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Current Status and Future Perspectives of Molecular Residual Disease Testing in Genitourinary Cancers

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ABSTRACT

While the clinical outcome for patients with resectable solid tumors has improved in recent years, the risk of postoperative recurrence underscores the need for effective monitoring in cancer patients. Molecular residual disease (MRD) refers to the presence of microscopic cancer that remains undetectable on conventional imaging or pathology. Because of the rapid advancement in circulating tumor DNA (ctDNA) analysis using next-generation sequencing technology, MRD testing using ctDNA has demonstrated significant potential for predicting recurrence in various types of cancer. Similar data are found in genitourinary (GU) cancer, and pivotal research has gradually shed light on the importance of MRD in predicting tumor recurrence. To address these critical advancements in MRD testing in GU cancers, we conducted a review of the clinical utility of MRD testing for GU cancers. In this review, we provide an overview of the potential utility of ctDNA-based MRD detection for GU cancers and highlight several ongoing clinical trials for the development of MRD-guided treatments with ctDNA. ctDNA-based MRD testing has the potential to personalize cancer precision medicine in GU cancers, guiding adjuvant therapy decisions, improving early detection of recurrence, and refining surveillance.

1 | Introduction

Genitourinary (GU) cancers are a group of malignancies that affect the urinary and reproductive systems, including the kidney, bladder, prostate, testicles, and genital organs [1]. Recently, a number of genomic and molecular characterizations have provided insight into the carcinogenesis and progression of GU cancers [2–5]. Although localized GU cancers are generally curable with definitive treatments including surgery, the clinical prognosis of patients with distance metastasis is grim, with the 5-year survival rates between 18% and 51% [6], and is dictated by the location and the number of metastases. Considering above, early detection of recurrence can improve the clinical prognosis of GU cancer patients, with the need to develop novel, noninvasive biomarkers for predicting tumor recurrence after surgery-based treatment.

Liquid biopsy is becoming an essential resource for providing information on the biological characteristics of cancer with minimum invasiveness, enabling longitudinal and real-time

Abbreviations: BC, bladder cancer; BCR, biochemical recurrence; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; GU, genitourinary; KC, kidney cancer; LOD, limit of detection; MRD, molecular residual disease; NAC, neoadjuvant chemotherapy; NGS, next-generation sequencing; PC, prostate cancer; RCC, renal cell carcinoma; RFS, recurrence-free survival; RT-PCR, reverse transcription PCR; UC, urothelial carcinoma; UTUC, upper urinary tract carcinoma; VAF, variant allele frequency; WGS, whole-genome sequencing.

monitoring compared to cancer tissue-based tests in oncology [7–9]. With the advancement of next-generation sequencing (NGS) technology, circulating tumor DNA (ctDNA) receives plenty of attention, which consists of DNA fragments released by tumor cells into the bloodstream and can be used to detect cancer-related genomic alterations in the peripherblood [10, 11]. ctDNA analysis offers several advantages over traditional tissue biopsies, including noninvasiveness, real-time information, and the ability to capture tumor heterogeneity [12–15]. Additionally, several studies have shown that ctDNA analysis can predict treatment response, monitor disease progression, and guide targeted therapies for various types of cancer [16].

Recently, several studies revealed that postoperative ctDNA-guided detection of molecular residual disease (MRD) is useful for the prediction of recurrence risk in various types of cancer because ctDNA has shown high sensitivity and specificity in detecting genetic mutations, potentially enabling early-stage cancer detection and improving current diagnostic methods [10, 17]. Moreover, several clinical trials have indicated that adjuvant therapy can improve clinical outcomes in cancer patients, including GU cancers [18–22]. However, predicting the population that can benefit from additional adjuvant therapy remains challenging, leading to overtreatment of patients with systemic therapies. Notably, this unmet clinical need has created a burgeoning field of solid tumor oncology.

In this review, considering the rapid development of NGS-based ctDNA analysis, we aim to summarize the current evidence on MRD testing on GU cancers and potential challenges for further application of ctDNA-guided MRD testing as a measure of therapeutic intervention in clinical studies of GU cancers.

