7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

Real world evaluation of the bladder urine test

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Conflict of interest disclosure

I have no potential conflict of interest to report

The Gold Standard for Bladder Cancer detection and NMIBC surveillance

https://bolgehospitalinternational.com/departments/cystoscopy/

What do patients think about cystoscopy?

Painful
Embarrassing
Accurate
Intrusive
Uncomfortable
Anxiety
Fear
Security
Invasive
Hurts
Stressful
Discomfort

Is cystoscopy so good?

Discomfort

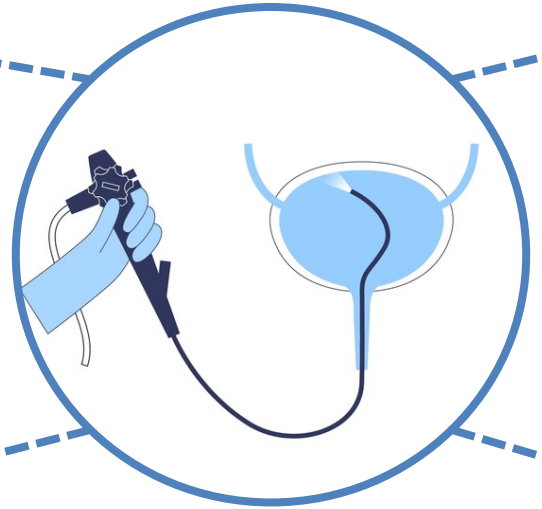
Experienced by 50%

Schroek et al
2024, Eur Urol OS

Side-effects

2-3% UTIs

Gregg et al
2018, J Urol



Cost

≈200-280 $
/cystoscopy

Scillipoti et al
2025, Eur Urol

Inaccuracy

9,4% NMIBC missed
31% unnecessary TURBT

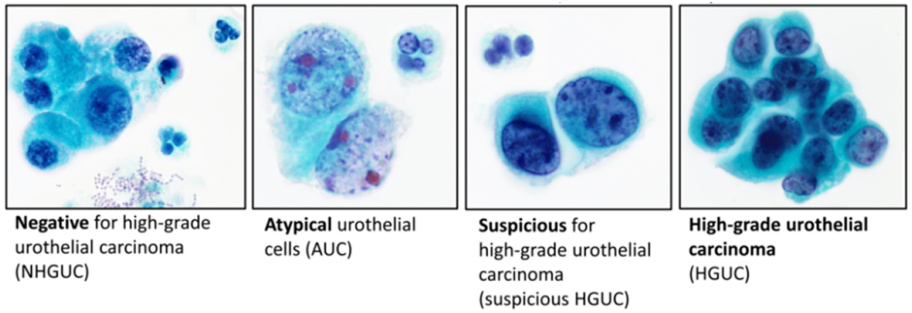
Guldhammeer et al
2025, Cancers

It is not the perfect test

https://www.shutterstock.com/es/search/cystoscopie?image_type=illustration&dd_referrer=https%3A%2F%2Fwww.google.com%2F

Cytology: We'll always have…

…the Paris system (TPS 2.0)



Negative for high-grade urothelial carcinoma (NHGUC)

Atypical urothelial cells (AUC)

Suspicious for high-grade urothelial carcinoma (suspicious HGUC)

High-grade urothelial carcinoma (HGUC)

- Non-invasive
- Highly specific (≈ 90%)
- Sensitive for HG disease
- Reveals non-visible lesions

- Poor SN for LG disease
- Dependent on cytopathologist expertise
- Indeterminate reports

