

EDITORIAL

Liquid biopsy in genitourinary oncology: From molecular detection to longitudinal precision cancer care

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Liquid biopsy is rapidly reshaping precision oncology by enabling minimally invasive and repeatable assessment of tumor-derived molecular signals. Genitourinary (GU) malignancies—including prostate, bladder, and kidney cancers—represent a particularly compelling setting for this approach because both blood and urine can provide clinically relevant and complementary information^[1]. Advances in circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), circulating tumor cells, extracellular vesicles, RNA, methylation, and other molecular analytes are extending liquid biopsy beyond genomic profiling toward early detection, risk stratification, treatment selection, response assessment, molecular residual disease (MRD) detection, and recurrence monitoring. In this issue of *UroPrecision*, two articles illustrate both the breadth and translational potential of the field. Eskandar reviewed the evolving landscape of liquid biopsy across prostate, bladder, and renal cancers, whereas Xu and colleagues reported a multicenter evaluation of an improved urine-based *PCA3* assay using microseminoprotein-beta (*MSMB*) as a reference gene, including the feasibility of non-digital rectal examination urine collection^[2,3]. Together, these studies highlighted a broader transition in GU oncology: from static, procedure-dependent assessment toward longitudinal molecular characterization using accessible body fluids. The next phase of the field will require prospective clinical validation, standardized pre-analytical and analytical workflows, demonstration of clinical utility, and integration of blood- and urine-based

multi-omic measurements with pathology, imaging, and clinical information.

1 | A NATURAL SETTING FOR LIQUID BIOPSY

Precision oncology has traditionally depended on tissue. Histopathology remains indispensable for diagnosis, classification, and characterization of GU malignancies, while tissue-based molecular testing provides important genomic information for an increasing number of patients. Yet a tissue specimen represents a tumor at a particular anatomical location and moment in time. Repeated tissue sampling is often impractical, and tumor heterogeneity and molecular evolution during treatment may limit the ability of an archival specimen to represent the biology of contemporary disease.

Liquid biopsy provides a fundamentally different opportunity. Tumor-derived DNA, RNA, cells, extracellular vesicles, proteins, and other analytes can be recovered from body fluids and interrogated repeatedly over the course of disease. As summarized by Eskandar in this issue, the rapidly expanding liquid-biopsy toolbox now encompasses ctDNA/cfDNA, circulating tumor cells, extracellular vesicles and exosomes, circulating RNA species, proteomic biomarkers, and metabolomic signatures across prostate, bladder, and renal cancers. These technologies are being investigated across a remarkably broad spectrum of clinical applications,

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including diagnosis, prognostication, treatment selection, therapeutic monitoring, recurrence assessment, and MRD detection^[1].

GU oncology is particularly well-positioned to benefit from this evolution because it offers access to two complementary liquid-biopsy compartments: blood and urine.

Blood provides a systemic window into disease and is particularly valuable for molecular profiling of advanced and metastatic cancers, assessment of treatment response, characterization of emerging resistance, and detection of residual disease. Urine, by contrast, provides a uniquely accessible and anatomically relevant biospecimen for malignancies involving the urinary tract and may contain tumor-derived material at concentrations not necessarily reflected in peripheral circulation. The accessibility of urine also creates opportunities for frequent sampling and potentially decentralized or home-based testing. The Eskandar review^[2] similarly emphasized the patient-friendly nature of urine sampling and its particular relevance to GU malignancies.

Rather than viewing blood and urine as competing specimen types, the field should increasingly consider them as complementary molecular windows. The optimal specimen will depend on tumor type, disease stage, anatomical location, biological question, and intended clinical use.

2 | FROM A LIQUID BIOPSY TO A LONGITUDINAL BIOPSY

Perhaps the most important conceptual advance is that the value of liquid biopsy does not reside solely in replacing a tissue biopsy. Its greater potential may lie in transforming cancer assessment from an episodic event into a longitudinal process.