2 | Search Strategy

We established a working group to develop a position paper on the appropriate clinical use of MRD Testing under the direction of the Japan Society of Clinical Oncology (JSCO). In this review, we updated the information on GU cancers: prostate cancer (PC), bladder cancer (BC), upper urinary tract carcinoma (UTUC), renal cell carcinoma (RCC), and kidney cancer (KC).

We performed a search in PubMed using the keywords PC, BC/UTUC, and RCC/KC in combination with circulating tumor DNA and surgery for each of them yielded 8, 21, and 12 reports, respectively, as of December 2024. Two reviewers (T. K. and H. M.) screened all titles and abstracts.

3 | Overview for MRD Using ctDNA Analysis

The detection of ctDNA in patients with early-stage solid tumors who have completed curative-intent definitive therapies, including surgery or radiation therapy, defined here as MRD to differentiate detection by ctDNA in solid tumors from “minimal” residual disease in hematologic malignancies [23]. Although the clinical benefit of ctDNA analysis using comprehensive genomic profiling in advanced-stage patients has been demonstrated in numerous studies, the assays used in advanced-stage settings lack the sensitivity required to detect ctDNA in the early stage or postcurative-intent therapy settings [24]. Generally, NGS or other methods have a limit of detection (LOD) for the variant allele frequency (VAF) with 0.1%–11%, driving the adoption of novel sensitive assays for the detection of MRD in these settings. Droplet digital polymerase chain reaction (ddPCR) first emerged with high sensitivity and low cost, and obtaining the results in a short period. In the early period of MRD testing, ddPCR can perform a limited gene analysis using existing probe sets with LOD of 0.01%–0.1% [25, 26]. Several groups have subsequently proved the utility of ddPCR-based ctDNA analysis by means of individualized ddPCR probes corresponding to mutational profiles in a database [27, 28]. More recently, whole genome sequencing (WGS)-based MRD assays have demonstrated the ability to detect ctDNA with an LOD of 0.0001% [29–31].

The detection rate of ctDNA varies widely across cancer types depending on tumor shedding characteristics, tumor burden, and location, which are closely related to the feasibility of MRD testing [17]. For instance, colorectal, nonsmall cell lung cancer, and BC have strong ctDNA shedding and have demonstrated that MRD positivity strongly correlates with recurrence, leading these cancers to the forefront of clinical trials and regulatory approval for MRD-guided therapy. On the other hand, in a subset of cancers, including RCC, pancreatic cancer, and glioma, the effectiveness of ctDNA assessment remains controversial because of the low rate of ctDNA shedding, leading to the necessity to develop a sensitive detection method for ctDNA in these cancers.

In general, NGS-based approaches with high-throughput ability and high sensitivity can classify MRD testing into two broad categories: tumor-naïve and tumor-informed approaches [23, 32, 33]. The tumor-naïve assay is a nonpersonalized testing approach that detects ctDNA in blood without requiring prior sequencing of the patient's tumor tissue, and is widely used in early cancer detection, genomic profiling for targeted therapy selection, and monitoring treatment response, especially when tumor tissue is unavailable [34–36]. In contrast, the tumor-informed assay is a personalized molecular testing approach designed based on the unique somatic mutations identified from a patient's own tumor tissue, which enables the reduction of false-positive findings and an increase in sensitivity compared to the tumor-naïve approach [37–39]. However, the tumor-informed approach definitely requires tumor biopsy or surgical tissue for genotyping and may pose several limitations, such as longer turnaround time and potentially overlooking of subclones in distant metastases [40]. To date, the US Food and Drug Administration and European Medicines Agency have already approved some MRD assessments, with the fact that MRD test results have affirmed clinical benefit in phase III trials. Importantly, several pivotal clinical trials have already been launched to evaluate ctDNA-based MRD-guided therapies in patients with colorectal cancer and bladder cancer, particularly to determine whether MRD testing can guide adjuvant treatment decisions and improve patient outcomes.