Wojcik et al. 2022 J Am Soc Cytopathol

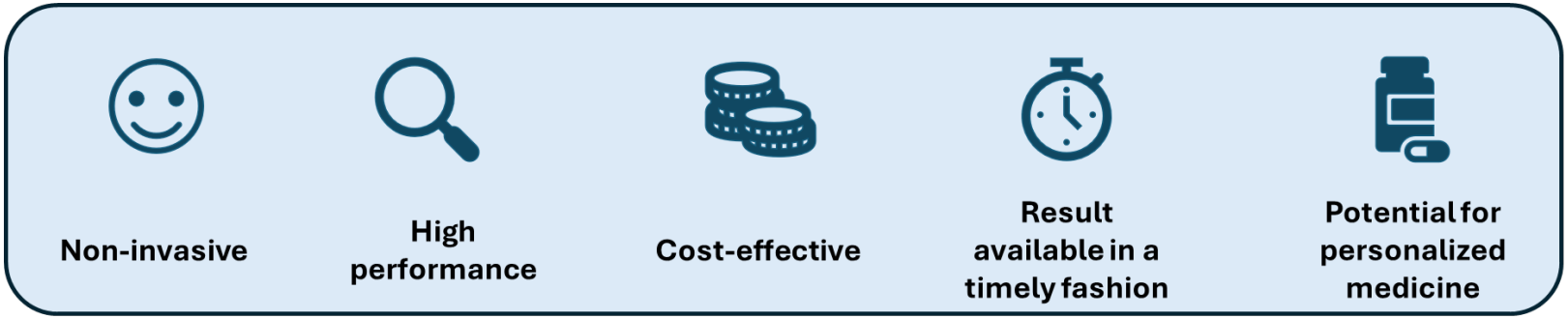
Diagram of TPS 2.0. by Mikael Häggström, Public Domain

In search of Bladder Cancer Biomarkers

- ✓ Can biomarkers enhance performance of the combination of cystoscopy and cytology?

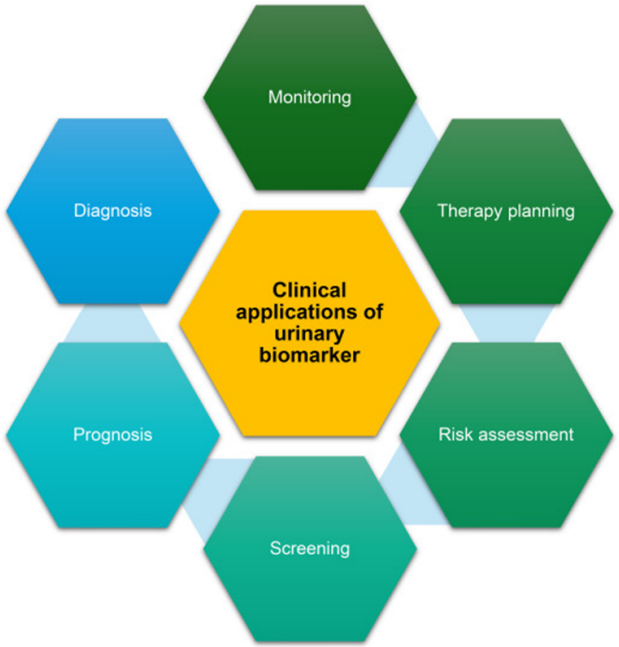
- ✓ Can biomarkers replace some use of cystoscopy?

What should an ideal biomarker be like?