A tissue biopsy asks, in effect, *What is this tumor?* Liquid biopsy can repeatedly ask additional questions: *Is tumor-derived molecular material detectable? Is the disease responding? Has residual disease persisted after treatment? Is recurrence emerging? Has the molecular profile changed? Is a resistance clone appearing?*

This distinction is particularly important in GU malignancies, where patients frequently move through prolonged disease courses and multiple interventions. The clinically relevant applications of liquid biopsy therefore span a continuum: detection and diagnosis → molecular characterization → risk stratification → treatment selection → early response assessment → MRD detection → recurrence surveillance → resistance profiling.

The technologies required at each point need not be identical. Broad genomic profiling may be appropriate when the goal is treatment selection or identification of resistance mechanisms, whereas highly sensitive targeted or personalized assays may be necessary when the clinical question is whether extremely low levels of residual

disease remain after definitive treatment. Methylation, fragmentomic, transcriptomic, and other epigenomic signals may further extend sensitivity and biological information beyond conventional mutation detection^[4].

This transition—from a single molecular snapshot toward a longitudinal molecular record—may ultimately represent the most consequential contribution of liquid biopsy to precision oncology.

3 | PROSTATE CANCER: MAKING MOLECULAR TESTING LESS INVASIVE AND MORE ACCESSIBLE

Prostate cancer illustrates both the promise and the challenges of liquid biopsy. Prostate-specific antigen (PSA) transformed prostate cancer detection and monitoring, but its limited cancer specificity can contribute to unnecessary diagnostic procedures. Plasma ctDNA, meanwhile, becomes increasingly informative in advanced prostate cancer but can be difficult to detect in localized disease because of low tumor shedding^[5]. The Eskandar review highlighted this disease-stage dependence while describing complementary roles for urine-based assays in earlier disease and blood-based ctDNA and circulating tumor cells in advanced disease.

The study by Xu and colleagues^[3] provided an instructive example of how improvements in both assay biology and specimen collection may increase the translational potential of urine testing. The investigators replaced the conventional *KLK3* reference gene with *MSMB* for normalization of urinary *PCA3* expression. In their initial cohort, *PCA3/MSMB* achieved an area under the curve (AUC) of 0.869 compared with 0.830 for *PCA3/KLK3*, with sensitivity of 82.1% and specificity of 77.8%. An independent cohort of 350 patients produced similar performance, with sensitivity of 82.63% and specificity of 77.50%.

Of particular interest is the evaluation of specimen collection. Among 117 patients with paired samples, *PCA3/MSMB* demonstrated comparable performance in non-digital rectal examination (DRE) and post-DRE urine, with AUCs of 0.850 and 0.859, respectively.

The importance of this observation extends beyond *PCA3* itself. A biomarker achieves clinical impact only when analytical performance can be combined with a practical clinical workflow. Eliminating the requirement for DRE before urine collection could simplify testing, facilitate repeat sampling, and potentially enable collection outside specialized urology settings. The authors appropriately identify home-based collection, simplified primary-care workflows, and repeated testing as potential advantages.

At the same time, additional evidence will be necessary before broad clinical implementation. The study population consisted entirely of Chinese men; long-term prognostic outcomes were not assessed, and direct

comparisons with other contemporary biomarker approaches were not performed. These limitations underscore an important principle for the entire liquid-biopsy field: analytical validity and diagnostic accuracy are essential milestones, but ultimately, clinical utility must be demonstrated in the population and decision point for which a test is intended.

4 | BLADDER CANCER: URINE AS A TUMOR-PROXIMAL LIQUID BIOPSY

Among GU malignancies, bladder cancer may offer one of the most compelling opportunities for urine-based molecular testing. Cystoscopy and cytology remain central to diagnosis and surveillance, but repeated invasive procedures create a substantial burden for patients and healthcare systems. Urine is in direct contact with urothelial tumors and can contain tumor-derived cells, DNA, RNA, proteins, and extracellular vesicles^[6].

The Eskandar review^[2] summarized multiple urine-based approaches—including DNA methylation, mRNA signatures, tumor-associated mutations, and extracellular-vesicle biomarkers—that have demonstrated encouraging performance in bladder cancer detection and surveillance.