4 | Current MRD Assays in Prostate Cancer

PC remains a substantial global health challenge and is the second most prevalent noncutaneous malignancy among men in

Japan [6]. The incidence of PC has increased significantly over the past few decades. In 2024, it is estimated that approximately 91 800 new cases of PC will be diagnosed among Japanese men, making it the most commonly diagnosed cancer in this group [6]. For localized PC after prostatectomy, recurrence surveillance is normally performed using the tumor-specific marker, prostate-specific antigen (PSA), which precisely reflects tumor recurrence. The recurrence rate of PC after prostatectomy is approximately 20%–400%, with many studies reporting biochemical recurrence (BCR) (elevated PSA levels) in this range following radical prostatectomy for localized PC [41, 42]. To date, postoperative nomograms have been developed to predict the probability of recurrence by incorporating factors such as PSA level, Gleason grade, extracapsular extension, surgical margins, and lymph node involvement [43].

Considering this feature of PC, there have been relatively few reports on MRD testing. However, with advancements in ctDNA analysis, several studies have shown that detecting ctDNA before surgery influences the biochemical recurrence-free survival (RFS) of patients undergoing total prostatectomy for localized PC (Table 1) [44–46]. For instance, Pope et al. demonstrated that both BCR survival (hazard ratio [HR], 3.3 [95% CI: 1.4–8.1], $p = 0.0001$) and RFS (HR, 2.8 [95% CI: 1.1–7.1], $p = 0.0055$) were significantly shorter in patients who tested positive for preoperative ctDNA compared to those who were ctDNA-negative with a tumor-informed preoperative ctDNA analysis using whole-genome sequencing to enhance sequencing depth [44]. Moreover, Fei et al. reported that the detection rate of ctDNA was 65.5% in preoperative blood samples, and 85.3% of patients with detectable ctDNA achieved biochemical recurrence [45]. Furthermore, they emphasized that patients with undetectable ctDNA experienced significantly longer biochemical RFS compared with those who had detectable ctDNA (not available vs. 8.2 months; HR, 0.14 [95% CI: 0.09–0.24], $p < 0.01$), indicating preoperative ctDNA status was a significant prognostic factor of disease recurrence. Considering that WGS can detect mutations with a VAF of 0.0001% [47], further investigations are required to determine whether perioperative or postoperative MRD status with ctDNA is independently associated with RFS and other clinical prognostic indicators, regardless of PSA levels.

5 | Current MRD Assays in Urothelial Carcinoma

Urothelial carcinoma (UC) comprises BC and UTUC, accounting for approximately 90% and 10% of UC cases, respectively. Recurrence rates following radical cystectomy for BC vary widely, with local recurrence reported between 30% and 544% and distant recurrence reported to be up to 50% [48, 49]. A Canadian multi-institutional study found a 40% cumulative incidence of pelvic relapse in patients with pT3/T4 UC, which deeply affects the clinical prognosis [50].

In BC, ctDNA is thought to be detectable in more than 75% of patients with advanced BC and is consistently shed more than in other types of tumors [51, 52], leading to accumulating evidence in ctDNA analysis [53–56]. Christensen et al. first reported that activating hotspot mutations in *FGFR3* and *PIK3CA* in urine and plasma samples may be useful for diagnosing progression and metastasis by means of targeted sequencing with ddPCR in patients with BC [57]. Recently, several clinical studies using Signatera, a tumor-informed assay, have shown the clinical benefit of MRD detection after curative-intent radical cystectomy (Table 2). Birkenkamp-Demtröder and Christensen et al. reported that the postoperative MRD positivity rate was 26.6%, the overall recurrence rate in postoperative MRD-positive patients was 76% (13 of 17 patients), and the 12-month recurrence rate of 59% (10 of 17 patients) [58]. In contrast, most significantly, the recurrence rate was 0% in MRD-negative patients, suggesting ctDNA status was a strong predictor of tumor RFS after radical cystectomy [58, 59]. Interestingly, the median time from MRD positivity to clinically confirmed recurrence during surveillance was 96 days. Ben-David et al. also showed that detectable ctDNA before surgery (HR, 4.5 [95% CI 1–19], $p = 0.04$) and detectable ctDNA at the postoperative period (HR, 9.9 [95% CI 2.6–37], $p < 0.001$) were predictive of disease recurrence [60]. These results implied that ctDNA assessment for early risk stratification and relapse detection in BC is feasible and provides a basis for clinical trials that evaluate early therapeutic interventions.

