity among studies in terms of Sp, PPV, and NPV. The pooled DOR was 12.00 (95% CI 1.63–88.64). Cxbladder Monitor reached an AUC of 91.7% for the detection of recurrence. A subgroup analysis for HG recurrence was also not feasible.

3.3. Network meta-analysis

Thirteen studies were available for NMA [17–19,21,23–26,30,33–35,37]. The networks of eligible comparisons are graphically represented in network plots on the diagnostic values of UBTs for the diagnosis of NMIBC recurrence in Figure 6. The results of the current NMA revealed that the Se (OR 68.2, 95% CrI 7.51–1.26e + 03), Sp (OR 0.41, 95% CrI 0.04–4.34), PPV (OR 1.31, 95% CrI 0.15–10.1), and NPV (OR 14.0, 95% CrI 3.28–116) of the Uromonitor test were significantly higher than those of any other tests for the detection of NMIBC recurrence (Fig. 7). The results indicated consistency between the direct and indirect evidence in all outcomes. As such, the consistency model was applied to the current study (all $p > 0.05$).

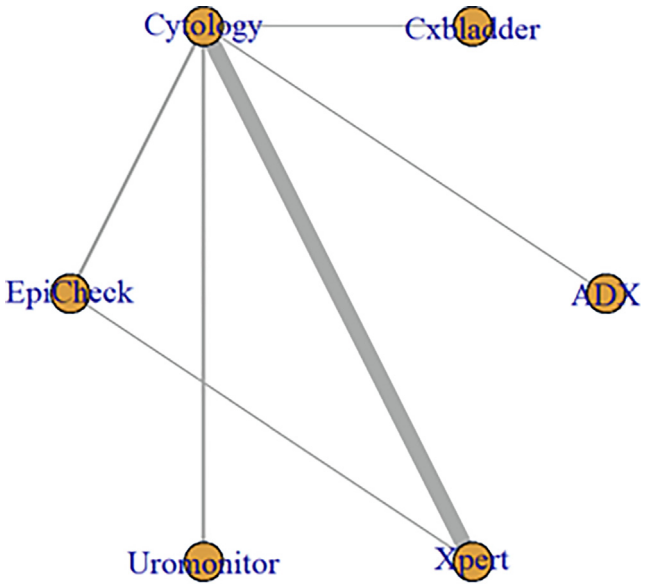

Fig. 6 – Evidence network plot of diagnostic value of cytology and five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for the detection of NMIBC recurrence. NMIBC = non–muscle-invasive bladder cancer.

An exploratory analysis of the SUCRA values of the diagnostic performance of different UBTs indicated that the Uromonitor test might be ranked first in terms of Se, PPV, and NPV (0.90, 0.73, and 0.98, respectively), while cytology ranked first in terms of Sp (0.94; Supplementary Table 2). The funnel plot identified two studies over the pseudo–95% CI for Se, four studies for Sp, four studies for PPV, and one study for NPV (Supplementary Fig. 10).

3.4. Performance in primary diagnosis

Seven studies reported on the diagnostic values of the novel UBTs for the detection of NMIBC during initial diagnosis [34,39–44]. Table 2 summarizes the characteristics of included studies and their main outcomes.

In the studies on initial diagnosis setting, the Xpert bladder cancer test has been shown to have Se varying between 73% and 79% regardless of the presence of hematuria [39,40]. In terms of Sp, the Xpert bladder cancer test had the highest estimates of 90% in patients with hematuria [40]; in the overall population, it ranged from 77% [40] to 84% [39]. The ADXBLADDER test demonstrated Se up to 87% in patients diagnosed with HG NMIBC, compared with 48–55% in patients diagnosed with LG tumors [41,42]. Similarly, Cxbladder (mix of Triage and Detect) reached the highest Se value of 97% in patients with HG tumors [43,44].

In general, there was a lack of data on the use of the novel UBTs in the initial diagnosis setting. Additionally, some of the studies poorly reported the clinicopathological characteristics of patients diagnosed with NMIBC. Hence, despite the promising results of some tests, large-scale studies are definitely warranted to confirm and validate these tests in this indication.

3.4.1. Combinations

Four studies reported the diagnostic value of different combinations of UBTs for the detection of recurrence during NMIBC follow-up (Supplementary Table 3) [21,23,26,29]. Nevertheless, data on benefits of combinations are limited, and no formal analysis can be performed. More studies are still needed in the future and should implement their cost.

