

REVIEW ARTICLE

Liquid biopsy in genitourinary oncology: Current clinical applications and future prospects across prostate, bladder, and renal cancers

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Abstract

Liquid biopsy has emerged as a transformative approach in oncology, providing minimally invasive access to tumor-derived biomarkers with applications across diagnosis, prognosis, therapeutic guidance, and disease monitoring. This literature review synthesizes evidence from 125 studies evaluating circulating tumor DNA, circulating tumor cells, extracellular vesicles, RNA species, and proteomic or metabolomic signatures in prostate, bladder, and renal cancers. The findings demonstrate that liquid biopsy technologies have shown substantial promise in early detection, risk stratification, and longitudinal surveillance, while also offering novel insights into therapeutic resistance and clonal evolution. However, clinical translation remains constrained by pre-analytical variability, assay standardization challenges, limited sensitivity in low-tumor-burden settings, and the need for prospective validation in large, diverse populations. Despite these barriers, ongoing technological advances and integration with multi-omics approaches are likely to accelerate the adoption of liquid biopsy as a complement to conventional tissue-based diagnostics and imaging in genitourinary oncology.

KEYWORDS

circulating biomarkers, minimal residual disease, molecular monitoring, non-invasive diagnostics, precision oncology, tumor heterogeneity

1 | INTRODUCTION

Liquid biopsies are garnering considerable attention in genitourinary oncology, particularly across prostate, bladder, and renal cancers. Prostate cancer remains a leading cause of cancer morbidity and mortality among men worldwide, while bladder and renal cell carcinoma (RCC) contribute significantly to global cancer burden and healthcare cost, especially given their high recurrence rates and challenges in early detection and monitoring^[1]. Conventional diagnostic and surveillance tools—such as serum prostate-specific antigen

(PSA), transrectal or transperineal needle biopsy, imaging, and cystoscopic evaluation—display well-documented limitations. PSA lacks specificity and varies with prostate volume, leading to overdiagnosis and overtreatment, while tissue biopsies are invasive, prone to sampling bias, and carry risks including pain, bleeding, and infection. In bladder cancer management, cystoscopy remains the standard for detection and surveillance, but is invasive, costly, and poorly tolerated by many patients^[2]. Renal biopsies are often limited by anatomical inaccessibility, tumor heterogeneity, and procedural risks, while radiologic imaging

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may inadequately capture dynamic tumor biology or minimal residual disease^[3].

In response to these limitations, liquid biopsy has emerged as a compelling non- or minimally-invasive approach for cancer detection and management. Defined as the molecular analysis of circulating tumor-derived materials—such as CTCs, cell-free DNA (cfDNA) or ctDNA, exosomes, extracellular RNAs, and other analytes—from body fluids like blood or urine, liquid biopsy offers several unique advantages. It enables repeated sampling over time for real-time disease monitoring, captures spatial and temporal tumor heterogeneity more comprehensively than single-site tissue biopsy, and bypasses the procedural risks associated with invasive sampling^[4]. Furthermore, the accessibility of urine—especially relevant to GU malignancies—facilitates frequent and patient-friendly surveillance: urine-based biomarkers, such as cfDNA methylation patterns, exosomal RNAs, and mutated DNA panels, show promising sensitivity and specificity that may outperform standard screening modalities. For instance, urine-derived cfDNA assays detecting telomerase reverse transcriptase (TERT) promoter mutations via digital PCR have achieved sensitivities up to 92% and specificities around 96% in early bladder cancer detection^[5].

Given the mounting translational evidence, yet limited clinical adoption and standardization, a scoping review is particularly well-suited to this field. By mapping existing studies on liquid biopsy across prostate, bladder, and renal cancers—highlighting biomarker types, sample sources, analytic platforms, clinical contexts, and research gaps—a scoping review can guide future efforts in clinical validation, standardization of methodologies, and integration into clinical decision-making frameworks^[6]. The aim of this review is therefore to systematically synthesize the current clinical applications of liquid biopsy in genitourinary oncology, with emphasis on diagnostic, prognostic, therapeutic, and monitoring roles, while also identifying research gaps and future prospects that could accelerate its integration into precision cancer care.

2 | METHODOLOGY

A structured literature search was conducted to identify studies evaluating the clinical applications and future prospects of liquid biopsy in prostate, bladder, and renal cancers. Major scientific databases—including PubMed/MEDLINE, Embase, Web of Science, and Scopus—were searched for articles published between January 2015 and August 2025. Additional relevant references were retrieved through manual screening of bibliographies from key publications.

2.1 | Search strategy

The search combined controlled vocabulary (MeSH/Emtree terms) and free-text keywords related to liquid biopsy (e.g., “circulating tumor DNA” OR “cell-free DNA” OR “ctDNA” OR “cfDNA” OR “circulating tumor cells” OR “CTCs” OR “extracellular vesicles” OR “exosomes” OR “microRNAs” OR “proteomics” OR “metabolomics”) and genitourinary malignancies (“prostate cancer” OR “bladder cancer” OR “urothelial carcinoma” OR “renal cancer” OR “kidney cancer”). An example full PubMed search string is provided in Table S1 to ensure reproducibility.

2.2 | Study selection process

All search results were imported into EndNote X9 for deduplication. Titles and abstracts were independently screened by two reviewers. Full-text review was then performed for potentially eligible studies. Any disagreements were resolved through consensus or, when necessary, arbitration by a third reviewer. Reasons for full-text exclusions were documented.

2.3 | Eligibility criteria

Studies were included if they met the following criteria:

- Population: Human subjects with prostate, bladder, or renal cancer.
- Intervention/index test: Any liquid biopsy analyte (ctDNA/cfDNA, CTCs, exosomes/extracellular vesicles, circulating RNAs, proteomics, metabolomics).
- Clinical context: At least one of diagnosis/early detection, prognostication, treatment selection or monitoring, progression/recurrence assessment, or minimal residual disease (MRD) detection.
- Study design: Prospective or retrospective clinical studies, including cohort, case-control, diagnostic accuracy, or interventional biomarker studies.

Exclusion criteria comprised:

- Case reports, reviews, editorials, or conference abstracts without full text.
- Preclinical, animal-only, or purely methodological studies without human data.
- Studies not directly addressing liquid biopsy in genitourinary cancers.

2.4 | Data extraction and synthesis

Following application of these criteria, 125 studies were included in the synthesis. Data were extracted on study design, population, analyte type, assay platform, sample

size, clinical context, and key findings. Extracted information was organized thematically by cancer type (prostate, bladder, renal) and biomarker class (ctDNA/cfDNA, CTCs, exosomes/extracellular vesicles, RNA signatures, proteomic/metabolomic markers).

