Urinary biomarkers in bladder cancer surveillance: where do we stand?

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Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
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Stock shareholder	None
Other support (please specify):	None

Definitions

Marker	Measurable indicator of outcome: disease presence, recurrence, progression, response
Biomarker	Marker that serves as surrogate of biology Marker that is validated and re-evaluated = biomarker

Why are urinary markers attractive?

- Cystoscopy gold standard for surveillance
- Invasive
- Expensive
- Time consuming
- Limited resources
- Up to 10% of significant lesions still missed by cystoscopy
- Complications (UTI, haematuria)

Replace or deintensify cystoscopic surveillance

The good urinary marker

- Rapid
- Objective
- Easy to perform and interpret
- High sensitivity and specificity
- Reproducible
- Cost-effective

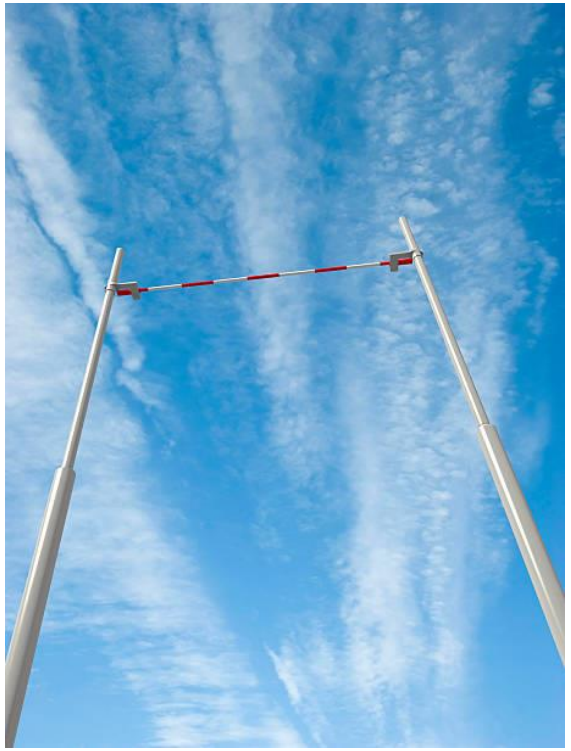
Use of Urinary Biomarkers for Bladder Cancer Surveillance: Patient Perspectives

