Review Article

Molecular Residual Disease-guided Adjuvant Treatment in Resected Colorectal Cancer: Focus on CIRCULATE-Japan

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Abstract

The body of evidence supporting the utility of the detection of molecular residual disease (MRD) in resected colorectal cancer (CRC) using circulating tumor DNA (ctDNA) analysis is rapidly growing. Furthermore, this evidence provides the rationale for escalation and de-escalation adjuvant chemotherapy (ACT) strategies using ctDNA MRD analysis. This has led to various randomized clinical trials, and CIRCULATE-Japan is one of the largest of these trial platforms. In this review, we provide an overview of the potential utility of ctDNA-based MRD detection for escalation and de-escalation ACT approaches. Furthermore, we highlight the feasibility using ctDNA clearance as a surrogate endpoint for ACT trials in patients with resected CRC, based on findings of the CIRCULATE-Japan project.

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Introduction

The use of liquid biopsy technologies, especially the analysis of circulating tumor DNA (ctDNA), is rapidly advancing for various cancer types across different disease stages. Plasma ctDNA, a short fragment of tumor-derived DNA of approximately 130–150 base pairs, is released from tumor cells into the plasma through apoptosis, necrosis, and secretion.[1] The half-life of ctDNA is much shorter than that of tumor makers and it disappears rapidly after curative resection if there is no residual tumor.

In patients with advanced-stage cancers, the clinical utility of ctDNA analysis has been demonstrated for treatment selection and efficacy monitoring and identification of the most appropriate subsequent treatment following drug resistance.[2,3] The Cancer Genome Screening Project for Individualized Medicine in Japan (SCRUM-Japan) is one of the largest biomarker screening programs for patients with advanced solid tumors worldwide.[4] Based on the SCRUM-Japan project, GOZILA, a nationwide ctDNA screening project for advanced gastrointestinal cancers using Guardant360 CDx, a 74-gene ctDNA assay, was launched in Japan in 2018.

Compared with the SCRUM-Japan GI-SCREEN, a tissue-based genotyping study, GOZILA demonstrated a significantly shorter turnaround time and accelerated clinical trial enrollment without compromising efficacy as a useful feature of ctDNA genotyping.[5] The confirmed utility of ctDNA genotyping has encouraged ctDNA-guided investigator-initiated clinical trials for rare subtypes, which are ongoing. One of these trials, TRIUMPH, demonstrated the efficacy of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2 (*HER2*)-amplified colorectal cancer (CRC).[6] These effects were prospectively confirmed using tumor tissue or ctDNA analysis, which resulted in the first global approval for this indication.

These studies indicate that the evidence for ctDNA genotyping in advanced solid tumors is establishing its usefulness. Furthermore, rapidly accumulating evidence supports the clinical validity of ctDNA analysis for molecular residual disease (MRD) detection and monitoring as the next promising application. Data mainly from case/control and longitudinal cohort studies demonstrate that ctDNA detection immediately after therapy completion or during surveillance is predictive of a high risk of recurrence of various cancers, including CRC.

However, the clinical utility of ctDNA MRD detection and monitoring has not been established and relevant prospective randomized trials are required. In this review, we provide an

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overview of the potential utility of ctDNA-based MRD detection for escalation and de-escalation adjuvant treatment strategies in patients with resected CRC based on the CIRCULATE-Japan project. We also highlight ongoing clinical trials for developing ctDNA MRD-guided treatments and surrogacy of ctDNA clearance as an endpoint for trials and discuss future perspectives.

Current Evidence for ctDNA-based MRD Detection in Resected CRC

In patients with stage III colon cancer who have undergone potentially curative resection, disease recurrence is thought to arise from clinically occult micrometastases present at the time of surgery. The goal of adjuvant chemotherapy (ACT) is to eradicate micrometastases, thereby increasing the cure rate. ACT with fluoropyrimidines alone has been well-established to decrease the risk of death by 10% to 15% in stage III colon cancer, with an additional 4% to 6% with oxaliplatin-containing combinations.[7,8] In patients with resected stage II colon cancer, to determine the indication for ACT, clinicopathological high-risk factors are used.