Urine biomarkers in bladder cancer

Clinical applications

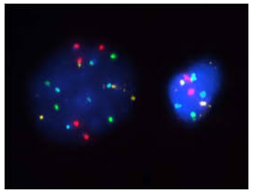


Das et al 2025, Molecular foundations of urinary biomarkers

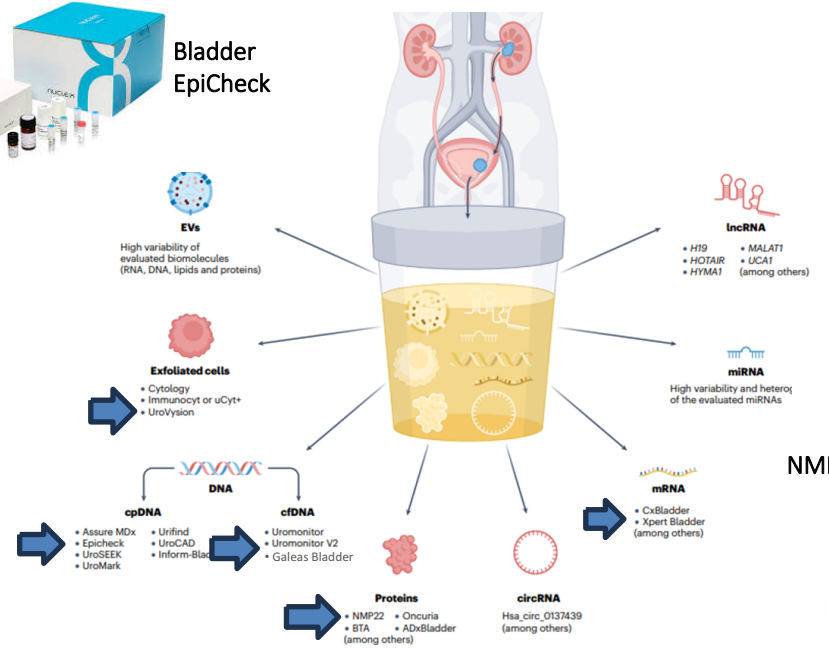
Urine biomarkers in bladder cancer

Biomarkers/tests according to tumor-derived material

UroVysion



Bladder EpiCheck



NMP22

Mass et al 2023, Nat Rev Urol

BC primary diagnosis: urine biomarkers

Confirm the presence of disease

- **High SP:** the test correctly identifies patients without cancer
- **High PPV:** test positive -> ↑ probability that the patient truly has cancer

Table 1
Commercially available biomarkers for bladder cancer detection

Class	Marker	Molecule	Reference	Year	Sensitivity	Specificity
Protein	BladderChek (Alere NMP22 Bladder, Abbot Labs)	Nuclear Matrix Protein 22	Grossman et al,[9] 2015	2005	55.7%	85.7%
	Bladder Tumor Antigen (Polymedco, USA) – POC and ELISA	Human complement factor H-related protein	Guo et al,[40] 2014 (POC) Glas et al (ELISA)	2014 2003	67% 75%	75% 65%
	UBC	Cytokeratin	Lu et al	2018	59.3%	86.1%
Cell Based	UroVysion (Abbott Laboratories)	Fluorescence in situ Hybridization	Hajdinjak	2008	72%	83%
RNA	CxBladderTriage; CxBladderDetect; CxBladderResolve	*IGF, HOXA, MDK, CDC, IL8R*	Kavaliers O'Sullivan Raman	2015 2012 2021	95%[a] 82% 92.4%[b]	98%[a] 85% 93.8%[b]
	Xpert Bladder Detection (Xpert; Cepheid)	*ABL1, CRH, IGF2, UPK1B, ANXA10*	Van Valenberg	2020	78%	84%

Lotan et al 2023, Urol Clin North Am

CxBladder Triage Plus

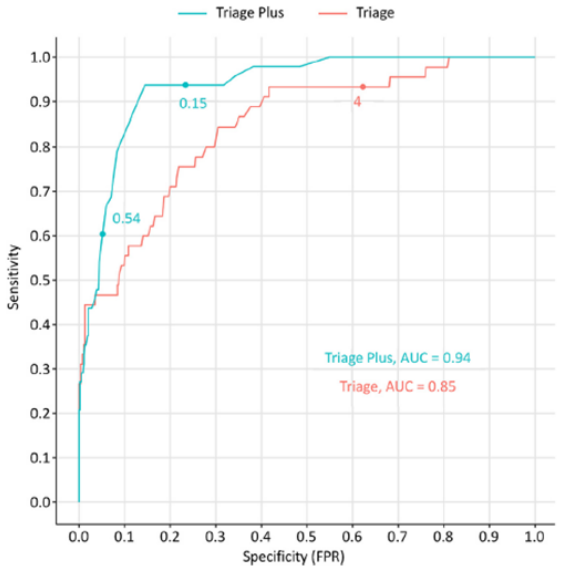
- Multicenter, prospective, observational study
- 615 patients with hematuria (48 with BC; 35 HG, 3 ≥ T2)
- CxBladder Triage Plus: 5 UC-associated mRNAs and 6 DNA SNPs from *FGFR3* and *TERT*

Score ≥ 0.15 (Low vs intermediate/high risk)

Assay	N	Performance characteristic, % (95% CI)				
		Sensitivity	Specificity	PPV	NPV	TNR
Triage Plus						
Overall population	587	94 (83–99)	77 (73–80)	26 (20–34)	99.3 (97.9–99.9)	71 (67–75)
AUA MH risk category[a]						
Low/negligible	17	NA	82 (57–96)	0 (0–97)	100 (76.8–100)	82 (57–96)
Intermediate	49	NA	82 (68–91)	0 (0–23)	100 (91.2–100)	82 (68–91)
High	254	89 (65–99)	76 (70–81)	22 (13–33)	98.9 (96.1–99.9)	71 (65–77)
GH	267	97 (83–100)	76 (70–81)	34 (24–45)	99.4 (97.0–100)	68 (62–73)