2.5 | Risk of bias and quality assessment

Given the heterogeneity of included studies, formal evidence appraisal was performed:

- Diagnostic accuracy studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, focusing on patient selection, index test conduct, reference standards, and flow/timing.
- Prognostic and monitoring studies were appraised with the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool, addressing bias from confounding, participant selection, classification of interventions, and outcome assessment.

Two reviewers independently rated study quality; discrepancies were resolved by consensus. A concise summary table of study quality is provided in Table S2.

2.6 | Transparency of the review process

The overall flow of study identification, screening, exclusions, and final inclusion is illustrated in a PRISMA 2020 flow diagram (Figure 1). This diagram details the number of records retrieved from each database, duplicates removed, records screened, full texts assessed, exclusions with reasons, and the final 125 studies included in the review.

3 | OVERVIEW OF LIQUID BIOPSY TECHNOLOGIES

Liquid biopsy encompasses diverse modalities—including circulating tumor cells, cell-free DNA or circulating tumor DNA (cfDNA/ctDNA), exosomes and

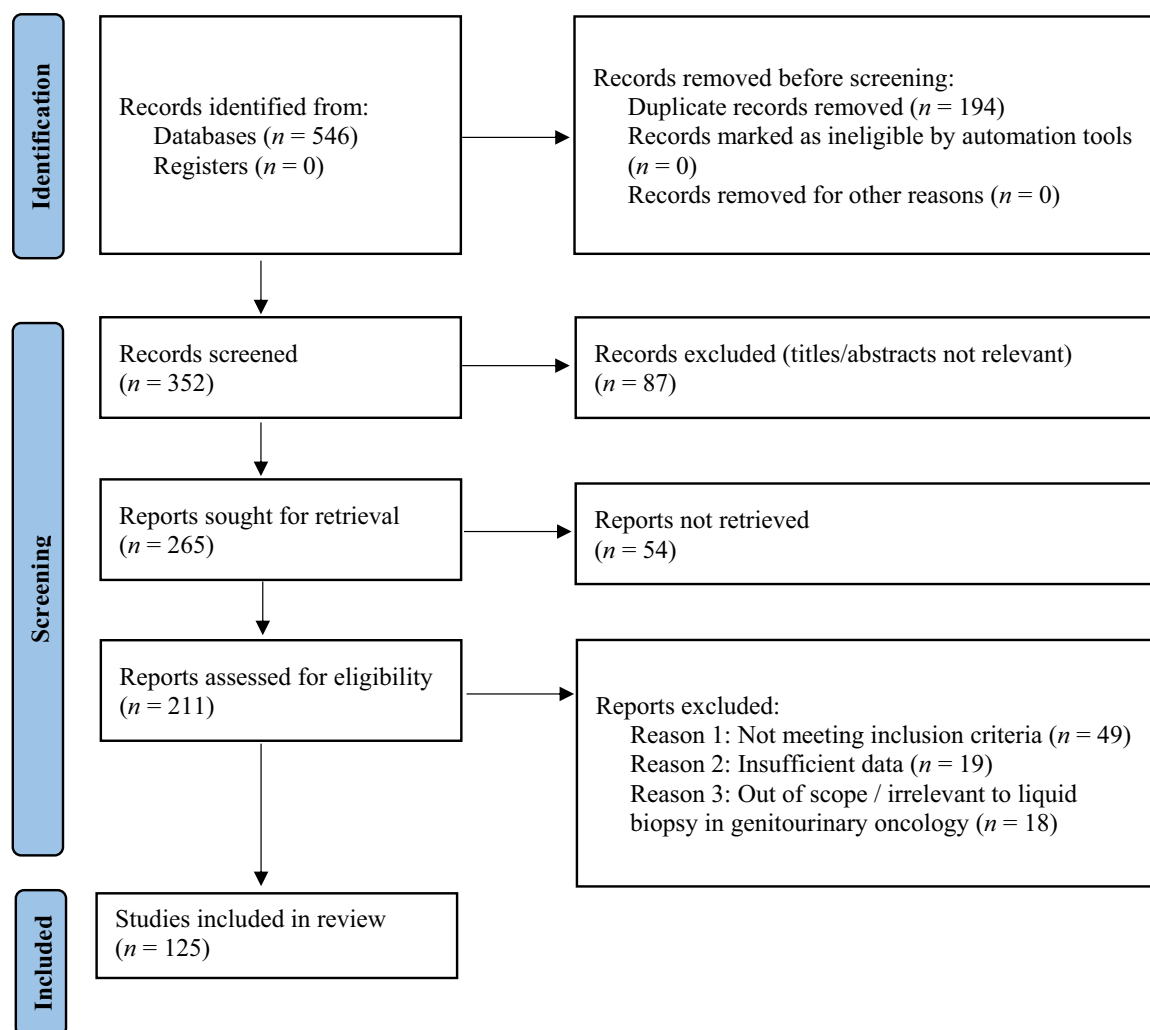


FIGURE 1 PRISMA 2020 flow diagram.

extracellular vesicles, circulating RNAs, as well as proteomic and metabolomic analyses—each leveraging advanced platforms such as digital PCR, next-generation sequencing (NGS), and microfluidic systems. CTC enumeration, commonly performed with the FDA-approved CellSearch system, demonstrates tangible prognostic value in genitourinary oncology. For example, in a study of metastatic genitourinary cancers, CTCs were detectable in 75% of patients, and baseline presence correlated significantly with shorter overall survival ($p = 0.022$)^[7]. Another study using an automated microfiltration device captured CTCs in all eight metastatic prostate cancer patient samples, reporting a mean concentration of 21 ± 2.96 CTCs/mL (median 21 CTCs/mL), underscoring detection sensitivity^[8]. Nonetheless, CTC analysis faces inherent challenges: they are rare—typically just 1–10 per milliliter of blood amid millions of leukocytes—imposing stringent requirements on assay sensitivity and purity.

cfDNA/ctDNA analyses hold promise across GU malignancies, enabling detection of genomic alterations predictive of prognosis, treatment response, and minimal residual disease. Recent comprehensive reviews highlight ctDNA's roles in early detection of RCC, monitoring recurrence in bladder cancer, and predicting therapeutic response in castration-resistant prostate cancer^[9,10]. Although explicit quantitative detection thresholds vary with assay and tumor type, emerging platforms—such as deep targeted sequencing—have enabled measurement of tumor fraction in cfDNA as a continuous variable correlating with overall survival and metastatic potential in oligometastatic prostate cancer^[11].