These factors are pathological T4, localized perforation, bowel obstruction, lymphatic/vascular invasion, perineural invasion, poor differentiation, positive margins, and <12 lymph nodes dissected.[9] For patients with resected rectal cancer, ACT selection is often extrapolated from experience in colon cancer, although total neoadjuvant treatment strategy is more common. Although risk stratification using these factors and ACT have improved prognosis, it is still insufficient with a recurrence risk of ~30% even after ACT.[10] In addition, oxaliplatin-based ACT causes peripheral neuropathy during and after chemotherapy, which may greatly impair the patient's quality of life.

Therefore, developing a biomarker that can accurately diagnose the risk of recurrence and identify patients who truly need postoperative ACT is desirable. Early detection of recurrence and therapeutic interventions may improve the prognosis of patients with recurrent CRC. Tumor markers and radiographic imaging such as computed tomography (CT) are used as diagnostic tools for detecting recurrence. However, tumor markers are not satisfactory in both sensitivity and specificity, and radiographic imaging cannot identify micrometastases.

MRD detection using ctDNA is a potentially non-invasive recurrence prediction tool for various cancer types, including CRC.[11] The recurrence risk of patients with postoperative positive ctDNA is markedly higher than previously reported (Figure 1). [12,13] Numerous retrospective studies have reported high specificity and almost 100% positive predictive value for clinical recurrence in patients with ctDNA-defined MRD-positive resected CRC.[14-18] The average time from ctDNA MRD detection in plasma to recurrence detecting using CT imaging was several months.

This finding suggests that ctDNA-based MRD detection may provide an opportunity for early intervention before radiographic evidence of recurrence and potential eradication of micrometastases.[2] MRD assays can be categorized into two types of liquid biopsy: (1) tumor-informed assay, which detects ctDNA MRD using mutational signatures derived from genomic sequencing of the primary tumor to create patient-specific assays, and (2) plasma-only assay that identifies ctDNA using a fixed gene panel, DNA methylation analysis, or both and does not require prior tumor tissue profiling (Table 1).

The result of the first randomized trial that assessed the utility of ctDNA MRD-guided treatment decisions in resected CRC was recently reported. In the DYNAMIC randomized phase II trial, 455 patients with resected stage II CRC were randomly assigned to receive ctDNA-guided or standard management.[19] In the former group, ctDNA analysis was performed on plasma specimens collected 4 and 7 weeks after surgery, and only patients with a positive result received the physician's choice of ACT.

At a median follow-up of 37 months, fewer patients in the ctDNA-guided group than in the standard management group received ACT (15.3% versus 27.9%, respectively; relative risk 1.82, 95% confidence interval [CI] 1.25–2.65). Notably, patients with high-risk disease in the standard management group were more than two times more likely to receive ACT than those in the ctDNA-guided group were. The non-inferiority of ctDNA-guided treatment to standard management was confirmed based on 2-year recurrence-free survival (RFS) rates of 93.5% and 92.4%, respectively.

The results of the DYNAMIC trial provide evidence to support the notion that ctDNA positivity is a promising marker to guide treatment decisions in stage II CRC. However, because the efficacy of ACT has not been evaluated in ctDNA MRD-positive and-negative patients, the predictive value of ctDNA MRD remains unclear. To address this knowledge gap, several interventional trials are ongoing and CIRCULATE-Japan is one of the largest project platforms involving such trials.

CIRCULATE-Japan, Large ctDNA MRD-guided Trial Program

We launched a large trial platform named CIRCULATE-Japan, enrolling patients with resectable CRC, to evaluate the clinical utility of ctDNA MRD detection. The platform includes an observational (GALAXY) and two randomized phase III trials (VEGA and ALTAIR). The GALAXY study is a prospective large-scale registry designed to monitor ctDNA for 5,200 patients with clinical stage II to IV or recurrent CRC who underwent complete surgical resection, using the Signatera MRD blood test.[20] Blood samples were collected before and 4, 12, 24, 36, 48, 72, and 96 weeks after surgery. Investigators receive the results of ctDNA assays in a timely manner and patients were subsequently enrolled into affiliated randomized trials or standard-of-care (SOC) treatment based on ctDNA status.

Certain features of poor prognosis prompt practitioners to consider ACT after curative surgery. However, it is unclear whether postoperative positive ctDNA MRD can predict the benefit of ACT. To prospectively validate and build on previously published relevant evidence on resected CRC, the GALAXY study evaluated the impact of postsurgical ctDNA on the outcome data of 1,039 patients with resected CRC, its implications for the selection of ACT, and the association between ctDNA dynamics and prognosis.[12] Among 187 patients who were ctDNA-positive 4 weeks postsurgery, 61.4% (115/187) experienced recurrence, compared to 9.5% (81/852) of ctDNA-negative patients (hazard ratio [HR], 10.0; 95%CI, 7.7–14.0).