The IMvigor011 trial is a global, randomized, double-blind Phase III study evaluating adjuvant atezolizumab versus placebo in high-risk muscle-invasive bladder cancer (MIBC) patients who are ctDNA-positive within 12–200 weeks postcystectomy (Table 3) [61, 62]. Eligible participants undergo serial ctDNA testing for up to 12 months; those who become ctDNA-positive without radiographic recurrence are randomized (2:1) to receive atezolizumab every 28 days for up to 1 year or matching placebo. The primary endpoint is disease-free survival in the ctDNA-positive population. ctDNA-negative patients remain on surveillance and are not randomized. This study was built on pivotal findings from IMvigor010 with MRD testing using Signatera. In this study, ctDNA-positive status identified patients with shorter overall survival (OS) and showed longer OS in those treated with atezolizumab group versus observation (HR: 0.59 [95% CI: 0.41–0.86], $p = 0.0024$) [62]. Subsequently, interim results of IMvigor011 presented at the 2024 European Association of Urology annual meeting showed that 17 relapses occurred of 171 patients with serially negative MRD status over a median follow-up of 16 months, and the 18-month disease-free and OS rates were 88% and 98%, respectively. Preliminary findings from the TOMBOLA trial presented at the European Society for Medical Oncology Congress in 2024 also indicated that ctDNA testing could help identify patients with BC who may benefit from early postcystectomy immunotherapy (Table 3) [63]. Overall, 57% of the enrolled patients were ctDNA-positive after surgery, with 75% detected within 4 months of surgery. The median lead time between ctDNA detection and visible metastases on CT scans was 43 days, with 20% of the ctDNA-positive patients eventually showing metastases. In contrast, only 3% of the ctDNA-negative patients developed metastases during the follow-up period. MODERN trial is a phase II/III trial assessing ctDNA-guided adjuvant therapy in patients with BC (Table 3). In cohort A, patients with detectable ctDNA following cystectomy are randomized to receive either adjuvant nivolumab alone or in combination with relatlimab, a LAG-3 inhibitor. In cohort B, patients without detectable ctDNA are randomized to receive adjuvant nivolumab or undergo ctDNA-based surveillance. Collectively, these prospective trials may optimize clinical trial design and improve cost-effectiveness by avoiding unnecessary treatments.

TABLE 1 | MRD studies in prostate and kidney cancer.

Tumor type	Author	PMID	Sample size	Median observation period (months)	Analysis method	Assay method	T stage	Target stage (UICC)	Preoperative ctDNA/postoperative MRD positive rate			Median (units) or rate (%, duration) of recurrence/progression-free survival by preoperative ctDNA/postoperative MRD		Comparison of preoperative ctDNA/postoperative MRD positive vs. negative in terms of recurrence			
									Preoperative	Postoperative	Over time	Positive patients	Negative patients	HR or OR (95% CI)*	*p*	Sensitivity	Specificity
Prostate	Pope B, et al., 2024	38378299	118	35	NGS	Tumor-informed	cT1-cT3	NA	16.0%	NA	NA	NA	NA	2.8 (1.1–7.1)	0.0055	NA	NA
Prostate	Fei X, et al., 2023	36915250	131	10	NGS	Tumor-informed	cT1-cT4	NA	65.5%	NA	NA	NA	NA	0.14 (0.09–0.24)	<0.01	NA	NA
Prostate	Lau E, et al., 2020	32807235	189	NA	PCR	Tumor-naive	cT1c-cT3a	NA	12.0%	NA	NA	NA	NA	2.4 (1.2–4.8)	0.014	NA	NA
Kidney	Correa A, et al., 2024	39013784	45	62	NGS	Signatera	NA	I-IV	50.0%	27.0%	NA	NA	NA	Preoperative 2.7 (1.02–7.15) Postoperative 3.23 (1.52–6.98)	Preoperative 0.046 Postoperative 0.003	NA	NA
Kidney	Park JS, et al., 2024	38475661	48	31.8	NGS	Tumor-informed	cT1a		20.8%	NA	NA	NA	NA	NA	NA	NA	NA
Kidney	Buttner T, et al., 2024	38322559	45	63	RT-PCR	Tumor-naive	NA	I-IV	NA	37.8%	NA	NA	NA	NA	0.005	NA	NA
Kidney	Jung M, et al., 2019	30626634	100	NA	RT-PCR	Tumor-naive	pT1-pT4	I-IV	12.0%	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI, confidential interval; ctDNA, circulating tumor DNA; HR, Hazard ratio; MRD, molecular residual disease; NA, not available; NGS, next-generation sequencing; OR, odds ratio; RT-PCR, reverse transcription PCR; UICC, Union for International Cancer Control.
*Values for MRD-negative patients relative to those for MRD-positive patients.