Score ≥ 0.54 (Low/intermediate vs high risk)

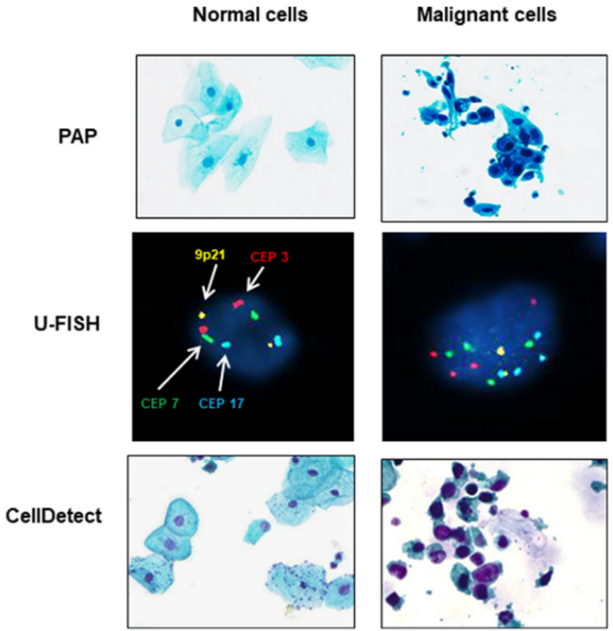
Triage Plus at the 0.54 threshold	N	Performance characteristic, % (95% CI)				
		Sensitivity	Specificity	PPV	NPV	TNR
Overall population	587	60 (45–74)	95 (93–97)	51 (37–64)	96.4 (94.5–97.8)	90 (88–93)
AUA MH risk category[a]						
Low/negligible	17	NA	100 (80–100)	NA	100.0 (80.5–100)	100 (80–100)
Intermediate	49	NA	98 (89–100)	0 (0–97)	100.0 (92.6–100)	98 (89–100)
High	254	56 (31–78)	96 (93–96)	53 (29–76)	96.6 (93.4–98.5)	93 (89–95)
GH	267	63 (44–80)	92 (88–95)	51 (34–68)	95.2 (91.6–97.6)	86 (81–90)



Salvage et al 2026, Urol Oncol

CellDetect and Urovysion

- 264 patients with suspicious BC (128 with BC; 97 HG, 25 ≥ T2)



Shefer et al 2023, Urol Oncol

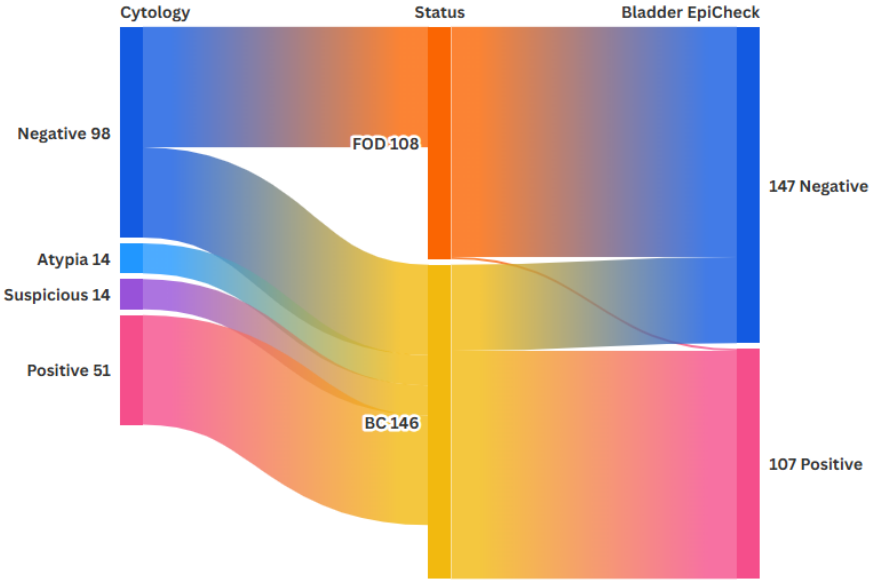
Table 2 Diagnostic value of CellDetect, FISH and cytology in UC