Ofer Yossepowitch, Harry W. Herr and S. Machele Donat*

From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York

75% if urine test >95% accurate

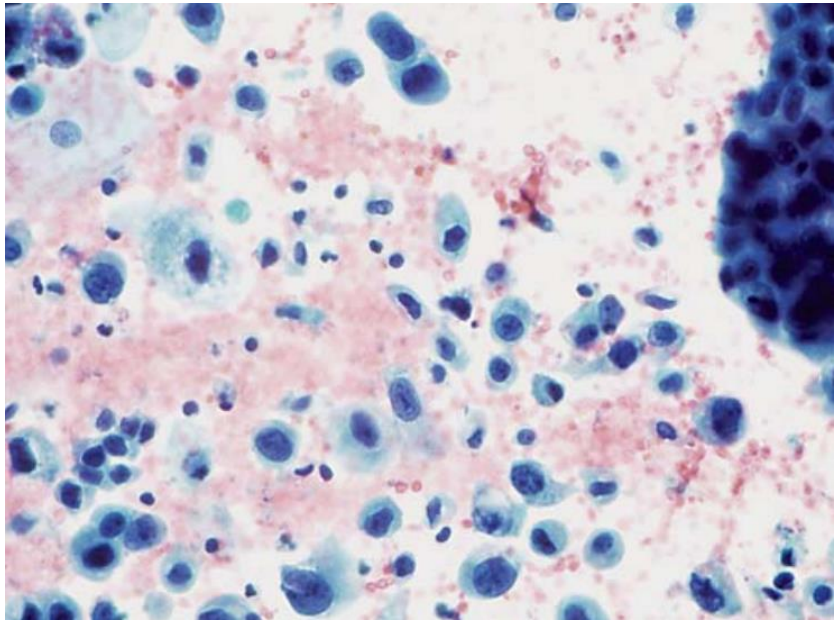
+21% if urine test 90 to 95% accurate



Yossepowitch et al. J Urol 2007

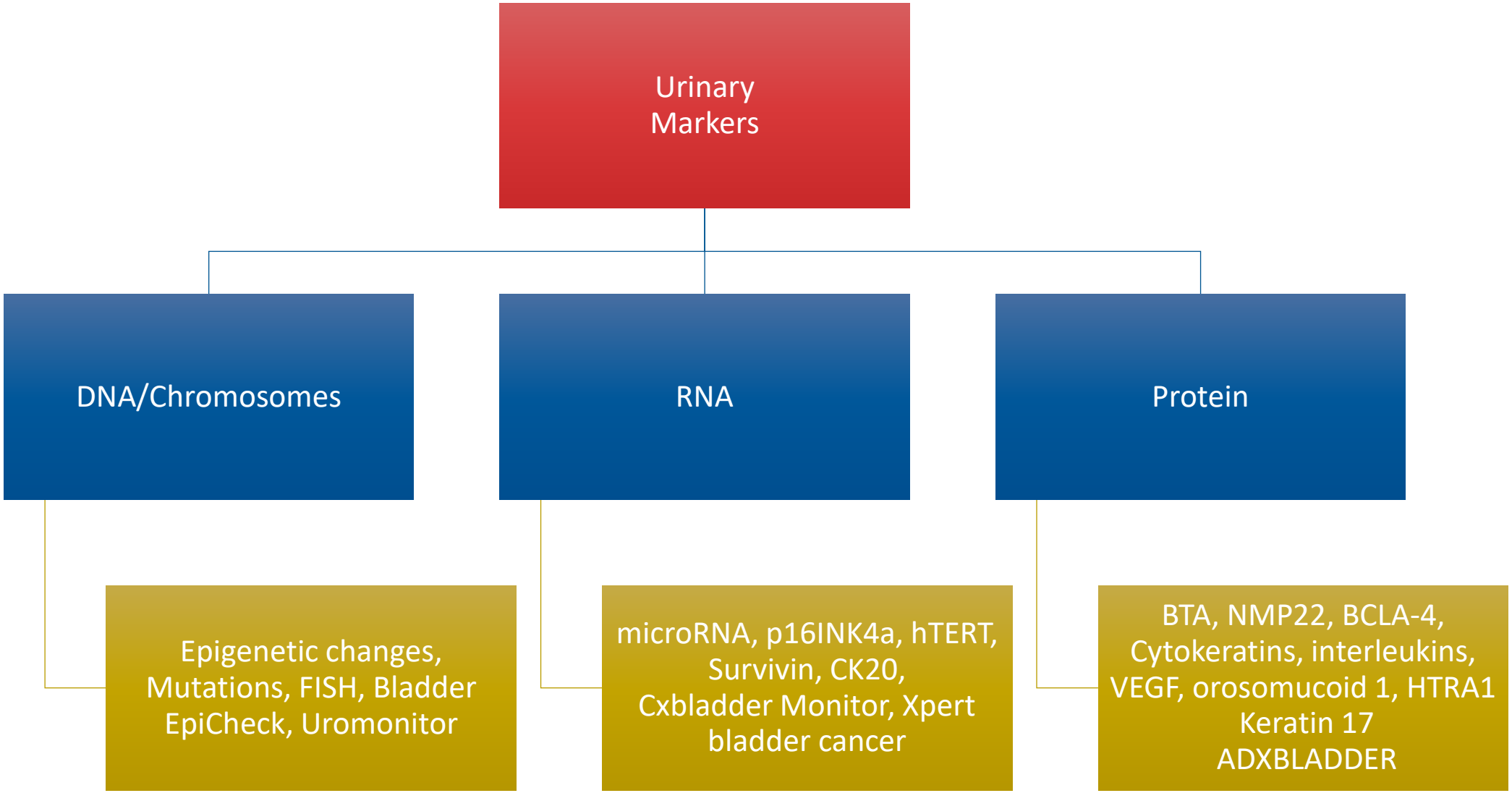
Urinary cytology

- Established together with cystoscopy
- Overall sensitivity 44%
  - Sensitivity for low grade 4-31%
  - Sensitivity for high grade 70-80%
- Specificity 96%
- Variability in interpretation
- Paris system
  - Improved sensitivity
  - Improved negative predictive value
  - AI-assisted diagnosis (Kappa >0.95)



High grade urothelial carcinoma

Mowatt et al. Health Technol Assess 2010
Barkan et al. Acta Cytologica 2016
Yamasaki et al. BMC Urol 2022
Yuan et al. Diagn Cytopathol 2022
Ou et al. Cancer Cytopathol 2022