3.5. Discussion

We conducted the first DTA and NMA of the diagnostic estimates of the most promising novel UBT. Our results demonstrate that many markers have good performance characteristics for the detection of recurrence during surveillance of bladder cancer.

Although the Uromonitor test had the highest diagnostic values among all the tests in our NMA, our results should be interpreted with caution due to the limited number of included studies; confirmation by future well-designed trials evaluating multiple UBTs focusing on the recurrence of NMIBC is necessary. Compared with our results among the novel UBTs, one of the most studied FDA-approved biomarkers, NMP22, was shown to have lower diagnostic estimates (pooled Se of 71% and Sp of 80%) [45]. Similarly, pooled Se and Sp of other FDA-approved tests such as BTA (58% and 79%, respectively) and ImmunoCyt/uCyt+ (75%

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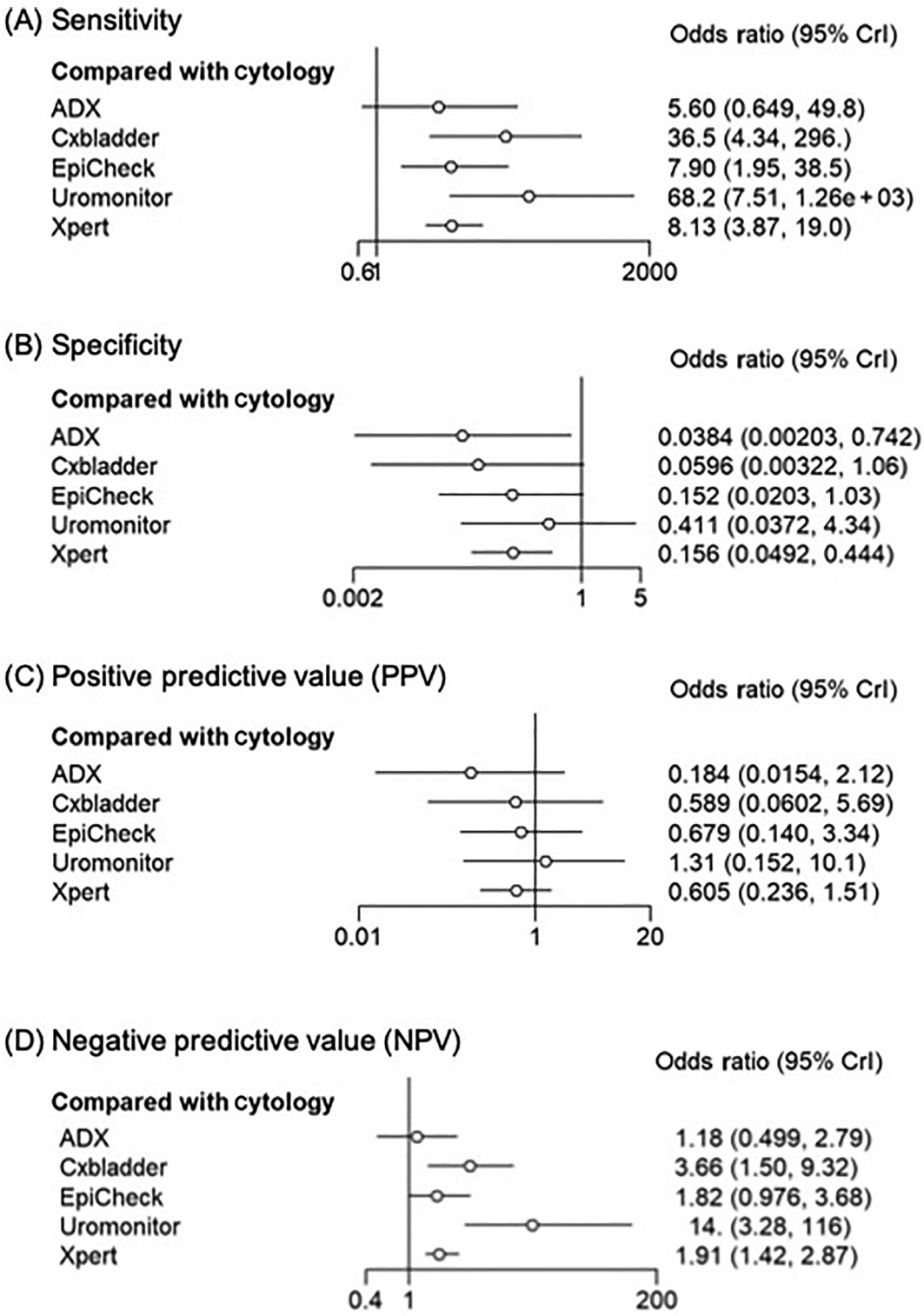

Fig. 7 – Forest plots representing five different urinary biomarker tests (Xpert bladder cancer, ADXBLADDER, Bladder EpiCheck, Uromonitor, and Cxbladder Monitor) for the detection of NMIBC recurrence compared with cytology. CrI = credible interval; NMIBC = non–muscle-invasive bladder cancer.

and 76%, respectively) were also lower [46]. Moreover, previous meta-analyses did not assess the possibility of avoiding unnecessary cystoscopies [1].