TABLE 2 | MRD studies in urothelial carcinoma.

Tumortype	Author	PMID	Sample size	Median observation period (months)	Analysis method	Assay method	Target stage (UICC)	Preoperative ctDNA/postoperative MRD positive rate			Median (units) or rate (%, duration) of recurrence/progression-free survival by preoperative ctDNA/postoperative MRD		Comparison of preoperative ctDNA/postoperative MRD positive vs. negative in terms of recurrence			
								Preoperative	Postoperative	Over time	Positive patients	Negative patients	HR or OR (95% CI)*	*p*	Sensitivity	Specificity
Bladder	Sfakianos JP et al., 2024	39073741	167	10	NGS	Signatera	I-IV	0/I: 37.5% II: 30.6% III: 57.0%	0/I: 3.3% II: 6.7% III: 40.0%	0/I: 14.3% II: 40.0% III: 56.8%	27.0% (1 year)	88.3% (1 year)	Postoperative 6.93 (2.4–20.05) Over time 23.02 (5.51–96.17)	Postoperative <0.001 Over time <0.001	NA	NA
Bladder	Nordentoft I et al., 2024	38811314	112	53.6	NGS	Tumor-informed		16.7%	25.9%	NA	NA	NA	23 (7.9–67.1)	<0.0001	91.0%	92.0%
Bladder	Ben David R et al., 2024	38521660	112	8	NGS	Signatera	I-IV	50.5%	19.8%	NA	16.0% (1 year)	47.0% (1 year)	9.9 (2.6–37.0)	<0.001	NA	NA
Bladder	Chauhan PS et al., 2023	36658307	74	23	NGS	Tumor-naïve		NA	Urine 72.2%	NA	NA	NA	3	0.01	NA	NA
Bladder	Szabados B et al., 2022	35577646	36	25	NGS	Signatera		Baseline 62.5% After NAC 46.7%	14.0%	NA	NA	NA	78.22 (8.64–707.78)	0.0001	NA	NA
Bladder	Powles T et al., 2021	34135506	581	21.9	NGS	Signatera		NA	37.0%	NA	NA	NA	6.3 (4.45–8.92)	<0.0001	NA	NA
Bladder	Christensen E et al., 2019	31059311	68	21	NGS	Signatera		NA	26.6%	NA	59% (1 year)	NA	NA	<0.001	100.0%	98.0%
Bladder	Birkenkamp D et al., 2018	28958829	60	NA	ddPCR	Tumor-informed	I-IV	NA	75.0%	NA	NA	NA	NA	0.001	NA	NA
Bladder	Christensen E et al., 2017	28069289	27	NA	ddPCR	Tumor-informed		100.0%	NA	NA	NA	NA	NA	Plasma <0.0001 Urine 0.031	NA	NA
Upper urinary tract	Tamura D et al., 2024	38083992	23	24.7	ddPCR	Tumor-informed		NA	Plasma 52.2% Urine 47.8%	NA	NA	NA	NA	NA	NA	NA
Upper urinary tract	Nakano K et al., 2022	35293110	17	NA	NGS	Oncomine Pan-Cancer Cell-Free Assay	0a-IV	NA	58.8%	NA	NA	NA	6.259 (1.485–26.38)	0.0125	NA	NA

Abbreviations: CI, confidential interval; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; HR, Hazard ratio; MRD, molecular residual disease; NA, not available; NGS, next-generation sequencing; OR, odds ratio; RT-PCR, reverse transcription PCR; UICC, Union for International Cancer Control.
*Values for MRD-negative patients relative to those for MRD-positive patients.