But the future opportunity extends beyond simply asking whether urine testing can replace individual cystoscopies. A more consequential question is whether urine molecular profiling can help redefine how bladder cancer is managed longitudinally.

In non-muscle-invasive bladder cancer (NMIBC), serial urine testing could potentially contribute to recurrence surveillance and risk-adapted use of cystoscopy. In muscle-invasive disease, urine and plasma measurements may provide complementary assessments of response to neoadjuvant treatment and residual disease. Following definitive treatment, highly sensitive molecular assays may identify recurrence before it becomes clinically or radiographically apparent. In advanced urothelial carcinoma, blood-based genomic profiling can simultaneously identify actionable alterations and track molecular response or resistance.

Indeed, the review highlighted emerging evidence that postoperative ctDNA positivity after radical cystectomy can precede radiographic recurrence and that ctDNA dynamics may provide prognostic and predictive information during systemic therapy.

The long-term objective, therefore, should not necessarily be urine instead of blood or liquid biopsy instead of cystoscopy. It should be an integrated strategy in which urine, blood, pathology, imaging, and clinical assessment are deployed according to the biological and clinical question.

5 | KIDNEY CANCER: OVERCOMING THE CHALLENGE OF LOW SHEDDING

Renal cell carcinoma presents a different biological problem. Compared with some advanced GU malignancies, tumor-derived DNA can be relatively scarce in plasma, particularly in localized disease^[7]. This makes kidney cancer an important testing ground for the next generation of liquid-biopsy technologies.

Increasing sequencing depth alone is unlikely to solve every low-shedding problem. Improved sensitivity may come from combining multiple dimensions of tumor biology—including somatic mutations, methylation, fragmentation patterns, copy-number changes, RNA, extracellular vesicles, proteins, and potentially metabolomic features.

This is where multi-omics becomes more than a technological aspiration. Different analytes capture different aspects of cancer biology, and their integration may provide stronger signals than any single molecular class. Eskandar's synthesis similarly concluded that continued technological development and integration of multi-omic approaches are likely to accelerate clinical adoption, while emphasizing that sensitivity in low-tumor-burden settings remains a major limitation^[2].

Kidney cancer may therefore demonstrate an important lesson applicable throughout GU oncology: the future of liquid biopsy may depend not simply on detecting more DNA, but on extracting more biological information from each specimen.

6 | THE NEXT FRONTIER: MOLECULAR RESIDUAL DISEASE AND TREATMENT GUIDANCE

Among the many potential applications of liquid biopsy, MRD may ultimately be one of the most transformative.

After apparently curative surgery or other definitive therapy, conventional imaging may indicate no evidence of disease while microscopic malignant clones remain. Highly sensitive molecular assays create the possibility of detecting this residual disease before clinical recurrence. This could provide a new framework for postoperative risk stratification and, more importantly, for determining who requires additional therapy and who might safely avoid it.

The distinction is critical. A prognostic biomarker identifies patients at greater risk. A truly useful predictive biomarker should help determine whether changing treatment on the basis of the biomarker improves patient outcomes.

This should become a major priority for GU liquid-biopsy research. Future trials should move beyond demonstrating that molecular positivity is associated with recurrence. They should test whether biomarker-guided

escalation, de-escalation, or switching of therapy produces superior outcomes compared with conventional clinical decision making.

The ultimate destination is therefore not merely MRD detection, but MRD-guided intervention.

7 | FROM TECHNOLOGICAL PERFORMANCE TO CLINICAL UTILITY

Despite remarkable progress, several barriers continue to separate promising biomarker studies from routine clinical practice.

Pre-analytical variables—including collection tubes, specimen volume, processing time, storage, transportation, and nucleic-acid extraction—can materially affect assay performance. Analytical methods and positivity thresholds remain heterogeneous. Low tumor burden creates fundamental sensitivity challenges. Prospective validation in sufficiently large and diverse patient populations is required. Eskandar identified pre-analytical variability, assay standardization, sensitivity in low-tumor-burden disease, and prospective clinical validation as major barriers to translation.