	CellDetect		FISH		Cytology	
	+	−	+	−	+	−
UC	106	22	107	21	51	77
Non-UC	16	120	13	123	19	117
Sensitivity (%)	82.8		83.6		39.8	
Specificity (%)	88.2		90.4		86.0	

Shang et al 2021, Can Cell Int

Bladder EpiCheck

- 254 patients with symptoms suggestive of BC (146 with BC; 94 HG, 25 ≥ T2)



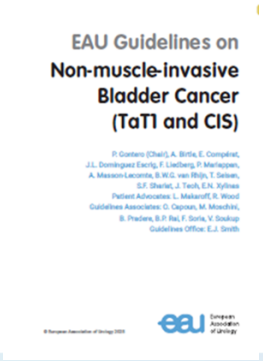
	Primary BC diagnosis	
	BE	**Cytology**
N samples	254	177
AUC (95% CI)	0.858 (0.811-0.906)	0.711 (0.637-0.784)
Sensitivity %, (95% CI)		
Overall	73 (65-79)	42 (34-51)
HG	92 (84-96)	60 (49-70)
Specificity %, (95% CI)	99 (95-100)	100 (94-100)

Figueras et al 2026, J Transl Med

Why are we not using these tests more?

Setting of primary diagnosis (hematuria evaluation)

- ✓ Many studies rely on **case-control designs** with artificially high disease prevalence (can lead to overestimated test performance, especially PPV)
- ✓ Limited validation of biomarkers beyond the initial discovery phase, with few studies assessing **real-world performance**


EAU Guidelines on
Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

5.7.2 ***Investigation of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)***

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, specificity is particularly important. Recently, CellDetect® and UroVysion™ have shown similar performance to detect BC and were both superior to cytology [136]. In addition, Xpert Bladder® had higher sensitivity and negative-predictive value than both cytology or UroVysion™ for the detection of BC in patients with haematuria [137].

NMIBC surveillance: urine biomarkers

ruling out disease and **not missing recurrence**

- **High SN:** identify patients with recurrence; avoid missing any HG tumor
- **High NPV:** test negative -> ↑probability that there is no tumor

Table 3
Commercially available biomarkers for bladder cancer surveillance

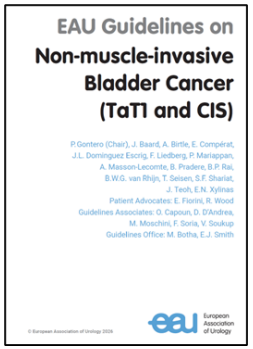
Class	Marker	Molecule	Reference	Yea	Sensitivity	Specificity
Protein	BladderChek (Alere NMP22 Bladder, Abbot Labs)	Nuclear Matrix Protein 22	Van Rhijn et al	200	71%	73%
	Bladder tumor antigen (Polymedco, USA) – POC and ELISA	Complement Factor H-related protein	Van Rhijn et al	200	58% (POC) 71% (ELISA)	73% (POC) 66% (ELISA)
Cell Based	Cytology	–	Freifeld et al	201	40.8%	92.8%
	UroVysion (Abbott Laboratories)	Fluorescence in situ hybridization	Dimashkieh et al	201	62.2%	86.2%
RNA	Cxbladder Monitor	*IGF, HOXA, MDK, CDC, IL8R*	Lotan et al,[11] 2009	201	91%	–
	Xpert BC	*ABL1, CRH, IGF2, UPK1B, ANXA10*	Pichler et al	201	84%	91%
DNA	Bladder EpiCheck (Nucleix)	Multigene methylation assay	Wasserstrom et al,[48] 2016	201	90%	83%