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Figure 1 Hazard ratio (HR) of recurrence in pathological stage II–III colorectal cancer (CRC). Circulating tumor DNA (ctDNA) molecular residual disease (MRD) positivity 4 weeks after surgery is associated with significantly higher risk of recurrence than any other biomarker. CDX2, caudal-type homeobox 2; MSI, microsatellite instability.

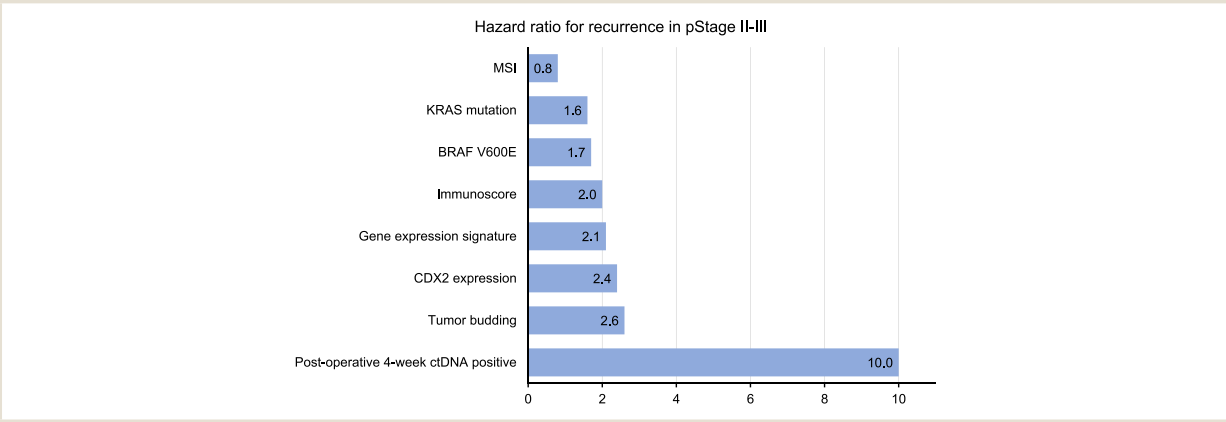

Table 1 Currently Available or Developed Circulating Tumor DNA (ctDNA) Molecular Residual Disease (MRD) Assays

Assay Name	Company	Type of Assay	Target
Guardant reveal	Guardant Health	Plasma-only	Cancer-specific mutations and DNA methylation
SafeSEQ	Sysmex Inostics	Plasma-only	Cancer-specific mutations
AVENIO ctDNA Surveillance kit	Roche	Plasma-only	Cancer-specific mutations in 197 genes
Signatera	Natera	Tumor-informed	16 somatic mutations selected from tissue WES
PCM	INVITAE	Tumor-informed	~50 variants selected from tissue WES
NeXT personal	Personalis	Tumor-informed	~1,800 specially-selected somatic variants from tissue WGS
RaDaR	Inivata	Tumor-informed	~48 tumor-specific variants from tissue WES
PredicineBEACON	Predicine	Tumor-informed	~50 somatic mutations selected for personalized MRD panel design, in combination with the use of a fixed core panel of 500 actionable/hotspot variants

Abbreviations: ctDNA = circulating tumor DNA; MRD = molecular residual disease; WES = whole-exome sequencing; WGS = whole-genome sequencing.

Furthermore, the 18-month disease-free survival (DFS) in ctDNA-positive and -negative patients was 38.4% (95%CI, 31.4–45.5%) versus 90.5% (95%CI, 88.3%–92.3%), respectively. These findings were consistent with those of previous studies showing the negative prognostic impact of positive ctDNA MRD. In addition, patients who were high-risk stage II/III and ctDNA-positive at 4 weeks derived significant benefit from ACT with an 18-month DFS of 61.6% and 22.0% in the ACT and observation groups, respectively (adjusted HR, 6.59; 95% CI, 3.53–12.3, Figure 2A). In contrast, ACT showed no statistically significant benefit in ctDNA-negative patients with an 18-month DFS of 94.9% and 91.5% in the ACT and observation groups, respectively (adjusted HR, 1.71; 95% CI, 0.80–3.7).