Urinary Markers
DNA/Chromosomes
RNA
Protein
Epigenetic changes, Mutations, FISH, Bladder EpiCheck, Uromonitor
microRNA, p16INK4a, hTERT, Survivin, CK20, Cxbladder Monitor, Xpert bladder cancer
BTA, NMP22, BCLA-4, Cytokeratins, interleukins, VEGF, orosomucoid 1, HTRA1 Keratin 17 ADXBLADDER

FDA-approved tests (20+ years ago)

Name	Antigen	Approval	Assay type
BTA Stat	Bladder tumor associated antigen	Diagnosis, follow-up	Colorimetric Antigen-Antibody reaction (point of care) [qualitative]
BTA TRAK	Bladder tumor associated antigen	Diagnosis, follow-up	Sandwich ELISA [quantitative]
NMP22	Nuclear matrix protein 22	Diagnosis, follow-up	Colorimetric Antigen-Antibody reaction (point of care) [qualitative, BladderChek]
NMP22	Nuclear matrix protein 22	Follow-up	Sandwich ELISA [quantitative]
ImmunoCyt/uCyt+	High-MW form of glycosylated CEA and MUCIN-like antigens	Follow-up	Fluorescent antibody cytology
UroVysion	Aneuploidy chromosomes 3, 7, 17, loss of 9p21	Diagnosis, Follow-up	FISH

Sensitivity and Specificity

Marker	%Sensitivity	%Specificity	%Sensitivity high grade
BTA Stat	29-83	56-86	62-75
BTA TRAK	53-91	28-83	74-77
NMP 22	47-100	55-98	75-83
Immunocyt/uCyt+	52-100 (M81)	63-75 (M75)	62-92
UroVysion	30-86 (M64)	63-95 (M73)	66-70

ADXBLADDER

- ELISA minichromosome maintenance protein (MCM) 5
- Relatively easy to perform
- Costs: 50-60 £/$/€ per test

Author	Setting	N	Sensitivity	Specificity	NPV
Dudderidge 2020	Diagnosis	856	OV: 73% HG: 86%	70-73%	96-100%
Anastasi 2020	Diagnosis	91	OV: 60% LG: 48% HG: 88%	88%	74%
Roupret 2020	Follow-up	1431	OV: 45% HG: 76%	71%	93%

Modified from: Wolfs et al. Urol Oncol 2021

ADXBLADDER during surveillance

- 1431 patients with NMIBC undergoing cystoscopic surveillance, 127 were found to have recurrence

	%Sensitivity	%NPV
All tumors	45	93
Stage		
pTa	38	93
pT1	75	100
pT2	100	100
All CIS*	71	100
Grade		
LG	30	94
HG	73	99
pTaLG	30	94
nonpTaLG	76	99

PPV = 13%
(those with a positive test that have bladder cancer)

Roupret et al. J Urol 2020

Bladder EpiCheck

- real-time PCR-based urinary test that detects changes in DNA methylation in a panel of 15 genomic biomarkers, EpiScore 0 to 100, 60+ positive
- Costs: 300 £/$/€ per test

Author	Setting	N	Sensitivity	Specificity	NPV	PPV
Wasserstrom 2016	Follow-up	222	OV: 90% HG: 95%	83%	97%	-
D'Andrea/Witjes 2019	Follow-up	357	OV: 67% HG: 89%	88%	94%	47%
Trenti 2019	Follow-up	243	OV: 62% HG: 83%	86%	79%	68%
Trenti 2020	Follow-up	487	OV: 64% HG: 79%	82%	89%	49%
Pierconti 2021	Follow-up	325	HG: 73%	HG: 71%		

Modified from: Wolfs et al. Urol Oncol 2021

Bladder EpiCheck – economic study

- Standard surveillance versus alternating cystoscopy with test in low grade intermediate risk NMIBC
- 2 year model

Country	Austria	Belgium	France	Germany	Italy	Netherlands	Spain	Switzerland	UK	USA
Currency	€	€	€	€	€	€	€	CHF	£	$
Marker cost parity point	289	277	161	184	301	349	148	401	365	421