TABLE 3 | Current MRD-based ongoing clinical studies in genitourinary cancers.

Tumor type	Study title	Country	Study design	Sample size	Assay method	Sponsor	Major eligibility criteria	Study outline
Bladder	MODERN (NCT05987241)	North America	Interventional, phase II/III	1190	Signatera	Alliance	pT3-pT4 or pT0/x-pT4/N+	Nivolumab, Nivolumab plus Relatlimab
Bladder	IMVigor011 (NCT04660344)	Global	Interventional, phase III	495	Signatera	Hoffman-La Roche	pT2-4a or N+, postoperative, MRD positive	RCT of Atezolizumab vs. Placebo
Bladder	TOMBOLA (NCT04138628)	Denmark	Interventional, phase II	282	Tumor-informed	Jørgen Bjerggaard Jensen	cT2-4a, postoperative, MRD positive	Atezolizumab
Bladder	MARIA (NCT05219734)	United States	Observational	400	NA	Invitae	Scheduled resection	MRD monitoring
Renal	MRD GATE RCC (NCT06005818)	North America	Observational	100	Signatera	The University of Alabama at Birmingham	Intermediate-high risk or high-risk	Pembrolizumab
Renal	MEMORY (NCT05917106)	China	Observational	450	ctDNA methylomics	Jinling Hospital	Scheduled resection	MRD monitoring
Renal	KIDNEY-PAGER (NCT06145139)	Denmark	Observational	500	NA	University Aarhus	Scheduled resection	MRD monitoring

Abbreviation: NA, Not available.

There are only two reports on MRD in UTUC patients, which account for approximately 10% of UC [64, 65]. Tamura et al. reported that all patients with intravesical recurrence after radical nephroureterectomy (RNU) were ctDNA-positive in the urine, which is a higher proportion of patients compared to that for positive cytology (60%) or CT (30%); additionally, positivity occurred 60 days earlier than it did with cystoscopy. Moreover, in all metastatic cases, ctDNA was found in the plasma at the time of metastasis after RNU [64]. Nakano et al. also reported that preoperative ctDNA in 43 patients with localized UTUC was an independent risk factor for poor RFS (HR, 4.565 [95% CI: 1.433–14.539], $p = 0.00102$); furthermore, early postoperative MRD positivity was significantly associated with poor RFS (HR, 8.027 [95% CI: 2.347–27.454], $p = 0.0009$) in multivariate analysis [65].

Collectively, these results suggest that serial measurement of ctDNA following curative-intent surgery in UC is a highly specific method for identifying patients who might benefit from early intervention at the time of MRD, offering a promising strategy for personalizing care and improving outcomes, especially in high-risk patients.

6 | Current MRD Assays in Kidney Cancer

The global incidence of KC continues to increase, with 431,288 new cases reported in 2020, representing 3% of all diagnosed cancers worldwide [66]. RCC is the most prevalent type of cancer, accounting for 90% of all KCs. Localized RCC is typically managed with surgical intervention, either partial or radical nephrectomy. Although surgery remains the most effective treatment option, disease recurrence occurs in 20%–400% of patients treated for localized RCC [67–69]. Predicting RCC recurrence after surgery is important for patient counseling and choosing postoperative surveillance strategies. To date, several clinicopathological parameters have been incorporated into scoring systems and have been proposed to provide additional predictive ability. Specifically, the Leibovich score guides prognostication and selection in adjuvant clinical trials of patients with locally advanced RCC after nephrectomy [70, 71]. In 2022, pembrolizumab was first approved as an adjuvant treatment for patients with a high risk of recurrence after nephrectomy [18, 19]. Although 65% of patients in the pembrolizumab group did not have a recurrence at 4 years, the placebo group showed a 57% recurrence rate. Therefore, ctDNA analysis may enable postsurgical risk stratification and adjuvant treatment decision-making.