These interim results of the CIRCUALTE-Japan trial strongly indicate that patients with positive ctDNA MRD received more benefit from ACT than those with negative ctDNA MRD did. Furthermore, a therapeutic strategy with ACT escalation and de-escalation for ctDNA MRD-positive and -negative patients, respectively, is warranted (Figure 2B). A retrospective analysis of a randomized phase III trial of adjuvant atezolizumab versus observation in operable urothelial cancer showing the survival benefit of adjuvant atezolizumab in ctDNA patients supports these findings.[19] However, the ctDNA-guided treatment strategy should be further investigated in randomized trials because of the lack of evidence from prospective studies.

To address this issue, the CIRCULATE-Japan project includes two randomized controlled trials evaluating escalation and de-escalation strategies. The VEGA trial is a randomized phase III study designed to test whether postoperative surgery alone is non-inferior to standard therapy with capecitabine plus oxaliplatin for 3 months.[20] Patients included in the VEGA trial are those with high-risk stage II or low-risk stage III colon cancer if the ctDNA

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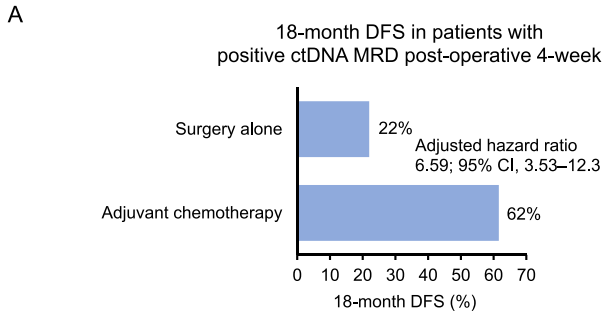
Figure 2 Escalation strategy based on circulating tumor DNA (ctDNA) MRD detection after curative resection. (A) The 18-month disease-free survival (DFS) in patients who showed ctDNA-based molecular residual disease (MRD) positivity 4 weeks after surgery in CIRCULATE-Japan project. (B) Ongoing randomized trials to evaluate ctDNA utility for optimization of adjuvant chemotherapy (ACT) using escalation strategy.



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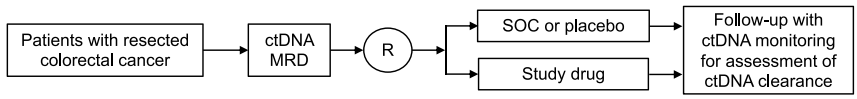

Patients	Study drug	Study
Stage IIA	FOLFOX	COBRA (NCT04068103)
Stage II	Capecitabine or CAPOX	CIRCULATE (NCT04089631)
Stage I or II	CAPOX or FOLFOX	IMPROVE-IT (NCT03748680)
Stage II or III	CAPOX, FOLFOX, or FOLFOXIRI	CIRCULATE-US (NCT05174169)
Stage III	5-FU, FOLFOX, CAPOX, or FOLFOXIRI	DYNAMIC-III (ACTRN126170015)
Stage I-IV or relapsed	FTD/TPI	ALTAIR (NCT04457297)
High-risk stage II or stage III	RO7198457	NCT04486378
High-risk stage II or stage III	GRT-C901/GRT-R902	NCT05456165

status is negative at week 4 after curative surgery in the GALAXY study. The ALTAIR double-blind, phase III study is designed to establish the superiority of trifluridine/tipiracil over the placebo in patients with resected CRC who are ctDNA-positive in the GALAXY study.[20] The CIRCULATE-Japan project will help determine whether measuring ctDNA postoperatively has prognostic or predictive value or both.

ctDNA Clearance as a Surrogate Endpoint for ACT Trials in CRC

The Adjuvant Colon Cancer End Points (ACCENT) collaborative group study demonstrated that DFS after 2- and 3-year follow-up periods is an appropriate endpoint for clinical trials involving the adjuvant treatment of colon cancer with 5-flurouracil (FU)-based chemotherapy based on an analysis of individual patient data from 20,898 patients in 18 randomized clinical trials of colon cancer adjuvant treatment.[21] This was further confirmed by the ACCENT group through an analysis of data from 12,676 patients from six trials showing the correlation between 2- and 3-year DFS and 5- and 6-year OS. The use of DFS as an alternative surrogate endpoint to OS reduces trial duration and cost and could potentially accelerate the time from therapeutic innovation to patient care.[22]

