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How ctDNA and utDNA are reshaping treatment pathways in bladder cancer

Implications for early access, health technology assessment (HTA) and reimbursement

BACKGROUND

Circulating tumor DNA (ctDNA) and urinary tumor DNA (utDNA) are minimally invasive biomarkers increasingly used to detect molecular residual disease and recurrence risk in bladder cancer. Recent studies suggest these biomarkers may move beyond prognostic assessment to guide treatment selection, escalation, and de-escalation strategies. As biomarker-guided treatment approaches emerge, continuous evidence monitoring becomes important for HTA, reimbursement, and clinical decision-making.

OBJECTIVES

To characterize the evolving role of ctDNA and utDNA in muscle-invasive (MIBC) and non-muscle-invasive bladder cancer (NMIBC) using **Oncoscope** Real-Time AI-Assisted Living Systematic Literature Review **(REAL-SLR)** database.

METHODS

Oncoscope REAL-SLR is a **PRISMA-aligned, continuously updated** evidence database organized by tumor type, including bladder cancer. REAL-SLR systematically identifies and structures the evidence from interventional clinical trials, regulatory approvals, clinical guidelines, and HTA reviews with daily updates. Studies are mapped according to clinical stage, treatment pathway, biomarker application, study design, and regulatory/guideline status.

RESULTS

- As of June 18th 2026, the REAL-SLR included 553 bladder cancer studies. 24 evaluated ctDNA and/or utDNA as predictive (n=20) or treatment-guiding (n=7) biomarkers.
- IMvigor011 and TOMBOLA demonstrated improved outcomes with adjuvant atezolizumab following radical cystectomy in ctDNA-positive MIBC population.
- DECIDING-I evaluated ctDNA/utDNA for early relapse detection, while another study demonstrated immunotherapy de-escalation in very high-risk NMIBC patients achieving complete response and negative utDNA.
- ctDNA was more frequently associated with survival-related outcomes (14 studies), whereas utDNA more commonly predicted local bladder outcomes and pathological complete response (7 studies).
- Evidence suggests ctDNA better reflects systemic recurrence risk, while utDNA may be more sensitive for residual intravesical disease.

KEY TAKEAWAYS

ctDNA and utDNA are EVOLVING from prognostic biomarkers into tools that directly influence treatment selection, escalation, and de-escalation decisions in bladder cancer.

This transition creates new biomarker-defined populations, treatment pathways, and comparator frameworks that may substantially AFFECT future trial designs, HTA, reimbursement, and VALUE-ASSESSMENT processes.

LIVING EVIDENCE approaches support identification of emerging evidence requirements and inform biomarker-driven treatment strategies.

Figure 1. **Continuously updated PRISMA (REAL-SLR framework) in bladder cancer**
(updated Jun 18, 2026)