In general, NMIBC has been shown to have considerable symptomatic health-related quality of life and economic burden [3,47]. The reduction of cystoscopy frequency as interventional procedures is not only to potentially improve the quality of life, but also to improve the value-based care of NMIBC. Therefore, this is the first study to show that the novel UBTs might be efficient in reducing the number of avoidable cystoscopies, with up to 740 cystoscopies avoided for 1000 patients. Nevertheless, the quality-of-life analyses

Table 2 – Characteristics of included studies reporting the diagnostic estimates of urinary biomarkers for diagnostics of NMIBC during initial diagnosis

Author (publication year)	Study design	Number of patients	Diagnosed BCa, *n* (%)	Stage, *n* (%)	Grade, *n* (%)	CIS, *n* (%)	Sensitivity (%)	Specificity (%)
Xpert bladder cancer								
Van Valenberg (2020) [39]	P	828	59 (7%)	NR	NR	NR	All: 78	84
							Microhematuria: 73	
							Macrohematuria: 79	
Wallace (2018) [40]	P	370	49 (10.8%)	Hematuria:	Hematuria:	Hematuria:	All: 73	All: 77
				Ta: 14 (64%)	LG: 8 (36%),	CIS alone: 1 (5%)	Hematuria: 73	Hematuria: 90
				T1: 2 (9%)	HG: 14 (64%)	CIS all: 1 (5%)		
				Greater T1: 3 (14%)				
ADXBLADDER								
Anastasi (2020) [41]	P	91	40	MIBC: 3/37 (8.1%)	LG: 21/37 (57%)	7 (18.9%)	All: 60	88.2
				NMIBC: 34/37 (91.9%)	HG: 16/37 (43%)		HG: 87.5	
							LG: 47.6	
Dudderidge (2019) [42]	P	856	74	NMIBC: 57	LG: 29,	8	All: 73	68.4
				MIBC: 16	HG: 42		HG NMIBC: 86	
				pTa: 40				
				pT1 and >: 34			LG NMIBC: 55	
							pT1 and >: 97.0	
							pT2 and >: 100	
							CIS: 88	
							pTa: 53	
Uromonitor								
Batista (2019) [34]	P	63	28 (44.4%)	NR	NR	NR	Uromonitor: 50	100
							Uromonitor-V2: 93.3	80
Cxbladder (mix of Triage and Detect)								
O'Sullivan (2012) [43]	P	485	66 (13.6%)	Ta: 37	LG: 32 (48.5%)	2 (3%)	All: 81.8	All: 85.1
								HG: 80.5
				T1: 16	HG: 29 (43.9%)		HG: 96.6	LG: 79
				T2: 9	Mixed: 4 (6%)		LG: 68.8	
				T3/greater: 2				
Davidson (2019) [44]	P	571	44	Ta: 21	LG: 12	1	All: 95.5	All: 34.3
								Macrohematuria: 32.8
				T1: 9	HG: 28		Macrohematuria: 95.1	Microhematuria: 42.6
				T2: 10			Microhematuria: 100	
				Tx: 3				

BCa = bladder cancer; CIS = carcinoma in situ; HG = high grade; LG = low grade; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; NR = not reported; P = prospective.

as well as the cost effectiveness of each UBT still need to be assessed specifically in each health care system. Such analyses for EpiCheck have shown potential cost effectiveness of this approach [48]. Moreover, as the included studies still suffer from limited follow-up, we also reported the predictive DTA of each UBT according to the 5-yr recurrence rate within each established NMIBC risk group. This information might be useful for interpreting the benefit of these tests according to the desired time length, early and long term, and to define their utility according to the follow-up.