Digital droplet PCR (ddPCR) of exosomal RNA for androgen receptor splice variant 7 (AR-V7) detection in metastatic castration-resistant prostate cancer provides another quantifiable liquid biopsy readout, with ddPCR sensitivity facilitating detection even in small sample volumes^[12]. Exosomes and extracellular vesicles offer unique biomarker opportunities by encapsulating tumor-derived proteins and RNAs. In prostate cancer patients, exosomal PSA assays achieved sensitivities between 96% and 98% and specificities from 80% to 100%—markedly outperforming serum PSA for distinguishing prostate cancer from benign prostatic hyperplasia^[13]. In bladder cancer, urinary exosomal markers have displayed robust diagnostic performance: a panel of three urinary exosomal lncRNAs (SPRY4-IT1, MALAT1, PCAT-1) achieved an area under the curve (AUC) of 0.813 versus 0.619 for urine cytology^[14], while serum exosomal biomarker panels demonstrated AUCs in the range of around 0.85, sensitivities 74%–82%, and specificities 78%–100% across multiple studies^[15–17].

Circulating RNAs—including miRNAs and lncRNAs—further enrich the liquid biopsy landscape. For instance, elevated exosomal miR-375 and miR-1290 correlated with shorter overall survival in castration-resistant prostate cancer, and incorporating these miRNAs into prognostic models improved AUC from 0.66 to 0.73^[18]. Urinary

exosomal miRNAs such as miR-196a-5p and miR-501-3p show promise for prostate cancer detection, while lncRNA LNMAT2 from exosomes yielded AUC values of 0.769 for bladder cancer diagnosis and 0.881 for lymph node-metastatic bladder cancer, also associating with shorter disease-free survival and overall survival^[19].

Proteomics and metabolomics approaches provide complementary insights by capturing tumor biology through protein expression patterns or metabolic perturbations. Urine-based metabolomic profiling by LC-MS distinguished bladder cancer from RCC with differential metabolic signatures^[20], while urine metabolomics targeting tryptophan metabolism pathways facilitated RCC prediction^[21]. These untargeted analyses yield quantitative metabolic features that may serve as disease-specific liquid biomarkers^[22].

Technical platforms such as digital PCR, NGS, and microfluidics underpin these liquid biopsy modalities. ddPCR offers ultra-sensitive detection of point mutations or transcript variants like AR-V7 with high precision. NGS enables broader mutational profiling and quantification of ctDNA fraction. Microfluidic devices, as exemplified by automated microfiltration systems, allow high-efficiency CTC capture (e.g., >93% recovery from spiked samples) and downstream molecular analyses^[8]. However, despite these advances, standardization remains a challenge across pre-analytical variables (sample collection, processing), platform variability, and biomarker thresholds, limiting cross-study comparability and clinical implementation^[23].

4 | LIQUID BIOPSY IN PROSTATE CANCER

Liquid biopsy has advanced beyond serum PSA, enabling detection of tumor-derived material in blood and urine with applications across diagnosis, prognosis, and therapy monitoring. Urinary exosomal RNA assays, particularly those quantifying prostate cancer antigen 3 (PCA3) and transmembrane serine protease 2-ETS-related gene fusion (TMPRSS2:ERG), provide clinically meaningful discrimination of significant prostate cancer ($\geq$ grade group 2). The ExoDx Prostate Intelliscore (EPI) has shown reproducible performance in biopsy-naïve men with PSA 2–10 ng/mL, with pooled sensitivity around 90% (95% CI: 85%–94%) and negative predictive value (NPV) around 88%–90% across >1200 patients in two multicenter validation studies ($n = 519$ and $n = 503$, respectively), reducing unnecessary biopsies by around 20%–27%^[24,25]. Plasma ctDNA remains difficult to detect in localized disease due to low tumor shedding, but methylome-based cfDNA profiling and low-pass whole-genome sequencing can capture tumor fraction and copy-number patterns in subsets of patients^[26–28].

Circulating tumor cells and ctDNA provide prognostic information at diagnosis and in early systemic therapy. In metastatic hormone-sensitive prostate

cancer, baseline CTC counts correlated with overall survival in cohorts totaling about 1200 patients, and improved risk prediction when combined with clinical factors^[29]. In castration-resistant disease, ctDNA tumor fraction and genome instability metrics are consistently associated with shorter progression-free and overall survival (hazard ratios for high vs. low ctDNA fraction around 2.0–3.5 across three studies with $n = 98$, $n = 171$, and $n = 219$ patients)^[28,30,31]. Large series also demonstrate increasing prevalence of targetable DNA repair defects (e.g., BRCA1/2) with higher ctDNA burden in advanced disease^[32].

Liquid biopsy is integral to guiding therapy, particularly for androgen receptor pathway inhibitors (ARPIs). AR-V7 detection in blood consistently predicts poor ARPI response but relative benefit from taxanes^[33,34]. Beyond splice variants, ctDNA profiling captures AR amplifications, ligand-binding domain mutations, and phosphatidylinositol 3-kinase PI3K/protein kinase B (AKT) co-alterations linked to resistance, with early ctDNA kinetics correlating with therapy response^[35–39].

Serial CTC counts and ctDNA burden complement each other as markers of disease trajectory. CTC shifts from unfavorable to favorable categories after treatment consistently predict improved survival, while persistent high counts indicate poor outcomes (≥ 5 CTCs/7.5 mL associated with hazard ratio (HR) for OS around 2.7; $n > 400$ patients across multiple trials)^[30,34]. Longitudinal ctDNA increases often precede radiographic progression by a median of 3–5 months ($n = 219$ metastatic castration-resistant prostate cancer (mCRPC) patients)^[28,31]. Post-local therapy MRD detection is challenging given low shedding, yet when detectable, ctDNA strongly predicts recurrence^[26,27] (Table 1).

Multiple assays have entered clinical practice. The FDA-approved FoundationOne Liquid CDx provides genomic profiling across > 300 genes and is validated as a companion diagnostic for homologous recombination repair (HRR) alterations in mCRPC treated with Poly (ADP-ribose) polymerase (PARP) inhibitors^[40,41]. Broad cfDNA profiling in advanced disease identifies DNA-repair alterations in around 10%–15% of cases, aligning with PARP inhibitor eligibility^[32,42]. In earlier disease, EPI testing can safely defer invasive biopsy^[24,25]. Together, these assays enable a practical workflow: urine-based exosome testing refines biopsy decisions in localized disease, while blood-based ctDNA and CTC profiling stratify risk, select targeted therapy, and monitor resistance and treatment efficacy in advanced settings^[29,35,38].