Lotan et al. Bladder Cancer 2021

EUROPEAN UROLOGY ONCOLOGY 4 (2021) 927–942

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology .com

European Association of Urology

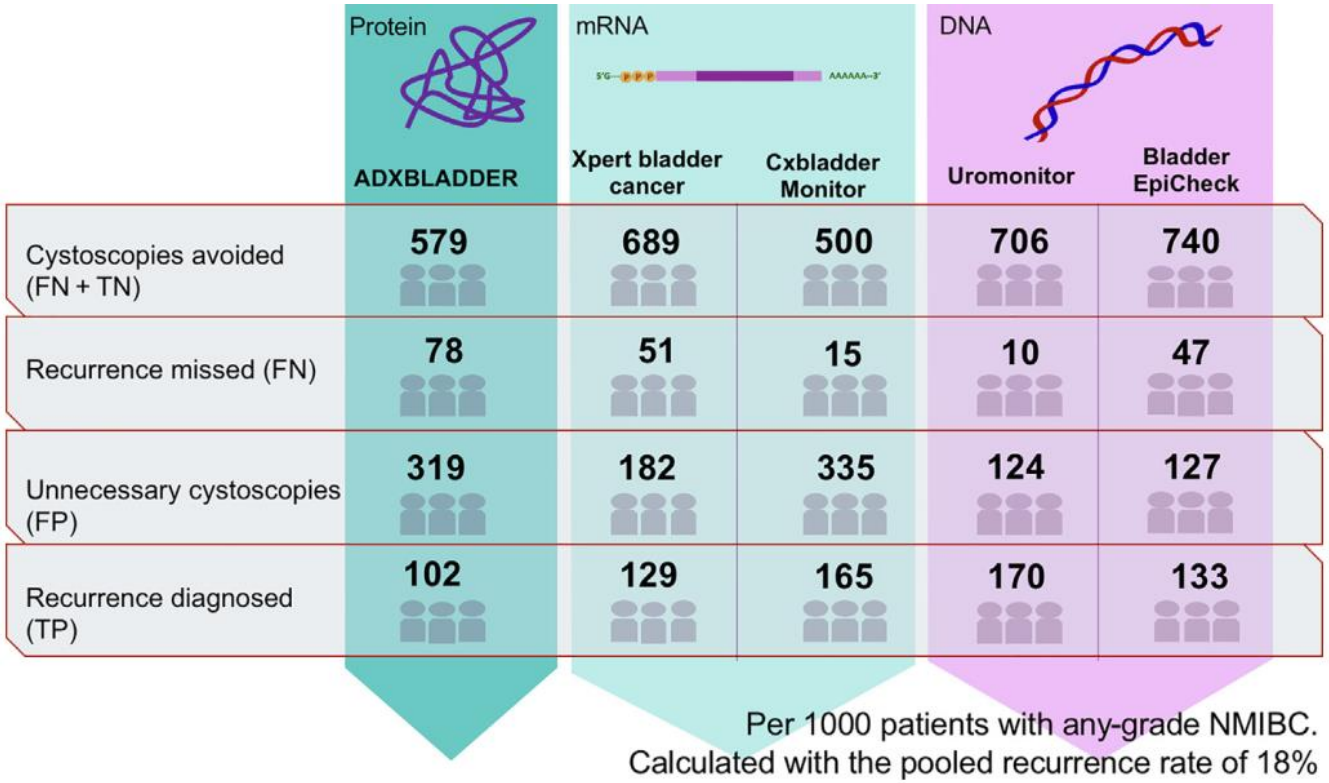
Review - Bladder Cancer

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

	Source	N studies	%Sens	%Spec	%PPV	%NPV	%AUC	
Xpert bladder cancer	RNA	10	72	76	43	92	81	*
Bladder EpiCheck	DNA	5	74	84	48	94	87	*
ADXBLADDER	Protein	3	57	62	29	82	60	*
Uromonitor	DNA	2	93	79	67	96	92	
Cxbladder monitor	RNA	2	94	61	16	98	92	*