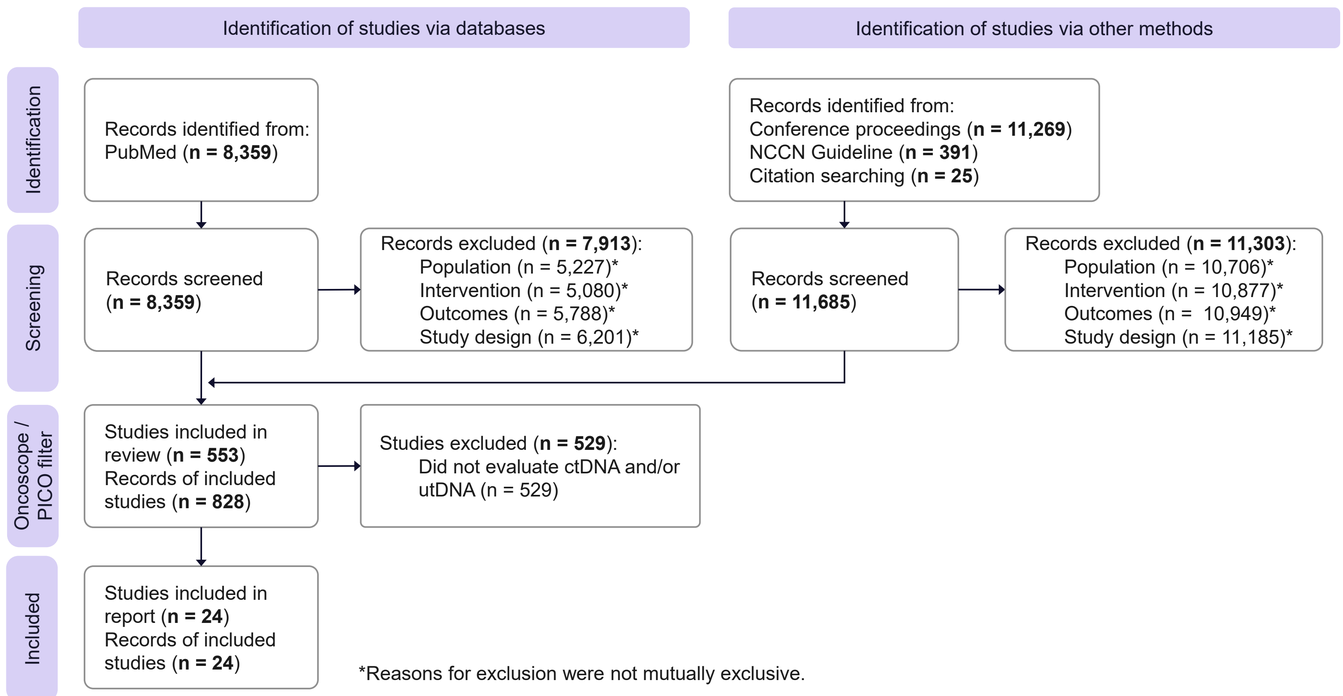


Figure 2. **REAL-SLR evidence capture summary (as of June 18, 2026)**

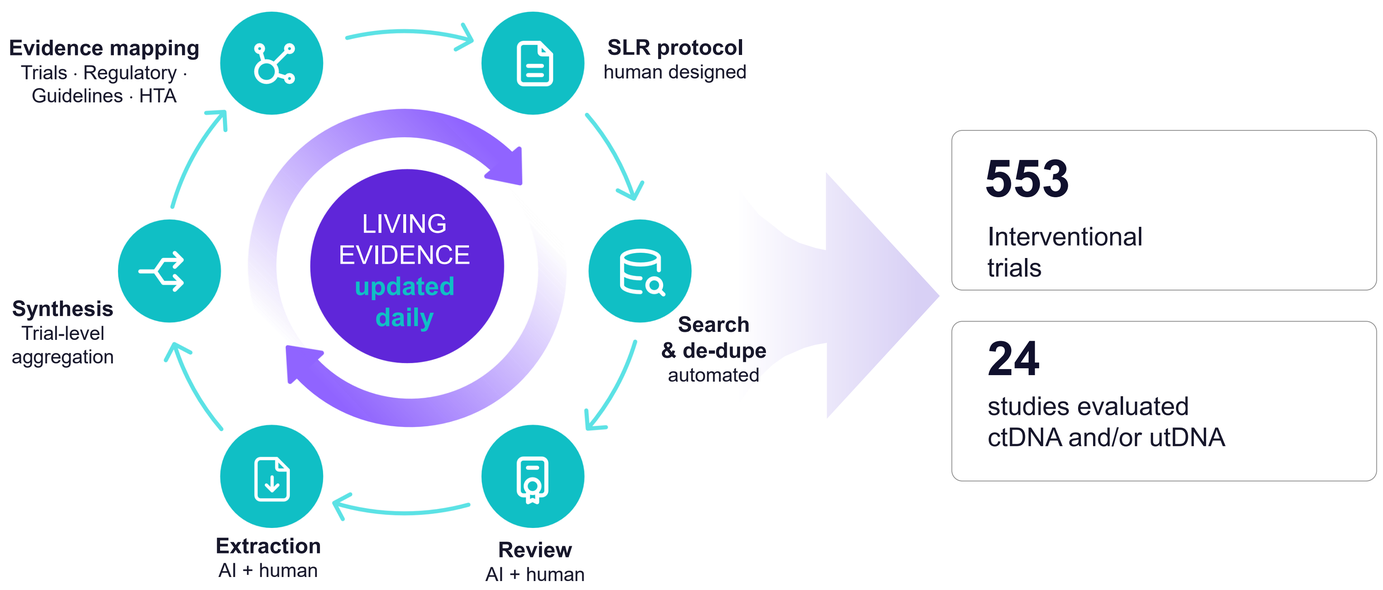


Figure 3. **Purpose and clinical signal of biomarker assessment**

20	7	14	7
studies with prognostic / predictive evidence	studies informing treatment guidance	plasma ctDNA studies	urine utDNA studies
Response, recurrence, survival	Escalation, surveillance, de-escalation	Survival, systemic recurrence	Bladder outcomes, pathological CR

Figure 4. **ctDNA and utDNA guiding treatment decisions**

Plasma ctDNA · adjuvant therapy and bladder sparing in MIBC

IMvigor011 — **Phase 3** · N=761
Post-RC · no radiographic disease · serial ctDNA for up to 1 year