5 | LIQUID BIOPSY IN BLADDER CANCER

Liquid biopsy strategies are increasingly integrated into the management of bladder cancer, with the goal of complementing or reducing reliance on cystoscopy and

cytology, particularly in the surveillance of non-muscle-invasive bladder cancer (NMIBC). Traditional voided urine cytology remains highly specific but has poor sensitivity for low-grade tumors. In contrast, multiple urine-based assays leveraging tumor-derived nucleic acids have demonstrated higher detection rates and more favorable NPVs, raising the prospect of extending surveillance intervals and decreasing procedural burden without compromising patient safety^[43–46].

Among the most extensively studied assays, Bladder EpiCheck®, a 15-marker DNA methylation panel, has shown overall sensitivity substantially higher than cytology, with pooled high-grade sensitivity 83%–90% (95% CI: 78%–94%; $n = 687$ patients across 3 prospective studies) and NPVs $> 90\%$ ^[43,44]. The mRNA-based Xpert® Bladder Cancer Monitor has also consistently outperformed cytology and UroVysion in head-to-head comparisons, with reported sensitivities in the range of 74%–84% overall (95% CI: 70%–87%) and high-grade sensitivity 83%–86% (95% CI: 79%–89%) across around 1000 patients, NPVs approaching 98%^[44–47]. Similarly, the Cxbladder® platforms (Detect, Triage, Monitor) employ multiplex urinary mRNA signatures and have demonstrated high NPVs across diagnostic, triage, and surveillance settings, with clinical studies showing reductions in cystoscopy utilization in both hematuria evaluation and NMIBC follow-up^[48,49]. Beyond these commercial tests, urine cfDNA assays provide additional opportunities by detecting canonical urothelial mutations such as TERT, fibroblast growth factor receptor 3 (FGFR3), PIK3CA, and epidermal growth factor receptor 2 (ERBB2). Validation of an ultra-deep urine cfDNA sequencing approach reported a sensitivity 86.8% (95% CI: 82%–91%) and specificity 81% (95% CI: 76%–85%) in an independent cohort of 164 patients^[50]. The Ur-omonitor® test, targeting TERT and FGFR3 alterations, has shown comparable performance with sensitivity and specificity in the 70% range, offering a lower-cost, pragmatic option for frequent surveillance^[51].

Beyond DNA- and RNA-based signatures, EVs and exosomes are emerging as complementary analytes. EV-derived RNAs, including MDK and KRT17, have demonstrated predictive utility in surveillance cohorts, with rising EV transcript levels anticipating recurrence in NMIBC follow-up^[52]. Meta-analyses across thousands of patients have further confirmed the diagnostic value of exosomal miRNAs and multi-marker panels, with pooled sensitivities and specificities in the 0.74–0.81 range and areas under the curve of 0.84–0.91, frequently outperforming single-marker approaches^[53,54]. These data suggest that EV assays may be particularly useful in cases where DNA-based testing yields inconclusive results or where additional biological insights are needed.

The role of liquid biopsy extends beyond diagnosis and surveillance into prognosis and treatment monitoring. Plasma and urine ctDNA now serve as important biomarkers of MRD and treatment response. In patients

TABLE 1 Key liquid biopsy assays and clinical performance in prostate cancer.

Assay/biomarker	Clinical context	Key findings/performance	References
EPI—urinary exosomal RNA (PCA3, TMPRSS2:ERG)	Diagnosis/biopsy deferral in men with PSA 2–10 ng/mL	AUC around 0.70–0.73; sensitivity: 90% (95% CI: 85%–94%) in > 1000 men; NPV: 88%–90%; reduced unnecessary biopsies by 20%–27%	McKiernan et al., 2016; McKiernan et al., 2018 ^[24,25]
Plasma ctDNA (methylome, low-pass WGS)	Early detection in localized disease	Detectable tumor fraction and CNAs in subsets despite low ctDNA shedding	Sumanasuriya et al., 2021; Shen et al., 2018; Nørgaard et al., 2023 ^[26–28]
CTC enumeration (CellSearch, FDA-cleared platform)	Prognosis in metastatic hormone-sensitive prostate cancer (mHSPC) and mCRPC	Baseline CTC categories (0, 1–4, $\geq 5/7.5$ mL) in $n = 1200$ patients; ≥ 5 consistently associated with HR for OS around 2.5–3.0	Goldkorn et al., 2024; Armstrong et al., 2020; Casanova-Salas et al., 2021 ^[29,30,34]
ctDNA tumor fraction/genome instability metrics	Prognosis in mCRPC	High vs. low ctDNA burden associated with HR 2.0–3.5 for OS (total $n \approx 500$ across 3 cohorts)	Nørgaard et al., 2023; Casanova-Salas et al., 2021; Fonseca et al., 2024 ^[28,30,31]
AR-V7 (blood-based assays: IHC, RT-PCR, ddPCR)	Treatment selection in mCRPC	AR-V7 positivity $\rightarrow$ poor response to abiraterone/enzalutamide (low PSA50, short PFS/OS); relatively greater benefit from taxanes	Scher et al., 2017; Armstrong et al., 2020 ^[33,34]
ctDNA profiling (AR, PI3K/AKT pathway)	Resistance monitoring	Captures AR amplifications, mutations (F877L, T878A), and dynamic “gene conversions” during therapy	Annala et al., 2018; Annala et al., 2021; Jayaram et al., 2021 ^[35–37]
ctDNA kinetics (on-treatment)	Pharmacodynamic biomarker	Early decline (4 weeks to weeks) in ctDNA fraction correlates with higher response probability and longer PFS	Tolmeijer et al., 2023 ^[38]
Baseline cfDNA concentration	Prognosis in taxane-treated mCRPC	Higher cfDNA associated with inferior OS	Mehra et al., 2018 ^[39]
FoundationOne Liquid CDx (FDA-approved cfDNA test)	Genomic profiling/therapy selection	Validated across > 7500 clinical samples; companion diagnostic for HRR mutations (BRCA1/2, ATM)	Woodhouse et al., 2020; Kim & Park, 2023 ^[40,41]
Broad cfDNA genomic profiling	Actionability in advanced disease	Identifies HRR defects in around 10%–15% late-line mCRPC; aligns with PARP inhibitor-responsive subgroups	Tukachinsky et al., 2021; De Bono et al., 2020 ^[32,42]

undergoing radical cystectomy, postoperative ctDNA positivity has been shown to predict molecular relapse several months before radiographic recurrence and to associate strongly with inferior recurrence-free and overall survival, while ctDNA clearance during neoadjuvant chemotherapy correlates with pathologic complete response and improved outcomes^[55,56]. In advanced disease, early reductions in ctDNA during systemic therapy have correlated with clinical benefit and survival, as demonstrated in exploratory analyses from KEYNOTE-361, where ctDNA dynamics were predictive of outcome independent of radiographic response^[57]. Moreover, the IMvigor010 trial highlighted ctDNA as a predictive biomarker for adjuvant immunotherapy: adjuvant atezolizumab conferred benefit only in ctDNA-positive patients, whereas ctDNA-negative patients derived no advantage, establishing liquid biopsy as a treatment-selection tool in the perioperative setting^[58] (Table 2).