The potential usefulness of ctDNA clearance as a surrogate endpoint has been suggested. Serial sampling of ctDNA during or after ACT has also been shown to correspond to clinical events, which may provide early information on the effects of adjuvant therapy, with numerous patients displaying a decrease during ACT. The CIRCULATE-Japan project also demonstrated an association between ctDNA clearance and prognosis in a larger sample size than that previously reported. ACT was associated with a higher estimated cumulative incidence of ctDNA clearance, at 68.48% (63/92) of patients by week 24 postsurgery, than that of patients who did not receive ACT (12.2%, 11/90 patients). Furthermore, the 18-month DFS rate was 81.4% (95% CI, 68.6%–89.3%) in patients who converted from ctDNA MRD-positive to -negative, which was higher than the 22.9% (95% CI, 14.3%–32.7%) observed in those who remained positive. This observation supports the usefulness of ctDNA clearance as an endpoint in ACT clinical trials. Ongoing prospective studies were designed to determine whether ctDNA can be successfully used as a surrogate endpoint for CRC. However, to validate the surrogacy of ctDNA clearance, pooled analysis of several randomized clinical trials should be performed.

Ongoing Clinical Trials

Ongoing randomized trials were designed to evaluate whether ctDNA can be used as a dynamic marker to optimize ACT through escalation or de-escalation. The eradication strategies included adjuvant fluoropyrimidine with or without oxaliplatin for ctDNA MRD-positive stage I/II patients (Trials: COBRA,

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NCT04068103; CIRCULATE, NCT04089631; and IMPROVE-IT, NCT03748680). Other strategies are folinic acid, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) or folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) for ctDNA MRD-positive stage III patients (trials: CIRCULAE-US, NCT05174169; CLAUDIA, NCT05534087; AFFORD, NCT05427669; and DYNAMIC-III, ACTRN126170015). The CIRCULATE-US study also assessed the non-inferiority of the surgery alone strategy compared to SOC for patients with ctDNA-negative stage III CRC (Figure 2B). Similar to the ALTAIR trial, another randomized trial (NCT05343013) evaluated trifluridine/tipiracil. The phase II NCT03803553 study used a biomarker-stratified approach with encorafenib, bimimetinib, and cetuximab for *BRAF* V600E CRC and nivolumab for high microsatellite instability (MSI-H) CRC in a ctDNA-positive population. The COSMOS-CRC-03 trial is evaluating the utility of the Guardant Reveal liquid biopsy test for predicting the recurrence risk in patients with resectable stage IV CRC (jRCT2072220055). Patients with negative ctDNA 4 weeks postsurgery will not receive ACT, whereas those with positive ctDNA will be randomly assigned to receive adjuvant FOLFOX or FOLFOXIRI plus bevacizumab treatment.

The ctDNA MRD detection technology provides a strategy to develop novel treatment approaches for resected CRC. Cancer vaccines have been used to explore immunotherapies for ctDNA MRD-positive resected CRC. ELI-002 is a KRAS-targeting vaccine under study in *RAS*-mutated and ctDNA MRD-positive solid tumors with MRD in the AMPLIFY-201 trial (NCT04853017). The use of mRNA-based cancer vaccines has also been explored as an individualized treatment option for high-risk patients. RO7198457, a personalized mRNA-based vaccine that specifically targets expressed tumor-associated antigens, has shown promising activity in combination with atezolizumab for various advanced cancers. In the phase II NCT04486378 trial, DFS was evaluated in stage II or III ctDNA-positive patients who were randomized to receive either RO7198457 or pursue watchful waiting. Other trials incorporating MRD-guided cancer vaccine therapy include those on another mRNA vaccine, GRT-C901 (NCT05456165), and a microbiome-derived therapeutic vaccine EO2040 (NCT05350501). Atezolizumab plus bevacizumab for ctDNA MRD-positive gastrointestinal cancers (NCT05482516) and temozolomide and irinotecan in patients with MGMT-silenced and ctDNA MRD-positive CRC (NCT05031975) have also been explored.