Beyond these technical considerations, future studies must increasingly be designed around a specific clinical decision rather than simply demonstrating that a biomarker can distinguish between two groups.

For every liquid-biopsy test, several questions should be explicit: *Who should be tested? At what point in the patient journey? From which specimen? What biological signal should be measured? What clinical action follows a positive or negative result? And most importantly, does acting on that result improve patient outcomes?*

These questions will distinguish biomarkers that are scientifically interesting from tests that genuinely change clinical practice.

8 | TOWARD INTEGRATED PRECISION GU ONCOLOGY

The two articles highlighted in this issue capture the field at an important moment. Eskandar provided a broad perspective on an increasingly diverse liquid-biopsy ecosystem spanning multiple analytes, platforms, malignancies, and clinical applications. Xu and colleagues demonstrated how focused innovation in a specific urine assay—including improvement of the molecular reference standard and simplification of specimen collection—may address practical barriers to implementation^[3].

Together, they point toward a future in which liquid biopsy is not a single technology or test but an integral component of the GU cancer-care continuum.

The next generation of precision GU oncology will likely combine the anatomical and histological resolution

of tissue pathology, the spatial information of imaging, the systemic perspective of blood, and the tumor-proximal information available from urine. Artificial intelligence and integrated multi-omic analysis may further connect these data streams and translate them into clinically actionable information.

The objective should therefore extend beyond replacing tissue biopsy, PSA, imaging, or cystoscopy individually. The larger opportunity is to create a more continuous, less invasive, and biologically informed model of cancer care—one capable of following the tumor as it evolves and enabling treatment to evolve with it.

For prostate, bladder, and kidney cancers, liquid biopsy is moving from a technological possibility toward clinical implementation. The challenge for the field is now to convert molecular sensitivity into clinical utility, clinical utility into improved outcomes, and episodic testing into longitudinal precision cancer care.

AUTHOR CONTRIBUTIONS

Shidong Jia and Liang Cheng conceived, wrote, edited, and approved this manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

Shidong Jia is an employee and stock owner of Predicine. The other author declares no conflicts of interest.

ETHICS STATEMENT

Neither ethics approval nor patient consent was required for this manuscript.

REFERENCES

1. Lee J, Chen F, Lopez-Beltran A, Necchi A, Cimadamore A, Spiess PE, et al. Urinary tumor DNA-based liquid biopsy in bladder cancer management: a systematic review. *Eur Urol Focus*. 2025;11(6):978–90.
2. Eskandar K. Liquid biopsy in genitourinary oncology: current clinical applications and future prospects across prostate, bladder, and renal cancers. *UroPrecision*. 2026;4(3):137–53.
3. Xu J, Yang L, Shi C, Jiang Y, Chen J, Sun X, et al. Novel reference gene microseminoprotein-beta based prostate cancer antigen 3 urine test: enhanced diagnostic performance for prostate cancer and feasibility of non-digital rectal examination urine sampling. *UroPrecision*. 2026;4(3):154–63.
4. Cristiano S, Leal A, Phallen J, Fiksel J, Adleff V, Bruhm DC, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature*. 2019;570:385–9.
5. Mayrhofer M, De Laere B, Whittington T, Van Oyen P, Ghysel C, Ampe J, et al. Cell-free DNA profiling of metastatic prostate cancer reveals microsatellite instability, structural rearrangements and clonal hematopoiesis. *Genome Med*. 2018;10:85.
6. Rac G, Patel HD, James C, Desai S, Caruso VM, Fischer DS, et al. Urinary comprehensive genomic profiling predicts urothelial carcinoma recurrence and identifies responders to intravesical therapy. *Mol Oncol*. 2024;18(2):291–304.
7. Nuzzo PV, Berchuck JE, Korthauer K, Spisak S, Nassar AH, Abou Alaiwi S, et al. Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. *Nature Med*. 2020;26:1041–3.