Lotan et al 2023, Urol Clin North Am

1. Detect HG recurrences

Table 8.1: Performance of multiplex urine markers in the surveillance setting

Multiplex urinary marker	Target	Sensitivity Overall*	HG*	Specificity Overall*	HG*	N studies/patients
XPERT BC® MONITOR [124]	5 mRNAs	52-91	79-100	41-91	76-91	11 studies 2,800 pts
EpiCheck™ [123]	15 DNA methylations	62-90	78-95	82-88		6 studies 2,236 pts
CX BLADDER [465]	5mRNAs	93	95	61	-	1 study 763 pts
UROMONITOR [466]	DNA mutations FDFGR3+TERT+K ras	49-93	-	86-99	-	5 studies 1,190 pts
Galeas Bladder [467]	Multiple DNA mutations (n= 443 in 23 genes)	86	100	63	-	1 study 293 pts

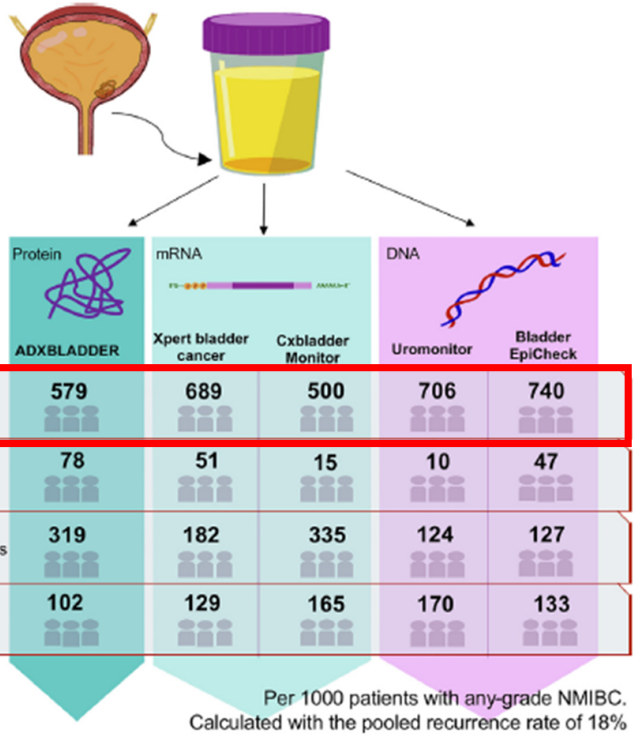


2. Avoid unnecessary cystoscopies

Discomfort, side effects, TURBT

3. Decrease costs

Dutch Healthcare could save up to **1.6M/yr**



Laukhtina et al 2021, Eur Urol Oncol

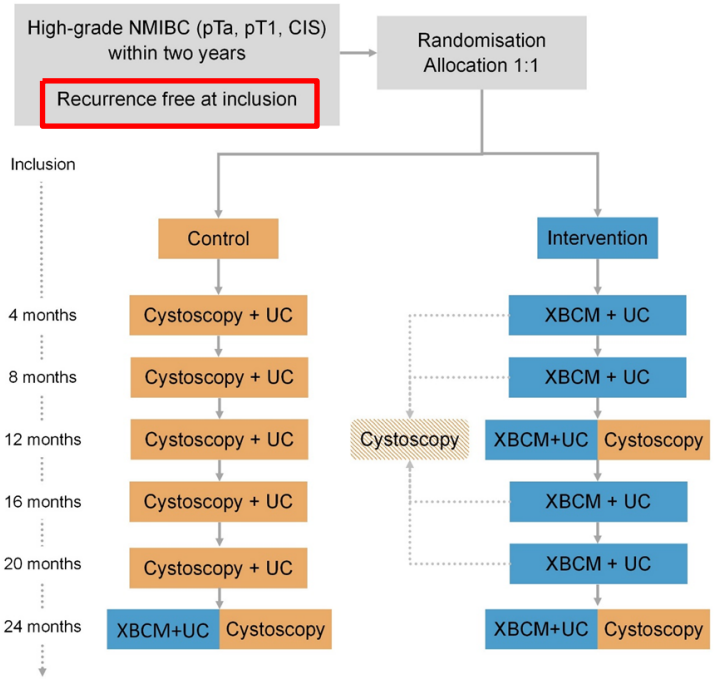
Why are we not using these tests more?