Challenges of Future ctDNA MRD Analysis

The major caveat of ctDNA MRD assays is the occurrence of some MRD-negative relapses, which may be due to inadequate sensitivity. Current tumor-based assays use mutational variants from targeted next generation sequencing (NGS) or whole-exome sequencing to design personalized ctDNA tests. However, only a low percentage of tumor mutations occur in the coding regions of the genome, where an exome can capture them. To find thousands of mutations in most tumors, which have low mutational burden, whole-genome sequencing may be appropriate for the identification of their unique mutations.[23,24]

Molecular profiling using multiomics, including methylome, fragmentome, and proteome profiling, beyond DNA analysis is another potential approach to improving the sensitivity of ctDNA MRD assays. Guardant Reveal is a plasma-only ctDNA assay that uses a multimodal approach for CRC detection, targeting common oncogenic mutations and regions expected to undergo epigenomic modification in cancer. We conducted the COSMOS-CRC-01 prospective study to evaluate the utility of Guardant Reveal in patients with resected CRC.[25] In the COSMOS-CRC-01 study, 93 patients with resectable clinical stage 0–III CRC were analyzed and MRD was detected in 23 (25%) four weeks after surgery. Interim results showed that MRD was positive in 9%, 61%, and 30% using genomic, epigenomic, and a combination of both calls, respectively. Furthermore, the lowest tumor fraction was $< 0.01\%$ and these findings suggest that epigenomic and genomic signatures are complementary for ctDNA MRD detection.

The integration of a non-liquid biopsy method for the prediction of recurrence risk may decrease the false-negatives of ctDNA MRD detection. Skrede et al. developed the DoMore-v1-CRC assay from scanned hematoxylin and eosin sections from 2,500 patients with CRC with $>$ 12,000,000 image tiles from patients with a distinctly good or poor disease outcome from four cohorts using a deep learning-based method.[26] In 1645 patients with a non-distinct outcome used for tuning, the histotyping score provided an HR of 3.84 (95% CI, 2.72–5.43) for poor versus good prognosis in the primary analysis of the validation cohort. In addition, the HR was 3.04 (95% CI, 2.07–4.47) after adjusting for established prognostic markers, which were significant in the univariable analyses of the same cohort, which were pN stage, pT stage, lymphatic invasion, and venous vascular invasion. These results indicate the potential usefulness of AI-based methods for recurrence prediction, which could be integrated with ctDNA MRD detection as a more accurate biomarker.

Conclusion

The obvious benefit of ACT in patients with a positive postoperative ctDNA test result in the CIRCULATE-Japan project suggest that clinical trials that evaluate ACT escalation and de-escalation strategies in resected CRC are warranted. Furthermore, ongoing clinical trials with a ctDNA clearance endpoint should be integrated in future projects to assess ctDNA clearance surrogacy for survival outcomes, which would accelerate ACT clinical trials. Along with these ongoing trials, the development of ctDNA MRD assays is advancing and the acquired knowledge will hopefully facilitate the future use of ctDNA MRD assays in patients with resected CRC.