* Significant heterogeneity

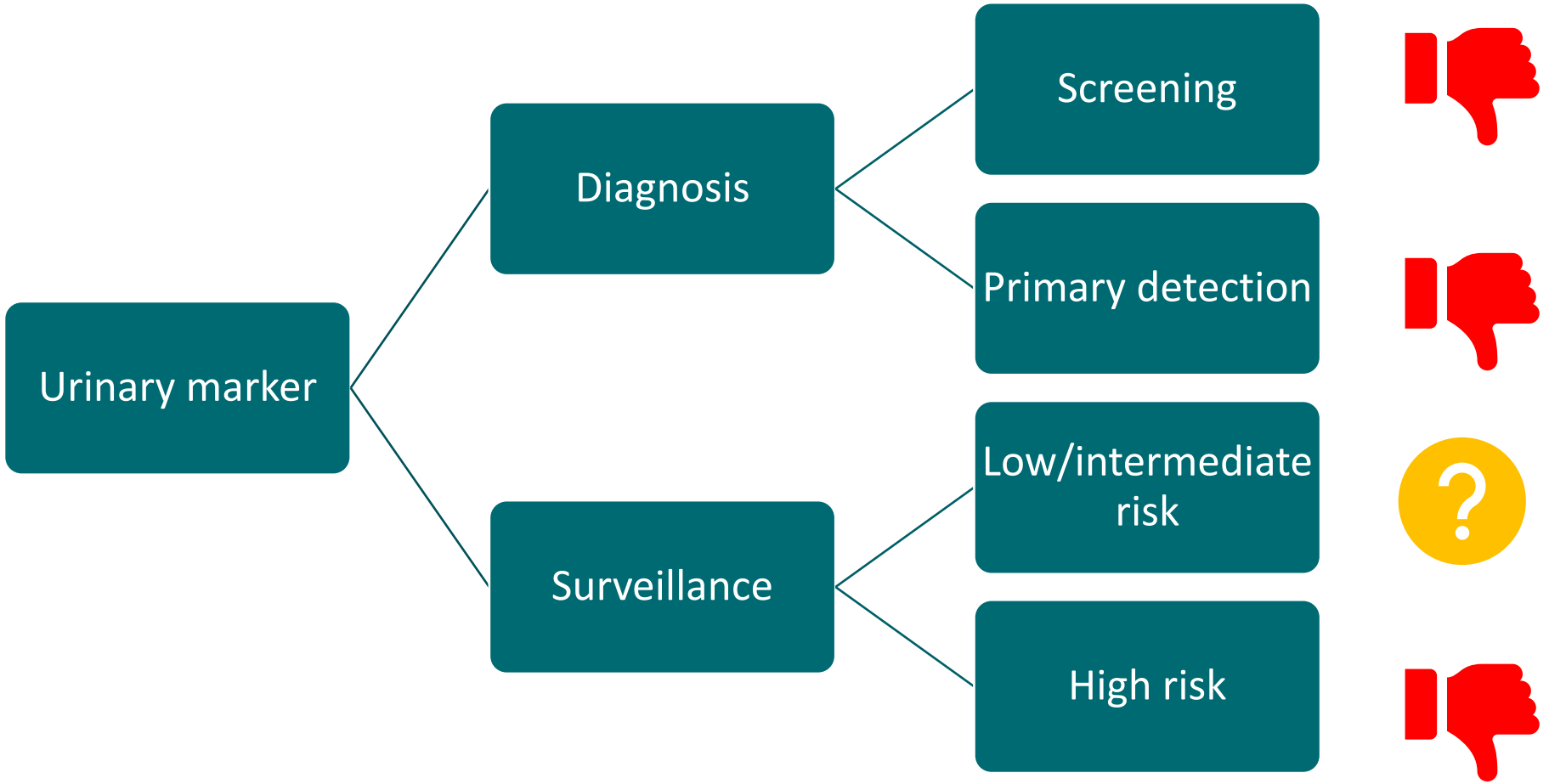
Laukhtina et al. Eur Urol Oncol 2021



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.

Laukhtina et al. Eur Urol Oncol 2021

Potential use of urinary markers

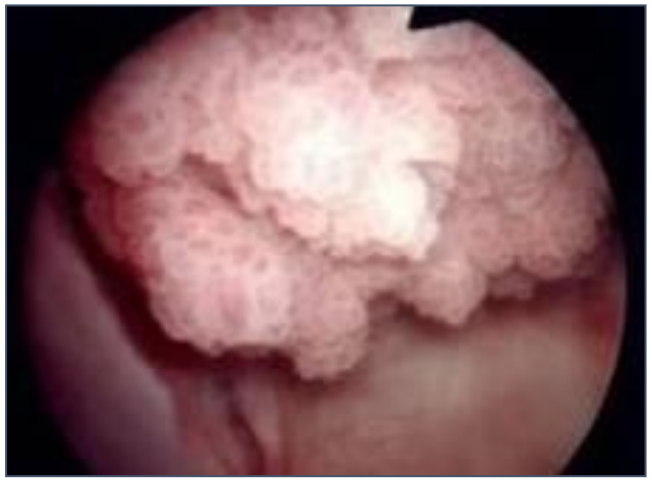


Surveillance I

- High risk
  - Goal: to detect recurrent tumors early
  - High sensitivity and specificity needed
  - Adjunct to cystoscopy
  - Urinary markers other than cytology not recommended