Comparative studies have shown that while UroVy-sion FISH remains widely used, it often underperforms newer assays, with sensitivities typically in the 50%–70% range and specificity between 80%–90%^[46]. In contrast, Bladder EpiCheck, Xpert Monitor, and Cxbladder have consistently demonstrated higher NPVs, supporting their use as “rule-out” tools that could safely reduce cystoscopy frequency in surveillance populations. The integration of urine-based DNA, RNA, and EV assays with plasma ctDNA is thus reshaping clinical practice, offering diagnostic and prognostic accuracy that can streamline patient management, personalize therapy allocation, and reduce the burden of invasive procedures. Ongoing prospective head-to-head studies comparing cfDNA next-generation sequencing, EV-based signatures, and established commercial platforms will be essential to define optimal cost-effective surveillance strategies and standardize liquid biopsy use across bladder cancer care.

TABLE 2 Summary of liquid biopsy assays in bladder cancer.

Assay/platform	Analyte	Clinical setting	Performance highlights	References
Bladder EpiCheck [®]	DNA methylation (15 markers)	NMIBC surveillance	HG sensitivity: 83%–90% (95% CI: 78%–94%; <i>n</i> = 687); specificity: 84%–88%; NPV > 90%	Trenti et al., 2019; D'Andrea et al., 2019 ^[43,44]
Xpert [®] Monitor	mRNA (5-gene panel)	NMIBC surveillance	Sensitivity: 74%–84%; overall (95% CI: 70%–87%; <i>n</i> ≈ 1,000); HG: 83%–86% (95% CI: 79%–89%); NPV: 93%–98%	D'Andrea et al., 2019; Pichler et al., 2018; Kavcic et al., 2022; D'Elia et al., 2021 ^[44–47]
Cxbladder [®] (detect, triage, monitor)	Multiplex urinary mRNA	Diagnosis, triage, surveillance	Detect: 77%/94%/96% (sens/spec/NPV); triage: 95%/46%/98%; monitor: 91%/39%/96%; reduces cystoscopy burden	Raman et al., 2021; Lotan et al., 2024 ^[48,49]
Urine cfDNA-NGS	Mutations (<i>TERT</i> , <i>FGFR3</i> , <i>PIK3CA</i> , <i>ERBB2</i>)	Diagnosis, MRD, surveillance	External validation: 86.8% sensitivity (95% CI: 82%–91%), 81% specificity (95% CI: 76%–85%); <i>n</i> = 164	Ward et al., 2023 ^[50]
Uromonitor [®]	Targeted DNA mutations (<i>TERT</i> , <i>FGFR3</i>)	NMIBC recurrence monitoring	Sensitivity: 73.5%; specificity: 73.2%	Batista et al., 2019 ^[51]
EV-based assays	mRNA, miRNA, proteins	Diagnosis, surveillance	AUC: 0.76–0.91; multi-marker EV panels outperform single markers	Murakami et al., 2024; Zhao et al., 2024; Long et al., 2024 ^[52–54]
Plasma cfDNA (tumor-informed/naïve)	cfDNA mutations, dynamics	Post-cystectomy, advanced disease, therapy monitoring	Detects relapse median 3 months before imaging (<i>n</i> = 68 RCC patients); cfDNA clearance associated with pathologic CR (<i>n</i> = 39)	Christensen et al., 2019; Christensen et al., 2023; Powles et al., 2024; Powles et al., 2024b ^[55–58]

6 | LIQUID BIOPSY IN RCC

RCC presents unique challenges for biomarker development, given its marked intratumoral heterogeneity, stromal complexity, and sampling limitations for anatomically difficult lesions. These factors often limit the representativeness of tissue biopsies and make liquid biopsy an attractive, though technically demanding, alternative^[59]. A consistent limitation has been low ctDNA yield compared with other solid tumors: plasma ctDNA detection rates in metastatic RCC vary from about 30% to 70%, based on cohorts of $n = 30$ –220 patients; sensitivity highest in bulky/progressive disease^[60,61]. Tumor-informed sequencing approaches and ultra-deep targeted assays can improve sensitivity, with preoperative ctDNA detectability in many higher-stage patients^[62].

Among circulating analytes, exosomal and cell-free RNAs appear more robust than ctDNA for diagnosis. The most consistently replicated marker is miR-210, detected in urine and plasma, with pooled sensitivity 75%–83% and specificity of 75%–82% across about 400 RCC patients (95% CI: 70%–85%)^[63]. Panels of circulating noncoding RNAs have also shown encouraging diagnostic performance, with reported AUCs of 0.75–0.90, including a five-lncRNA panel achieving 91% specificity and clinically relevant sensitivity even in stage I disease^[64]. While individual markers vary, these studies illustrate the potential of RNA-based liquid biopsy in RCC.

Technical refinements in ctDNA detection—including molecular barcoding, ultra-deep coverage, and integration of fragmentomics and methylation features—have recently increased analytical sensitivity. Novel fragmentomic and methylome-aware assays reported in 2024–2025 improved tumor fraction estimation even in low-shedding cases^[65,66]. Clinical applications are also emerging: serial ctDNA trajectories correlate with treatment response, with pilot studies demonstrating that tumor-informed approaches such as TARDIS can distinguish partial versus complete responders on immunotherapy and predict progression ahead of imaging^[67,68].

Extracellular vesicles provide another promising avenue, with urinary EV cargo often yielding higher concentrations than plasma. EV-derived RNAs such as MDK, KRT17, and the miR-210 family achieve diagnostic AUCs in the 0.72–0.86 range, and longitudinal monitoring shows that rising EV transcript levels may precede clinical recurrence^[52,69]. Pooled analyses suggest exosomal noncoding RNAs reach sensitivities of around 0.74–0.81 and specificities of about 0.78–0.85 across aggregated RCC data sets^[70,71] (Table 3). Although these require multicenter validation, they reinforce the relative promise of EV assays in this disease.

For therapy monitoring, ctDNA changes during systemic treatment have correlated with response and survival across RCC cohorts. Early decreases in ctDNA tumor fraction or methylation-based signal are associated with longer progression-free and overall survival^[74,75]. In pilot

checkpoint inhibitor studies, ctDNA dynamics predicted progression earlier than imaging, highlighting their potential as pharmacodynamic biomarkers^[68]. Broader genitourinary analyses confirm that when ctDNA is detectable at baseline, on-treatment trajectory is prognostic, although the statistical power in RCC remains smaller than in prostate or bladder cancer^[76,77].