Disclosure

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References

1. Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Analysis of the size distributions of fetal and maternal cell-free DNA by paired-end sequencing. *Clin Chem*. 2010;56:1279–1286. doi:10.1373/clinchem.2010.144188.
2. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol*. 2019;5:1124–1131. doi:10.1001/jamaoncol.2019.0528.
3. Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature*. 2021;595:432–437. doi:10.1038/s41586-021-03642-9.
4. Bando H. The current status and problems confronted in delivering precision medicine in Japan and Europe. *Curr Probl Cancer*. 2017;41:166–175. doi:10.1016/j.currproblcancer.2017.02.003.
5. Nakamura Y, Fujisawa T, Taniguchi H, et al. SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN: path to the realization of biomarker-guided precision oncology in advanced solid tumors. *Cancer Sci*. 2021;112:4425–4432. doi:10.1111/cas.15132.
6. Nakamura Y, Okamoto W, Kato T, et al. Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: a phase 2 trial. *Nat Med*. 2021;27:1899–1903. doi:10.1038/s41591-021-01553-w.
7. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the Mosaic trial. *J Clin Oncol*. 2009;27:3109–3116. doi:10.1200/JCO.2008.20.6771.
8. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. 2011;29:1465–1471. doi:10.1200/JCO.2010.33.6297.
9. Baxter NN, Kennedy EB, Bergsland E, et al. Adjuvant therapy for stage II colon cancer: ASCO guideline update. *J Clin Oncol*. 2022;40:892–910. doi:10.1200/JCO.21.02538.
10. Oki E, Ando K, Taniguchi H, Yoshino T, Mori M. Sustainable clinical development of adjuvant chemotherapy for colon cancer. *Ann Gastroenterol Surg*. 2022;6:37–45. doi:10.1002/ags3.12503.
11. Kasi PM, Fehringer G, Taniguchi H, et al. Impact of circulating tumor DNA-based detection of molecular residual disease on the conduct and design of clinical trials for solid tumors. *JCO Precis Oncol*. 2022;6. doi:10.1200/PO.21.00181.
12. Kotaka M, Shirasu H, Watanabe J, et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational Galaxy study in CIRCULATE-Japan. *J Clin Oncol*. 2022;40:9. doi:10.1200/JCO.2022.40.4_suppl.009.
13. - Miyamoto Y, Hiyoshi Y, Sawayama H, et al. Precision medicine for adjuvant chemotherapy of resected colorectal cancer. *Ann Gastroenterol Surg*. 2020;4:635–645.
14. Reinert T, Schøler LV, Thomsen R, et al. Analysis of circulating tumour DNA to monitor disease burden following colorectal cancer surgery. *Gut*. 2016;65:625–634. doi:10.1136/gutjnl-2014-308859.
15. Murray DH, Symonds EL, Young GP, et al. Relationship between post-surgery detection of methylated circulating tumor DNA with risk of residual disease and recurrence-free survival. *J Cancer Res Clin Oncol*. 2018;144:1741–1750. doi:10.1007/s00432-018-2701-x.
16. Tie J, Cohen JD, Wang Y, et al. Serial circulating tumour DNA analysis during multimodality treatment of locally advanced rectal cancer: a prospective biomarker study. *Gut*. 2019;68:663–671. doi:10.1136/gutjnl-2017-315852.
17. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med*. 2016;8:346ra92. doi:10.1126/scitranslmed.aaf6219.
18. Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analyses as markers of recurrence risk and benefit of adjuvant therapy for Stage III colon cancer. *JAMA Oncol*. 2019;5:1710–1717. doi:10.1001/jamaoncol.2019.3616.
19. Tie J, Cohen JD, Lahouel K, et al. Circulating tumor DNA analysis guiding adjuvant therapy in Stage II colon cancer. *N Engl J Med*. 2022;386:2261–2272. doi:10.1056/NEJMoa2200075.
20. Taniguchi H, Nakamura Y, Kotani D, et al. CIRCULATE-Japan: Circulating tumor DNA-guided adaptive platform trials to refine adjuvant therapy for colorectal cancer. *Cancer Sci*. 2021;112:2915–2920. doi:10.1111/cas.14926.
21. Renfro LA, Sargent DJ. Findings from the adjuvant colon cancer end points (accent) collaborative group: the power of pooled individual patient data from multiple clinical trials. *Chin Clin Oncol*. 2016;5 80-80. doi:10.21037/cco.2016.12.02.
22. Sargent D, Shi Q, Yothers G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: data from 12,676 patients from Mosaic, X-ACT, PETACC-3, C-06, C-07 and C89803. *Eur J Cancer*. 2011;47:990–996. doi:10.1016/j.ejca.2010.12.015.
23. Subhash VV, Huang L, Kamili A, et al. Whole-genome sequencing facilitates patient-specific quantitative PCR-based minimal residual disease monitoring in acute lymphoblastic leukaemia, neuroblastoma and Ewing sarcoma. *Br J Cancer*. 2022;126:482–491. doi:10.1038/s41416-021-01538-z.
24. Tan AC, Saw SP, Lai GG, et al. Ultra-sensitive detection of minimal residual disease (MRD) through whole genome sequencing (WGS) using an AI-based error suppression model in resected early-stage non-small cell lung cancer (NSCLC). *Cancer Res*. 2022;82:5114.
25. Tsukada Y, Matsuhashi N, Murano T, et al. Impact of post-operative integrated genomic and epigenomic signatures of circulating tumor DNA (ctDNA) on recurrence in resected colorectal cancer: Initial report of a prospective ctDNA monitoring study COSMOS-CRC-01. *J Clin Oncol*. 2022;40:168. doi:10.1200/JCO.2022.40.4_suppl.168.
26. Skrede OJ, De Raedt SD, Kleppe A, et al. Deep learning for prediction of colorectal cancer outcome: a discovery and validation study. *Lancet*. 2020;395:350–360. doi:10.1016/S0140-6736(19)32998-8.

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