Surveillance II

- Low risk disease
  - Based on current levels of evidence, no urine marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency
  - <u>Not recommended</u>



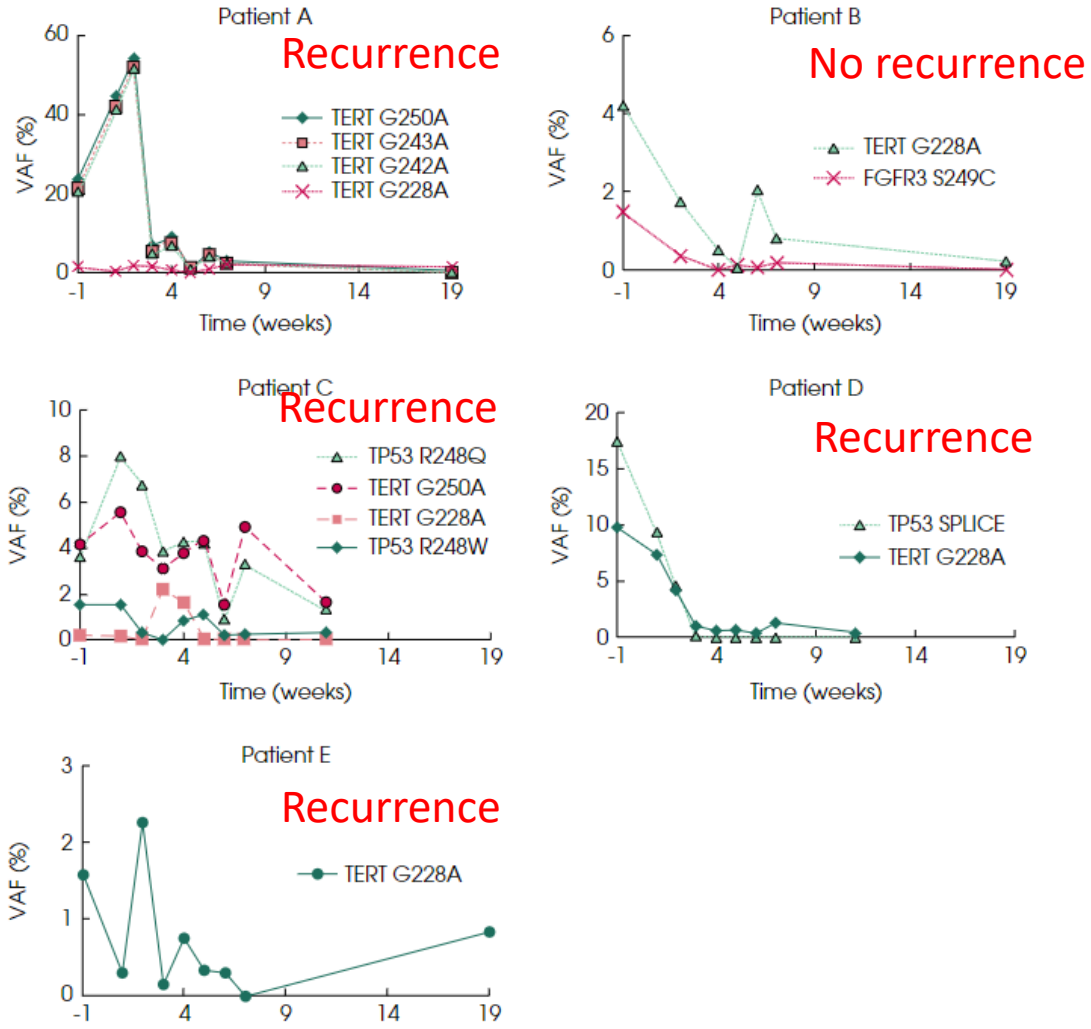
EAU guidelines 2022

Low risk NMIBC	Cystoscopy @3 months and 12 months, then annually for 5 years
High risk NMIBC	Cystoscopy and cytology every 3 months for 2 years, then every 6 months for 3 years, then annually
Intermediate risk	Individualised