Setting of surveillance (recurrence detection)

- ✓ Patients are more likely to have a tumor; **fear of missing a life-threating tumour** by urologists and patients
- ✓ **"Anticipatory positive result"** difficult to interpret (positive test before clinical evidence of recurrence)
- ✓ Up to 2025, lack of prospective studies defining consequence of a positive or negative test (**No RCTs**)

In the current absence of randomised trials investigating marker guided use of urinary molecular markers with non-inferiority design in predefined NMIBC risk groups, high-level evidence for clinical implementation is currently lacking. Consequently, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. Nonetheless, some urinary markers, chiefly those detecting multiple genetic alterations in the urine (so-called "multiplex" urine markers), have shown fairly high sensitivities to detect tumour recurrence, particularly in HG disease, along with very high NPVs to make the premises for their future implementation in follow-up [460, 462-464] (Table 8.1). Table 8.2 summarises the current recommended follow-up scheme for NMIBC according to the disease risk category.

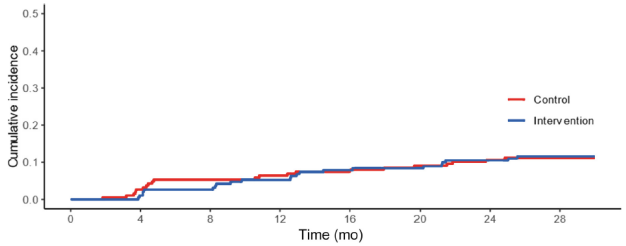
DaBlaCa-15 Trial



- Evaluate whether alternating the urinary biomarker **Xpert Bladder Cancer Monitor** (**XBCM**) with cystoscopy during follow-up can reduce the number of cystoscopies in patients with **HG NMIBC**
- **Prospective, multicenter, randomized non-inferiority** (RCT)
- **N=392** HG NMIBC patients (2019-2024)
- **Control arm**: Cystoscopy + cytology every 4 mo
- **Intervention arm**: XBCM + cytology every 4 mo, with mandatory cystoscopy at 12 and 24 mo.
- **Primary end point**: Recurrence-free survival (RFS) for HG NMIBC, MIBC or metastatic UC over 24 mo

Dreyer et al, Eur Urol 2025

DaBlaCa-15 Trial



Maintains oncologic safety

Provides **the first RCT-level evidence** supporting that alternating cystoscopy with a urinary biomarker is effective for HG NMIBC surveillance

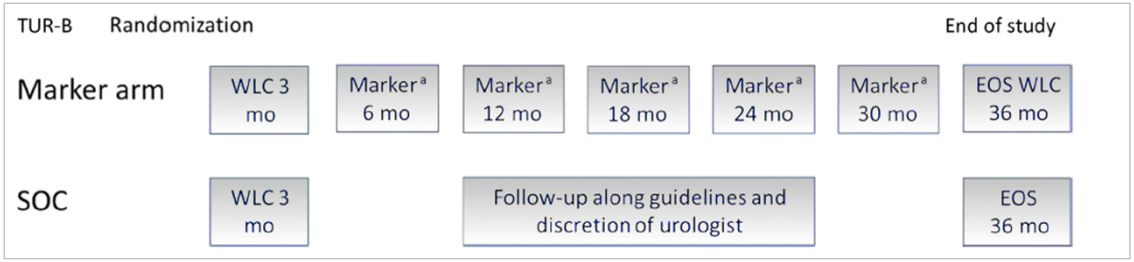
Test performance

SN 91%
NPV 99%
↓ Cystoscopies ≈ 55%
Anticipatory effect 59%

Bladder EpiCheck: patients neg.cystoscopy/ pos. biomarker test were **5.3 times** more likely to experience recurrence

(Fleshner et al, 2025 Bladder Cancer)

Uro*Follow* Trial



Multicenter randomized controlled trial (RCT)

N=214 patients with Ta G1-2/HG (2016-2022)

Standand of care (SOC) arm: Cystoscopy-based follow-up
Marker-algorithm (MA) arm: 6-monthly marker-based follow-up; cystoscopy only if MA positive after a negative 3-mo WLC.