Minimal residual disease detection after nephrectomy is an area of active investigation. Tumor-informed assays such as Signatera have shown higher positive predictive value than tumor-agnostic approaches, with ctDNA detectability associated with HR for recurrence > 3.0 (95% CI: 2.1–4.5) across prospective studies with $n = 100$ –180 patients; median relapse lead time 2–6 months^[72,73]. Post-operative ctDNA detectability frequently precedes radiographic relapse by several months, although overall sensitivity remains lower than in cancers with higher shedding^[73]. These findings suggest that ultra-sensitive personalized assays, together with optimized timing of sampling, will be required for MRD detection to become clinically actionable in RCC.

7 | COMPARATIVE INSIGHTS ACROSS GU MALIGNANCIES

Across genitourinary malignancies, clinical adoption of liquid biopsy is most advanced in prostate and bladder cancers and is least mature in renal cell carcinoma. Blood-based ctDNA profiling and CTCs analysis have gained routine clinical traction in advanced prostate cancer—where ctDNA fractions and mutation concordance with tissue rise sharply with stage—and have supported drug-selection decisions (e.g., PARP inhibitor eligibility) and resistance monitoring^[35,41]. Quantitatively, concordance between plasma ctDNA and tumor tissue mutation profiles increases from roughly 50% in localized prostate cancer to 80%–90% in metastatic disease, and median ctDNA tumor fraction values reported in metastatic prostate series commonly exceed 10%–15% in high-burden cases^[32,78]. In contrast, bladder cancer has seen the fastest clinical translation of urine-based liquid biopsy: urine tumor DNA (utDNA) and methylation panels demonstrate high sensitivity for tumor detection and particularly strong NPVs that enable risk-adapted cystoscopy strategies^[44,50]. For example, targeted ultra-deep urine cfDNA NGS pipelines reported external-validation sensitivity of about 86.8% at specificity around 81.0% in diagnostic cohorts^[50], and commercial urine tests (EpiCheck, Xpert BC Monitor, Cxbladder) report HG-weighted sensitivities commonly in the 80%–90% range with NPVs often $> 90\%$ for surveillance use cases^[44,49]. By contrast, RCC shows the lowest ctDNA detectability among GU cancers: population-level pan-cancer analyses found ctDNA detection in stage IV renal cancer at around 63% versus $> 70\%$ for most other solid tumors, and the median ctDNA tumor fraction in

TABLE 3 Summary of liquid biopsy approaches in renal cell carcinoma.

Biomarker/assay	Sample type	Key findings	Reported performance	References
ctDNA (tumor-agnostic panels)	Plasma	Detection limited, varies with disease burden	30%–70% detection ($n = 30$ –220 patients)	Yip & Hakimi, 2023; Patel et al., 2024 ^[60,61]
ctDNA (tumor-informed assays, e.g., Signatera, TARDIS)	Plasma	Improved detection and MRD prediction; early relapse signals	Detectability pre/post-nephrectomy linked to HR > 3.0 (95% CI: 2.1–4.5); relapse lead time 2 months–6 months; $n = 100$ –180	Ben-David, 2024; Chehrizi-Raffle, 2023; Correa, 2024; Basu, 2023 ^[62,68,72,73]
miR-210 (single marker)	Plasma/urine	Most consistently replicated RNA biomarker for ccRCC	Sensitivity: 75%–83%; specificity: 75%–82% ($n \approx 400$ patients; 95% CI: 70%–85%)	Le, 2024 ^[63]
lncRNA/miRNA panels	Plasma/serum	Multiplex signatures improve discrimination; stage I detection possible	AUC: 0.75–0.90; one panel with 91% specificity	Li, 2021 ^[64]
EV-derived RNAs (e.g., MDK, KRT17, miR-210 family)	Urine	Stronger analytical yield than plasma; longitudinal changes track recurrence	Diagnostic AUCs: 0.72–0.86; pooled sensitivity: 74%–81%; specificity: 78%–85% ($n \approx 300$)	Lee, 2021; Murakami, 2024; Dayati, 2024; Li, 2024 ^[52,69–71]
ctDNA fragmentomics/methylation assays	Plasma	Improved detection in low-shedding tumors; enhances tumor fraction estimation	Increased sensitivity versus variant calling alone	Peng, 2025; Liang, 2025 ^[65,66]
ctDNA dynamics during systemic therapy	Plasma	On-treatment changes correlate with response and survival	Early declines linked with longer PFS and OS	Omri, 2024; Mack, 2022; Zaman, 2023; Ma, 2025 ^[74–77]

metastatic RCC cohorts is considerably lower than prostate or bladder (mRCC median tumor fraction reported about 3.9% vs metastatic prostate around 15.3% and bladder about 24.6% in cross-tumor comparisons)^[72,79]. These quantitative contrasts underlie the differential pace of clinical adoption.

Biomarker reliability varies by fluid compartment and tumor type. Urine is inherently more tumor-proximal for urothelial tumors, increasing yield: urinary cfDNA and extracellular vesicle (EV)/exosomal cargo provide higher analytic sensitivity for bladder tumors than blood in many settings, particularly for localized and non-muscle-invasive disease^[80]. Head-to-head comparisons demonstrate that urine assays can detect tumor-specific alterations (*TERT*, *FGFR3*, methylation signatures) with sensitivities often exceeding blood ctDNA for early or intravesical disease; for example, in cohorts of hematuria patients, urine cfDNA panels achieved sensitivities in the 80%–90% range where blood ctDNA was frequently negative^[56]. Blood (plasma) remains the preferred matrix for systemic disease profiling—detecting actionable alterations, quantifying tumor fraction, and performing pan-tumor genomic profiling—because ctDNA in plasma better reflects metastatic burden and multi-site tumor heterogeneity. For RCC, urine EV assays can provide complementary signals, but plasma ctDNA yields are generally low, so panels that combine fragmentomics, methylation signatures, and exosomal RNA show the best analytic sensitivity in RCC cohorts^[81].