In patients initially diagnosed with Ta LG/G1–2 bladder cancer, use ultrasound of the bladder, and/or a urinary marker during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

Urine DNA for monitoring chemoradiotherapy response in muscle-invasive bladder cancer: a pilot study

- Part of the TUXEDO trial, panel of 29 genes
- Urine before, during and after treatment
- 2 of 4 patients who relapsed had undetectable variant allele frequencies
- Combination with plasma ctDNA?



Gordon et al. BJU Int 2022

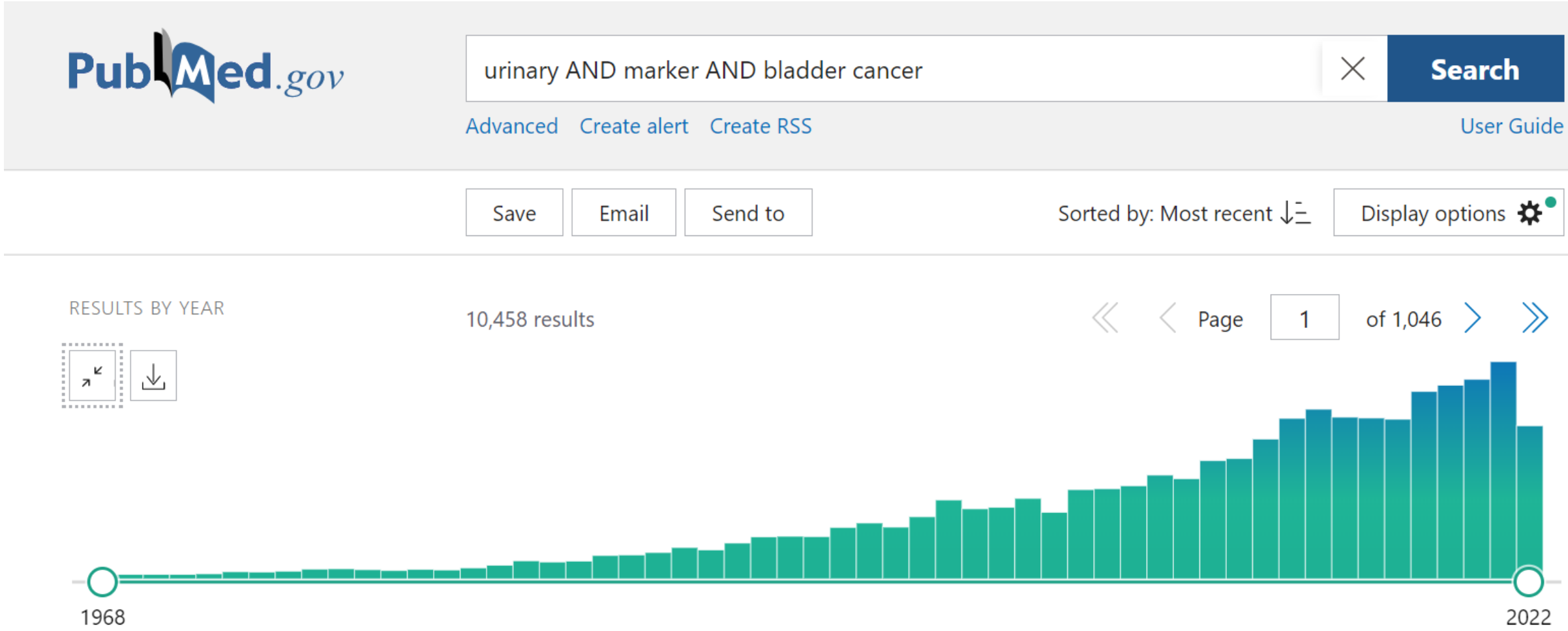
Issues

- Performance complexity (laboratory, stones, inflammation, instillation)
- Conflicting results (lower sensitivity)
- No comparison with cystoscopy as gold standard/reference (lead time for test?)
- Costs for infrastructure
- Research environment (?reproducible)
- Lack of validation studies