Our subgroup analysis on the detection of HG recurrence of NMIBC demonstrated similar diagnostic estimates to those in the overall population for three available UBTs (Xpert bladder cancer, Bladder EpiCheck, and ADXBLADDER). However, these results might be limited due to the number of studies. Further studies might help gain insight into that field (NCT04100733). Although we were not able to perform an analysis among LG tumors, it is one of the indications proposed by some authors during the follow-up [31,33,49–51]. Future prospective studies are necessary to prove the concept that the currently available markers could play an important role as an alternate to cystoscopy in patients with LG NMIBC (eg, UroFollow trial) [52].

Our results demonstrate that the novel UBTs have superior Se and NPV for the detection of recurrences to cytology. A combination of these different tests and/or combination with cytology might be of interest in select scenarios where the patient benefits from both high Se (ie, UBT) and high Sp (ie, cytology). All these UBTs need to be tested as reflex testing in patients with equivocal findings such as unclear cystoscopic finding or atypical cytology [53]. Nevertheless, further studies are needed to integrate all criteria needed to usher a UBT into widespread use, including cost, ease of use, and patient acceptance [54].

Although the novel UBTs showed promising results in the NMIBC setting, there is a lack of data for their use in the initial diagnosis setting [55]. The diagnostic estimates and specificity of Xpert bladder in patients with hematuria

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were promising but need validation [39,40]. To date, the guidelines do not recommend any UBT routinely in the initial diagnosis [56], but ongoing randomized trials are awaited to determine the benefit of biomarkers in this large patient group (NCT03988309). Therefore, cystoscopy remains as the gold standard in the investigation of visible hematuria. One could foresee a point of care test used by general practitioners and other nonurological specialists to select patients for fast-track referral to the urologist [57].

Our study has several potential limitations. The main limitation was the heterogeneity of patient populations in terms of inclusion criteria and clinicopathological features. Moreover, the studies demonstrated high heterogeneity regarding the prevalence of recurrence rate, which might be an important confounder. Different conditions and previous intravesical therapy may also influence the results. No study was precise enough to assess the impact of previous instillation on the diagnostic performance. As there was measurable significant heterogeneity across the studies, we used the random-effect model to account for the heterogeneity among studies; nevertheless, our conclusions should still be interpreted with caution. The difference in patient populations and reference standards in the included studies, as well as absence of data on blinding to pathologists or urologists, is likely to be the main reason for the notable risk of bias. Additionally, most of the studies did not report the cutoff of the UBT used. We were able to perform subgroup analyses for HG recurrence detection only, and not for LG NMIBC due to the lack of data in the literature. Nevertheless, as most UBTs had data on all recurrences and HG recurrences, it is unlikely that the analyses in LG recurrence would have yielded effect results. The included studies assessed the diagnostic performance of UBTs; however, data on its oncological impact are still lacking. CIS was underevaluated in many studies, which impacts the proportion of FP and FN findings, especially in patients under surveillance for CIS. The protocol of used cystoscopy follow-up was not reported in the majority of included studies. The cost effectiveness of individual UBTs that belong to national agencies was out of scope in the present meta-analysis. Still, well-designed large-scale trials comparing all UBTs head to head are required to confirm the findings of the present study and to propose detailed follow-up protocols using UBTs. Although UBTs have the potential to be used widely in the near future, cystoscopy cannot completely be abandoned and will continue to have an important role during the follow-up of NMIBC. Moreover, decision curve analyses will be needed to help clinicians assess the net benefit of UBTs in this setting. In the meantime, our results could help health care agencies and stakeholders decide whether these new UBTs might be of value to patients in their respective care area.

4. Conclusions

Our study supports the promising role of the novel commercially available UBTs for the diagnosis of recurrence during the follow-up of NMIBC. Their performance supports their potential value in preventing unnecessary cystoscopies. However, there are not enough data to support their use in the initial diagnosis setting. Our study might help policymakers and stakeholders, such as payors and patient advocacy groups, assess the implementation of these tests into daily practice.

***Author contributions*:** Benjamin Pradere had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pradere.
Acquisition of data: Laukhtina, Mori, Pradere.
Analysis and interpretation of data: Laukhtina, Mostafaei, Pradere.
Drafting of the manuscript: Laukhtina, Mori, D'Andrea, Soria, Teoh, Pradere.
Critical revision of the manuscript for important intellectual content: Compérat, Cimadamore, Moschini, Enikeev, Xylinas, Lotan, Palou, Gontero, Babjuk, Witjes, Kamat, Roupret, Shariat.
Statistical analysis: Shim, Rajwa.
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Administrative, technical, or material support: None.
Supervision: Shariat, Pradere.
Other: None.

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Appendix A. Supplementary data

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