Tumor biology shapes liquid biopsy yield through shedding rate, necrosis/apoptosis rates, vascularity, and intratumoral heterogeneity. Shedding rate correlates strongly with tumor burden and cell turnover: aggressive, high-grade urothelial tumors and advanced prostate cancers with visceral metastases shed more DNA into circulation and into organ-proximal fluids, increasing detection probability^[82]. Quantitatively, studies report ctDNA detectability rising from single-digit percentages in small localized tumors to >70%–90% in stage IV disease for many tumor types—but RCC is an exception with lower shedding even in metastatic settings (pan-cancer analysis showing stage-IV RCC ctDNA detection about 63.2%)^[83]. Spatial and temporal heterogeneity further influence biomarker signals: focal sampling with tissue biopsy may miss subclones that are readily captured in plasma ctDNA in advanced disease, enhancing the clinical value of liquid biopsy for resistance monitoring;^[4] conversely, in organ-confined disease the low fractional abundance of tumor DNA (often <0.1%–1% variant allele frequency) necessitates tumor-informed and ultra-sensitive assays to avoid false negatives^[80]. Finally, anatomic proximity matters: bladder tumors shed directly into urine yielding high local concentrations of tumor DNA and EVs, while prostate tumors may shed into prostatic fluid and urine after prostate massage, but blood remains the main source for detecting systemic disease and resistance mechanisms^[72].

8 | CLINICAL IMPLEMENTATION AND CHALLENGES

Clinical implementation of liquid biopsy has progressed rapidly but faces persistent technical and standardization challenges that limit routine adoption. Sensitivity, specificity, and reproducibility remain central concerns, particularly in MRD and early-detection contexts where very low variant allele fractions must be detected reliably. Assay performance is heavily influenced by pre-analytical factors such as tube type, sample handling, and processing delays, which can alter cell-free DNA yields and introduce variability in apparent mutant allele fractions. Inter-laboratory concordance studies demonstrate that reproducible results are achievable when standardized reference materials and harmonized bioinformatics pipelines are employed, but variability persists for low-frequency variants and copy-number measures, highlighting the need for external quality assessment and proficiency testing^[84–87].

Regulatory and economic considerations further complicate implementation. A limited number of comprehensive cfDNA assays have secured regulatory approval—such as FoundationOne® Liquid CDx, an FDA-cleared companion diagnostic for selected genomic alterations—yet most assays remain laboratory-developed tests with variable validation standards. Jurisdictional differences in oversight and evolving guidance from professional consortia underscore the need for harmonized reporting conventions and management of confounders such as clonal hematopoiesis of indeterminate potential, often requiring paired leukocyte sequencing^[40,88,89]. To support consistent practice, pragmatic safeguards have been proposed: (i) perform paired leukocyte sequencing when evaluating ctDNA in MRD settings, particularly in patients over 60 years or when variants fall in clonal hematopoiesis of indeterminate potential (CHIP) hotspot genes (e.g., *DNMT3A*, *TET2*, *ASXL1*);^[90,91] (ii) report variant allele frequency (VAF) together with assay limit of detection to enable contextual interpretation;^[92,93] and (iii) confirm putative CHIP-associated variants against matched tissue or leukocyte DNA before clinical reporting^[94,95]. Embedding these steps into laboratory workflows can reduce false positives and improve the reliability of ctDNA-based clinical decisions.

Ethical issues are increasingly prominent as liquid biopsy enters clinical practice. Incidental germline or non-tumor findings, particularly clonal hematopoiesis, occur in up to 20%–30% of older patients in large ctDNA cohorts, necessitating confirmatory testing and counseling^[96]. False positives in screening or surveillance can lead to unnecessary invasive procedures, heightened patient anxiety, and increased costs, underscoring the need for careful pretest counseling and clear post-test pathways^[97]. Patient-facing studies confirm that uncertain or incidental findings may exacerbate anxiety and decisional conflict, highlighting the importance of embedding psychosocial

support and transparent communication strategies into clinical programs. Additionally, issues of genomic data governance, cross-border data sharing, and commercial use of genomic information require explicit policies to ensure patients understand how their data are used and protected^[98]. Collectively, these challenges emphasize that technical standardization, regulatory clarity, economic viability, and ethical safeguards are all essential for the sustainable integration of liquid biopsy into routine oncology practice^[99–101].

9 | FUTURE DIRECTIONS AND EMERGING PROSPECTS

In the short term, liquid biopsy is advancing most rapidly in the context of MRD and adjuvant therapy. Tumor-informed ctDNA assays that track patient-specific variants are being incorporated into perioperative and systemic trials to guide therapy escalation or de-escalation^[102–105]. Early MRD studies in several tumor types consistently demonstrate lead times of months between ctDNA positivity and radiographic relapse and hazard ratios for recurrence greater than three for ctDNA-positive versus ctDNA-negative patients, benchmarks that have motivated analogous genitourinary (GU) cancer trials^[106,107]. Adaptive trial designs now use ctDNA persistence as a signal to intensify treatment—for example, in the ctDNA Response Adaptive Immuno-Chemotherapy study (NCT04093167) and other ongoing protocols^[108,109]. In addition, comprehensive cfDNA assays such as FoundationOne® Liquid CDx are already being used to identify actionable alterations with rapid turnaround times, enabling precision therapy allocation in advanced disease, including clinically relevant findings in metastatic castration-resistant prostate cancer cohorts^[110]. Together, these MRD-guided and ctDNA-adaptive approaches represent the most immediate clinical applications of liquid biopsy.

In the medium term, multi-omics and artificial intelligence (AI) models are expected to reshape early detection and monitoring strategies. Multimodal approaches that combine genomic, epigenomic, fragmentomic, and transcriptomic signals have demonstrated substantially improved sensitivity, specificity, and tissue-of-origin resolution compared with mutation-only panels. For example, the multimodal SPOT-MAS model achieved an AUC of 0.95 in validation, with sensitivities varying by cancer type and stage, while adding fragmentomic features improved tissue-of-origin localization to greater than 85%^[111,112]. Machine learning algorithms—including ensemble models, gradient-boosted trees, and XGBoost classifiers—are increasingly central to extracting signal from these high-dimensional data, with stacked models achieving superior performance compared with single-feature classifiers^[113–117]. These methods, tuned to maintain high specificity thresholds, consistently deliver sensitivities in the 60%–75% range across tumor types in validation cohorts, although

performance remains limited in low-shedding cancers such as certain breast tumors^[118]. Advances in feature selection and sequencing depth reduction continue to improve efficiency and cost-effectiveness, offering a realistic next step for integration into clinical workflows.

In the longer term, the greatest promise lies in population-level early cancer detection through multi-cancer early detection (MCED) assays. Prospective cohorts such as PATHFINDER have already demonstrated the feasibility of large-scale screening, with reported specificities near 99.5%, positive predictive values of approximately 43%, and cancer signal origin localization accuracy around 88%^[119]. Ongoing registration programs such as PATHFINDER-2, CCGA, and NHS-Galleri are enrolling tens of thousands of participants, with preliminary data suggesting improved predictive values while maintaining high specificity^[118,120]. While proof-of-concept for MCED is established, translation into mortality benefit will require randomized screening trials or large longitudinal registries that can demonstrate stage shifts and survival advantages^[121]. Ethical and economic considerations, including false positives, diagnostic cascades, and population-level cost, remain major challenges, but the trajectory points toward MCED as the most ambitious long-term application of liquid biopsy.