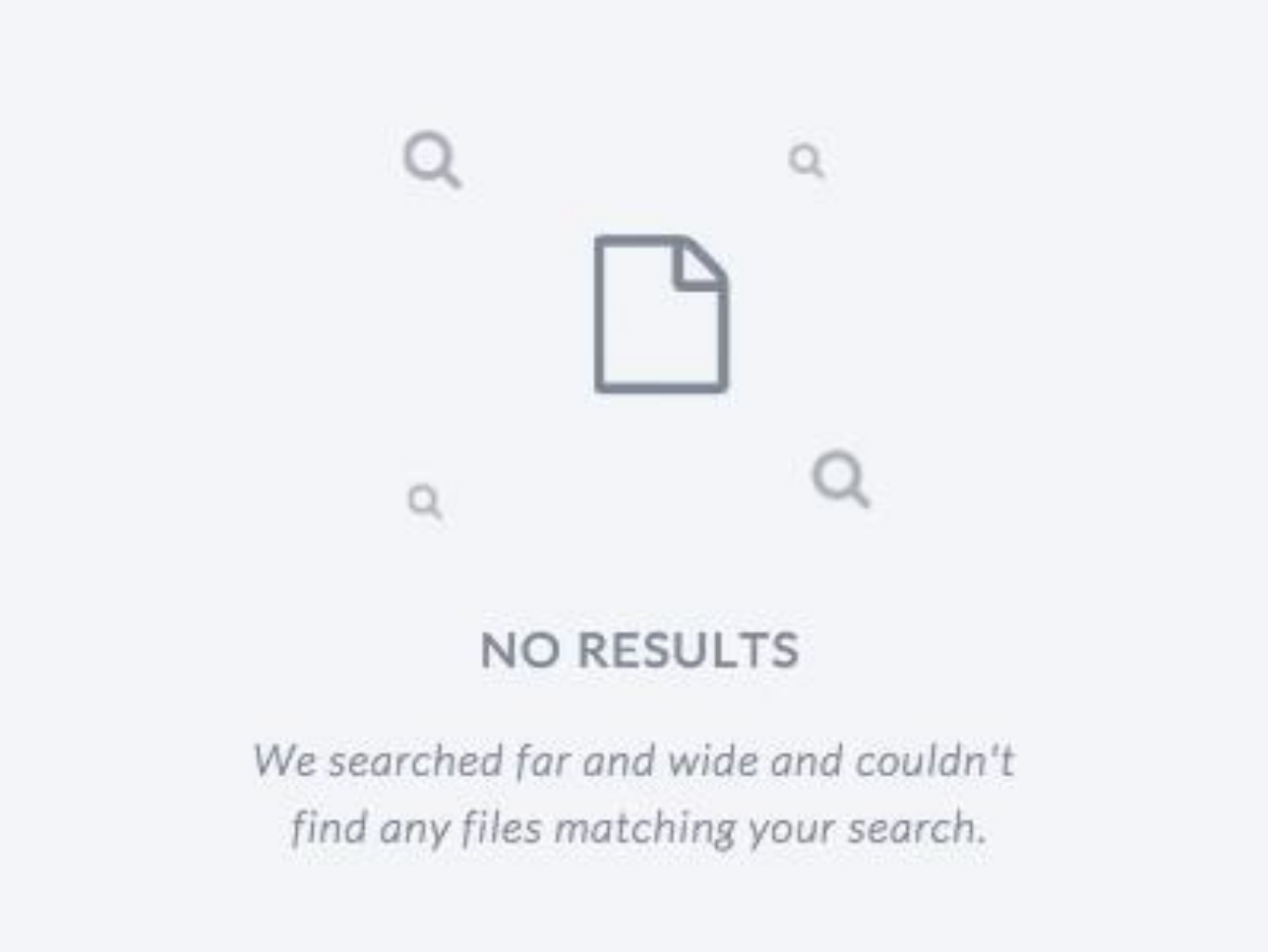
Conclusions

- Sensitivity is usually higher compared to urinary cytology
- Specificity is lower compared to urinary cytology
- No test has consistently demonstrated superior clinical utility to cystoscopy and cytology
- Unlikely that a single test will be identified for the different clinical scenarios because of molecular heterogeneity
- Not recommended by guidelines

Summary – urinary molecular markers



Summary – urinary molecular biomarkers



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Can urinary markers replace cystoscopy during surveillance?

No

Can urinary markers replace cystoscopy during surveillance?

No **Not yet**

Thank you!