In early landmark studies of advanced RCC, the detection rate was low, at approximately 50%, which led to the classification of RCC as a low-ctDNA malignancy [52]. Moreover, the absence of hotspot mutations complicates disease monitoring using ctDNA in RCC. Considering the above, the number of reports on MRD testing remains limited, with some studies focusing on perioperative methylation analysis of specific genes, considering the low levels of ctDNA (Table 1) [72–74]. For instance, the hypermethylated short stature homeobox gene 2 (*SHOX2*) within circulating cell-free DNA is a highly sensitive surrogate parameter for the presence of ctDNA in various types of cancer, including RCC, where it has high prognostic potential as a surrogate for tumor burden prior to nephrectomy [74]. So far, many studies have evidenced the strong association between *SHOX2* hypermethylation and cancer progression [75–77]. Buttner et al. also focused on the hypermethylation of circulating *SHOX2* and found that hypermethylated SHOX2-positive patients showed unfavorable OS (HR, 3.65 [95% CI: 1.41–9.46], $p = 0.004$) and RFS (HR, 5.89 [95% CI: 1.46–23.8], $p = 0.005$) [78].

Recent advances in NGS have enabled the detection of ctDNA at levels as low as 0.1%, revealing comprehensive genetic mutations characteristic of tumors in the peripheral blood. Pal et al. analyzed ctDNA in 220 cases of metastatic RCC (mRCC) using Guardant360 [79, 80]. They reported that the detection rate of ctDNA mutations was 78.6% and that increased p53 and mechanistic target of rapamycin pathway (e.g., *NF1* and *PIK3CA*) alterations in post-first-line patients with first-line vascular endothelial growth factor-directed therapy may underlie the mechanisms of resistance. Furthermore, Kato et al. found a high detection rate of ctDNA in 84.5% of patients with mRCC and that 46.8% of patients developed new ctDNA mutations during disease progression, which was significantly linked to a shorter time to progression ($p = 0.046$) [81]. This implies that routine ctDNA assessment during the clinical course of patients with mRCC may have therapeutic implications.

Based on the success of tumor-naïve assays in ctDNA analysis, tumor-informed assays are expected to increase ctDNA detection in localized RCC [82, 83]. Using customized cancer gene panels with 16 RCC-related genes, Park et al. reported that ctDNA was detected at the time of surgery in 75% of patients in the pT3a group (10/12); conversely, only 2.8% of patients exhibited pT1a (1/36) [84]. Based on radiological images, the detection of ctDNA was the only significant preoperative predictor of pT3a upstaging, especially in renal sinus fat invasion from cT1a. Considering that the WGS approach may detect gene alterations with a detection limit of 0.007% even in RCC [31], MRD testing may be useful for guiding the treatment of RCC after surgery for localized RCC.

Recently, several prospective studies have been reported for MRD monitoring in RCC (Table 3) [82, 85]. Basu et al. launched the MRD GATE RCC trial, in which ctDNA analysis was performed before and/or after the intended curative treatment for localized RCC to predict MRD. In this trial, participants will receive standard-of-care pembrolizumab only when they have MRD [82]. Iisager et al. also launched the KIDNEY-PAGER trial that applied WGS and cfMeDIP sequencing approaches to improve the sensitivity of detection. If patients are positive for ctDNA, they may benefit from a closer follow-up scheme, regardless of the Leibovich score, or require immediate intervention, such as adjuvant therapy [85]. As with the clinical trials in UC, these prospective trials may identify patients at high risk of relapse earlier than conventional imaging and avoid overtreatment with the reduction of medical costs.