Serial ctDNA	ctDNA+	(n=250) atezolizumab vs placebo (2:1)
	ctDNA−	(n=357) persistently negative · no adjuvant therapy

ctDNA+: DFS **9.9 vs 4.8 mo** (HR 0.64); OS **32.8 vs 21.1 mo** (HR 0.59)
ctDNA−: 2-year DFS 88% without treatment

TOMBOLA — **Phase 2** · N=192
Post-NAC + RC · serial tumor-informed ctDNA

Serial ctDNA	ctDNA+	atezolizumab started irrespective of imaging
	ctDNA−	immunotherapy only at radiographic relapse

1-year RFS **97% (ctDNA−) vs 76% (ctDNA+)**; complete response 60% (50/84) in treated ctDNA+; median lead time to imaging relapse 90 days

Response-adapted bladder sparing · ctDNA exploratory (allocation by cCR / genomics)

HCRN GU 20-444 — **Phase 2** · N=46
cCR after pembrolizumab → RC omitted.
Undetectable cycle-1 ctDNA: **MFS HR 11.2**, **OS HR 11.4**

RETAIN-1 / RETAIN-2 — **Phase 2** · N=111
DDR mutation + cCR → active surveillance.
Post-treatment ctDNA− vs +: recurrence **34.8% vs 85.7%**

Urine utDNA · bladder preservation and treatment de-escalation

PUNCH02 — Phase 2 · N=28 · HER2+ MIBC
Max TURBT → tislelizumab + disitamab vedotin ×4 → restaging · non-cCR → RC

utDNA in cCR patients	utDNA−	bladder preservation
	utDNA+	bladder preservation or RC (patient choice)

utDNA-defined cCR **71.4%**; bladder preserved in 100% of utDNA-defined cCR

DECIDING-1 — **Phase 2** · N=6 · HER2+ MIBC
Disitamab vedotin + toripalimab + RT · longitudinal utDNA and ctDNA

Serial utDNA	Response tracking and relapse surveillance during organ-sparing therapy

CR **5/6**; utDNA detected the single relapse early; plasma ctDNA largely undetectable

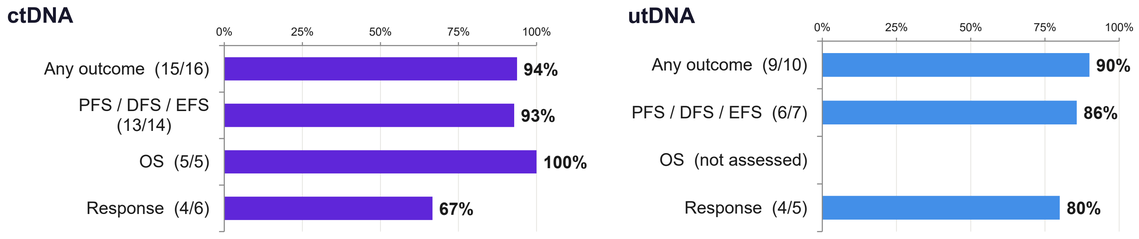
utDNA-guided de-escalation — **Cohort** · N=54 · NMIBC
Extensive very-high-risk NMIBC · CR after tislelizumab + nab-paclitaxel

utDNA at CR	utDNA−	(n=21) 3 further cycles, then stop
	not de-escalated	(n=33) continued therapy

RFS comparable (**HR 1.37; 95% CI 0.21–8.87**); any-grade AEs 72.5% vs 88.1%

(+) detectable; **(-)** undetectable; **Dashed boxes**: ctDNA not used prospectively for allocation.

Figure 5. **Prognostic significance of ctDNA and utDNA across clinical outcomes**



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ABBREVIATIONS

cCR, clinical complete response; **CI,** confidence interval; **CR**, complete response; **ctDNA**, circulating tumor DNA; **DDR,** DNA damage response; **DFS**, disease-free survival; **EFS**, event-free survival; **HR**, hazard ratio; **HTA**, health technology assessment; **MFS**, metastasis-free survival; **MIBC,** muscle-invasive bladder cancer; **NAC**, neoadjuvant chemotherapy; **NCCN**, National Comprehensive Cancer Network; NMIBC, non-muscle-invasive bladder cancer; **OS**, overall survival; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RC**, radical cystectomy; **REAL-SLR**, Real-Time AI-Assisted Living Systematic Literature Review; **RFS,** recurrence-free survival; **RT,** radiotherapy; SLR, systematic literature review; **TURBT**, transurethral resection of bladder tumor; **utDNA**, urinary tumor DNA.