10 | RESEARCH GAPS AND OPPORTUNITIES

Despite rapid technological progress, liquid-biopsy research remains characterized by a pressing need for large-scale, prospective validation studies that demonstrate clinical utility beyond analytical performance. Enthusiasts frequently cite high sensitivities and specificities from single-center discovery or small validation cohorts, yet systematic reviews and regulatory assessments emphasize that evidence of improved patient outcomes from ctDNA-guided interventions is still sparse outside specific contexts (e.g., advanced-disease companion diagnostics)^[88]. For example, a recent comprehensive review of commercial ctDNA MRD platforms concluded that—while analytic validation is often robust—evidence of clinical utility in post-curative settings remains limited, with many studies retrospective or small and only a minority of completed randomized, MRD-guided trials to date^[122,123]. In the broader landscape, meta-analyses in other tumor types (e.g., colorectal, lung) have aggregated data from >1200–1600 patients to quantify MRD prognostic performance (sensitivity and specificity ranges reported across pooled studies), illustrating the scale of evidence required to underpin practice change and underscoring the relative paucity of equivalently powered prospective data sets in genitourinary malignancies^[124]. Multi-center, randomized studies and registry-scale prospective cohorts that link liquid-biopsy results to

prespecified management changes (and ultimately to hard endpoints such as recurrence-free survival and overall survival) are therefore high-priority needs^[125].

Harmonization of pre-analytical, analytical, and bioinformatic protocols across institutions is another critical gap. International consortia and white papers have documented that pre-analytical factors—blood-tube type, time-to-processing, centrifugation speed, plasma storage temperature, and cfDNA extraction method—can each alter apparent mutant allele fractions by orders of magnitude and thereby shift a sample across clinical decision thresholds if not standardized^[126,127]. Ring-trial data and inter-laboratory comparisons demonstrate that while high-VAF calls (e.g., >1%) show good concordance, low-VAF variant calls (<0.1%) and copy-number measurements suffer from substantial variability unless labs adopt common standard operating procedure (SOPs), proficiency testing, and harmonized bioinformatic pipelines^[85,128]. The practical impact is that without harmonization, multi-site trials and registries will be difficult to interpret and meta-analyses will remain noisy.

There is a distinct shortage of longitudinal data that link serial liquid-biopsy measurements to prespecified clinical actions and patient-centered outcomes in GU oncology. While several high-quality single-center longitudinal cohorts and phase II studies have shown that postoperative ctDNA detection precedes radiographic relapse by a median lead time measured in months and is associated with hazard ratios for recurrence often >3^[129,130], these are typically observational and heterogeneous in timing, assay design, and follow-up cadence. Formal prospective studies embedding serial sampling into randomized treatment allocation are fewer: in other tumor types (e.g., colorectal) pooled meta-analyses aggregated >1200 patients to quantify MRD prognostic performance, but analogous longitudinal registries in prostate, bladder, and RCC are smaller and less mature^[131]. As a consequence, the optimal sampling schedule (preoperative baseline, immediate post-operative window, early adjuvant interval, and longer-term surveillance) and the thresholds for intervention remain incompletely defined for many GU contexts.

Evidence gaps are particularly pronounced for certain histologic and molecular subtypes. Rare variants—such as chromophobe RCC, translocation-associated RCCs, sarcomatoid features, micropapillary or plasmacytoid variants of urothelial carcinoma, and rarer non-clear-cell renal histologies—are underrepresented in liquid-biopsy cohorts, which are dominated by clear-cell RCC, conventional urothelial carcinoma, and common prostate histologies^[72]. As a concrete example, targeted ctDNA detection rates and exosomal biomarker performance have been reported principally in cohorts where clear-cell RCC represents the majority;^[132] for rare RCC subtypes, detection rates and biomarker signatures are insufficiently characterized, limiting

generalizability of existing algorithms and reinforcing the need to purposefully enroll these subtypes in future registries and trials^[133].

11 | LIMITATIONS OF THE EVIDENCE BASE

Despite the breadth of evidence synthesized in this review, several methodological limitations of the included studies warrant consideration when interpreting performance claims. First, the overall quality of studies was heterogeneous. While a subset of well-designed prospective diagnostic accuracy studies and multicenter cohorts demonstrated low risk of bias, a substantial proportion of evidence derived from small exploratory cohorts, retrospective analyses, or single-center studies. Sample sizes were often modest, particularly in renal and bladder cancer cohorts, limiting statistical power and generalizability.

Second, risk-of-bias assessment highlighted recurring issues, including convenience sampling, non-standardized reference comparators, short follow-up intervals, and incomplete adjustment for clinical confounders. These methodological weaknesses introduce uncertainty into reported estimates of sensitivity, specificity, and prognostic hazard ratios. For example, highly cited findings such as relapse detection months before imaging or sensitivities above 80% are often drawn from underpowered data sets without independent external validation.

Third, reporting practices were inconsistent across studies. Confidence intervals, denominators, and contextual patient characteristics were frequently absent, which may overstate the certainty of diagnostic or prognostic performance. In addition, variability in pre-analytical and analytical protocols across institutions complicates direct comparison of results and contributes to heterogeneity in observed effect sizes.

Taken together, these factors indicate that while liquid biopsy has clear promise, the strength of current evidence is uneven. Reported performance metrics should therefore be interpreted with caution, particularly in clinical decision-making contexts. Large, prospective, methodologically rigorous trials with standardized reporting will be essential to substantiate the clinical utility of liquid biopsy in prostate, bladder, and renal cancers.

12 | CONCLUSION

Liquid biopsy represents a rapidly evolving field with significant potential to transform the clinical management of prostate, bladder, and renal cancers. Current evidence supports its role in diagnosis, prognosis, treatment selection, and longitudinal monitoring, although challenges in assay sensitivity, reproducibility,

and standardization continue to limit widespread clinical implementation. The collective findings of this review highlight the need for large-scale prospective validation and harmonized methodologies. With continued technological refinement and integration into precision oncology frameworks, liquid biopsy is positioned to become an essential adjunct to conventional diagnostic and therapeutic strategies in genitourinary malignancies.

AUTHOR CONTRIBUTIONS

Kirolos Eskandar conceived the idea, performed the literature search, analyzed the data, and drafted and revised the manuscript.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

The author has nothing to report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.