7 | MRD Assays in Other GU Cancers

Most germ cell tumors are diagnosed as isolated testicular masses and managed surgically with radical orchiectomy [86]. Postorchiectomy surveillance is crucial for monitoring recurrence, especially in nonseminomatous germ cell tumors exhibiting high-risk features. Ben-David et al. evaluated the utility of

a personalized tumor-informed ctDNA assay for MRD detection and prognosis in stage I–III testicular cancer [87]. Among 35 patients, ctDNA positivity during postorchiectomy MRD and surveillance periods was strongly associated with inferior RFS (HR 11.8, 95% CI: 2.3–59.1, $p = 0.003$). ctDNA outperformed standard tumor markers in predicting outcomes, and multivariate analysis identified ctDNA positivity as the only independent predictor of poor RFS, highlighting its potential as a valuable prognostic tool. Hassoun et al. also reported longitudinal, tumor-informed ctDNA monitoring in 55 patients with stage I–III testicular cancer [88]. ctDNA positivity during MRD and surveillance windows was significantly associated with inferior RFS (HR 5.27, 95% CI 1.22–22.71, $p = 0.0026$), whereas elevated serum tumor markers were not. Notably, none of the patients with undetectable ctDNA relapsed, while 50% with detectable ctDNA did. These early studies provide valuable initial evidence that high-sensitivity ctDNA analysis may help guide treatment decisions and predict recurrence in patients with germ cell tumors.

Regarding other types of GU cancers, such as penile or adrenocortical cancer, there have been no reports, possibly due to the low number of cases.

8 | Challenges and Future Directions

Despite the spread of promising results of MRD testing, MRD testing is not reimbursed in many countries, including Europe, the United States, and Japan, since there are still a limited number of prospective trials to confirm its utility (Table 3). In GU cancers, when we encounter final results of these prospective trials, treatment strategies can be adaptively refined using ctDNA-based MRD detection and postoperative monitoring. For instance, the IMvigor010 trial failed to demonstrate the efficacy of atezolizumab therapy in 809 postradical resection patients with UC, whereas the IMvigor011 trial screened 800 patients with postradical resection BC, among whom 495 MRD-positive patients were included in the trial and re-examined the efficacy of atezolizumab. The MRD GATE trial was also launched to assess whether MRD-positive patients truly benefit from adjuvant pembrolizumab therapy in patients with high-risk, resected RCC while reducing overtreatment [82]. As seen from these features, selecting patients with a high risk of recurrence with ctDNA-based MRD assays encourages the development of new perioperative treatments by reducing sample size, the observational period for statistical testing, and development costs in various tumor types. Furthermore, MRD-guided treatments have the potential to reduce medical costs since they may avoid unnecessary treatment [89, 90].

Importantly, we are currently evaluating an ultrasensitive WGS-based MRD assay in the MONSTAR-SCREEN-3 study to establish a comprehensive pan-cancer MRD platform that includes traditionally low-shedding tumors [29], supporting the promotion of the development of new types of treatment.

9 | Conclusion

In summary, there is a certain degree of general consensus that MRD testing holds clinical validity in GU cancers, especially in bladder cancer. With the advancement of NGS technology, ctDNA-based MRD testing holds significant potential to guide therapeutic decision-making in GU cancers. MRD-guided strategies may also optimize clinical trial design and improve cost-effectiveness by avoiding unnecessary treatment. However, regulatory challenges remain, including assay standardization, a lack of FDA-approved MRD companion diagnostics for solid tumors, and limited reimbursement frameworks. Integration into routine practice will require consensus on assay methods, interpretation criteria, and demonstration of improved patient outcomes. Further large prospective trials are needed to validate clinical utility.

Author Contributions

Taigo Kato: writing – original draft, conceptualization, data curation. **Shugo Yajima:** writing – review and editing, data curation. **Yoshiaki Nakamura:** writing – review and editing, data curation, conceptualization, project administration. **Shin Kobayashi:** writing – review and editing, data curation, conceptualization, project administration. **Hideaki Miyake:** writing – review and editing, conceptualization, data curation, supervision.

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Conflicts of Interest

Hideaki Miyake is a member of the Editorial Board of the International Journal of Urology and the co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The others declare no competing interest.

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