Primary end point: (1) noninferiority of the MA compared with the SOC arm and (2) patient safety (detection **High Impact Tumor (HIT)**: HG Ta, Tis, or >T1)

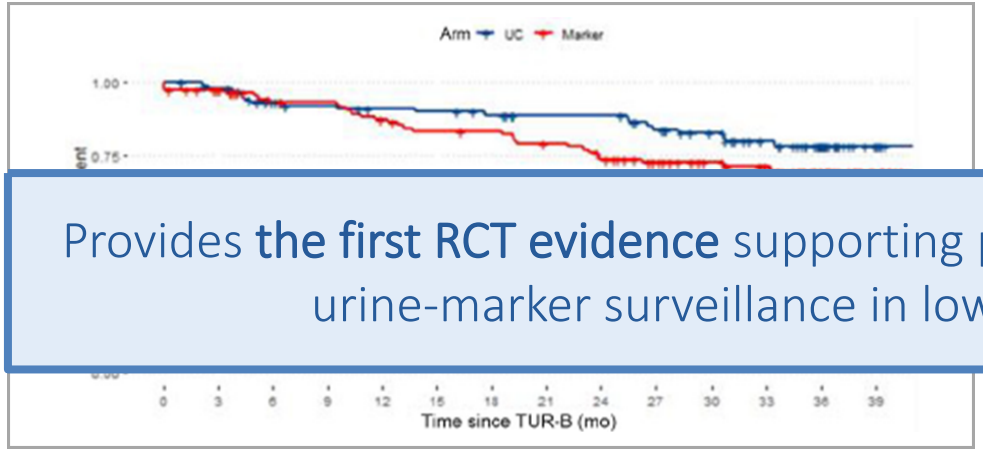
- Compared Marked-guided vs cystoscopy-based surveillance in low/intermediate–risk NMIBC patients

MA
Urine cytology
UroVysion FISH
NMP22
Ultrasound

Additional exploratory markers
XBCM
ADX-Bladder
UBC Rapid
CellDetect
BladderEpiCheck

Schmitz-Drager et al, 2025 Eur Urol Oncol

Uro*Follow* Trial



Maintains oncologic safety

MA

Provides **the first RCT evidence** supporting partial cystoscopy replacement by urine-marker surveillance in low/intermediate NMIBC

Missed HIT rec. **0** **0**

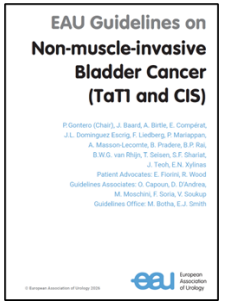
No. cystoscopies **148** **Vs** **549**

↓Cystoscopies ≈ 75%

Exploratory markers SN
XBCM 79%
BladderEpiCheck 86%
Both detected all HIT rec.

EAU guidelines 2026

Setting of surveillance (recurrence detection)



8.1.5.d Urinary molecular markers

Non-invasive follow-up strategies include urinary cytology and urinary molecular marker tests as an adjunct test to improve detection of HG disease at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies (marker guided use). In order to reduce or replace cystoscopy altogether, urinary markers should be able to detect recurrence in all or specific risk groups. However, the reported low sensitivity for LG recurrences limits their utility in this group [141, 514] although more recent studies have shown reasonable sensitivity of 40-65% in detecting LG recurrences [515, 516].

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hypothesis. However, the marker or combination of markers to be adopted remains unclear [127]. In patients with HG tumours and a negative follow-up cystoscopy, alternating the urine marker with current standard surveillance (a cystoscopy at follow-up year one and two) significantly reduced the number of follow-up cystoscopies without affecting detection of any recurrence at a median of two years follow-up [127]. XPERT BC® MONITOR showed high sensitivity (91%) for the detection of HG disease at the price of 16% PPV (false positive result in nearly one out of three patients). Table 8.2 summarises the current recommended follow-up scheme for NMIBC according to the disease risk category.

Take home message

Urinary biomarkers address **key limitations of cystoscopy**: discomfort, cost, inaccuracy and side effects

Currently, **none of the commercially available tests can replace cystoscopy** for **primary diagnosis** of bladder cancer

Level one evidence supporting the use of urinary biomarkers in the **follow-up of NMIBC**

- **DaBlaCa-15** supports non-inferiority of Xpert Bladder Cancer Monitor vs cystoscopy in HG NMIBC surveillance
- **UroFollow Trial** supports partial cystoscopy replacement by urine-marker surveillance in low/intermediate NMIBC

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Real world evaluation of the bladder urine test

Dra. Lourdes Mengual

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