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Article

Clinical Applications of Tissue-Free Molecular Residual Disease (MRD) in Colorectal Cancer—Real-World Utilization and Case Series in Asian and Middle Eastern Patients

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Abstract

Background: Despite well-established treatment and follow-up protocols for the management of colorectal cancer patients, recurrences are frequent. Post curative therapy, ctDNA-based molecular residual disease assessment has the ability to stratify patients into higher and lower risks of recurrence. Large-scale clinical trials are necessary to establish utility at a broad level, but physicians also need real-world evidence and case reports before utilizing MRD testing in routine practice. Methods: We analyzed real-world utilization patterns of Guardant Reveal in patients with CRC across stages by collating information from the test request form after the test was ordered as a part of routine practice in the AMEA region. Results: We report that 92% of the tests were utilized for stage II and stage III patients. The timing of the first MRD test order varies between stages, with a higher proportion of tests being ordered within the first 12 weeks of surgery for stage II (71.8%), while for stage III (50%) and stage IV oligometastatic (72%), the first test was ordered after 12 weeks of surgery. Conclusions: Case reports delineate physicians' perspectives on actions taken on the basis of MRD test results and outcomes.

Keywords: case series; molecular residual disease (MRD); colorectal cancer (CRC); liquid biopsy; Reveal; circulating tumor DNA (ctDNA); epigenomics; methylation

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1. Introduction

Colorectal cancer (CRC) continues to pose a significant public health challenge worldwide, with the Asia-Pacific, Middle East, and Africa (AMEA) regions carrying a considerable share of the burden. Globally, CRC is the third most frequently diagnosed malignancy and is the second leading cause of cancer-related mortality. This accounted for roughly

1.9 million new cases and more than 930,000 deaths in 2020 worldwide [1,2]. CRC incidence is projected to increase, largely driven by population growth, aging demographics, and shifts in lifestyle factors, including rising rates of obesity and dietary changes [3].

Across AMEA, the epidemiology of CRC demonstrates substantial variation based on the healthcare infrastructure. Countries such as Japan, South Korea, China, and Australia report some of the world's highest incidence rates, reflecting older populations and increased adoption of Westernized diets and lifestyles [4,5]. In East Asia, age-standardized incidence rates for CRC among men exceed 40 per 100,000 in several nations, paralleling figures seen in Europe and North America [4]. In contrast, many nations in Southeast Asia and South Asia maintain lower CRC rates, though recent years have shown upward trends, particularly in rapidly urbanizing regions [5].

Despite advances in screening, early detection, and treatment, CRC remains a substantial health burden in AMEA, contributing significantly to mortality, morbidity, and healthcare costs. Data from the Global Burden of Disease study highlight the considerable disability-adjusted life years (DALYs) lost due to CRC across many AMEA countries, underscoring its broad societal impact [6]. Adding to the concern is the rising incidence of early-onset CRC, diagnosed before age 50, which has been increasing in several AMEA countries over the past two decades—a pattern also observed in Western nations [7].

A persistent obstacle in CRC management is the risk of disease recurrence. Even after curative-intent surgery and standard adjuvant therapy, a significant proportion of patients ultimately experience relapse. Conventional surveillance relies on clinical examinations, carcinoembryonic antigen (CEA) monitoring, and imaging studies [8]. Frequency and tools for recurrence monitoring vary across various countries in AMEA and could also vary across institutions within each country. However, these methods often lack sufficient sensitivity to detect molecular residual disease (MRD) before the recurrence becomes large or clinical manifestations emerge [9]. Consequently, many recurrences are diagnosed at advanced stages, limiting therapeutic options. Studies indicate that approximately 30–40% of patients with stage II–III CRC will develop recurrence despite following guideline-recommended treatment pathways, highlighting the urgent need for more precise tools to assess recurrence risk and facilitate earlier intervention [10].

In recent years, MRD detection through circulating tumor DNA (ctDNA) analysis has emerged as a promising strategy to address this gap. MRD testing seeks to identify trace amounts of tumor-derived DNA circulating in the bloodstream, enabling the detection of minimal disease presence well before radiologic or symptomatic relapse [11]. Several studies have confirmed the prognostic value of MRD testing to stratify patients into high and low risk of recurrence in CRC, as well as other solid tumors [12].

Currently, MRD assessment is employed via two approaches. First is a tumor-informed assay that involves sequencing a patient's tumor tissue to pinpoint the most common somatic mutations, which are then monitored with customized plasma assays [13–15]. Second is a tissue-free assay that does not require prior tumor sequencing but instead analyzes ctDNA based on predefined panels of genomic alterations and/or methylation patterns. Each of these approaches has pros and cons, but both approaches have reported high prognostic value and PPV (positive predictive value) from observational studies [12,16].

Interest in integrating MRD testing into routine care has grown steadily across AMEA, driven by the region's significant CRC burden and the imperative for earlier, more precise identification of patients at risk of relapse. Wider adoption has been hindered because of a lack of reimbursement, guideline recommendations, and uncertainty about the benefit of interventions based on MRD test results.

As the body of evidence continues to expand, ctDNA-based MRD testing holds considerable potential to transform postoperative surveillance and guide personalized

therapy decisions for patients with CRC. Achieving widespread clinical integration in AMEA will depend on further research, policy support, and clinician education to ensure equitable access and optimize patient outcomes.

This real-world utilization assessment was conducted with the objective of delineating the usage of the MRD test in various stages of CRC from the patients who were prescribed MRD testing as a part of their clinical care. Also, ten clinical cases were selected, as they represent various clinical scenarios for the use of the MRD test in clinical practice.

2. Methods

2.1. Plasma Sample Analysis Methods

MRD analysis was performed using the analytically validated, commercially available tissue-free Guardant Reveal assay [12]. As previously reported, the Guardant Reveal assessment includes a review of ~2000 differentially methylated regions (DMRs) most strongly associated with colorectal cancer and classifies each sample as ctDNA detected (positive) or not detected (negative) based on a predefined statistical likelihood threshold that the patterns of methylation are tumor-derived.

For the present real-world utilization analysis, methylation-based MRD status was abstracted from the Guardant Reveal report as a binary result: ctDNA detected (MRD-positive) or ctDNA not detected (MRD-negative). No additional methylation calling, thresholding, or laboratory validation experiments were performed by the authors as part of this study; analytical validation and assay performance characteristics are described in the published Guardant Reveal validation studies [12].

2.2. Patient Cohort

Patients with CRC from the AMEA region who underwent the Guardant Reveal test as part of their routine clinical care were included in this analysis. MRD tests can be ordered for stage I, stage II, stage III, and oligometastatic stage IV post-surgery or post-adjuvant therapy [12]. The first 380 consecutive CRC patients with 524 longitudinal samples between July 2023 and May 2025 from AMEA with test results from the current commercially available version of Guardant Reveal were queried retrospectively. Data was analyzed through May 2025 for patients with a test result and documented clinical stage. Based on the timing of the MRD test order, we classified them into post-resection (defined as the first test ordered within 12 weeks of surgery) or during surveillance (defined as the first test ordered more than 12 weeks after surgery). Clinical factors (age, sex, stage at diagnosis, date of surgery, adjuvant therapy status, timing of MRD test ordered) were extracted (when available) from test requisition forms submitted when the test was ordered. Selected patient's additional information was included to describe the steps taken by treating physicians based on the test results. Individual patients' consent to use de-identified data was obtained by their respective treating physicians. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Advarra (protocol code: Pro00034566/CR00218935, approved on 9 September 2019 and was last renewed on 7 July 2023).

2.3. Data Extraction and Statistical Analysis

This study is a retrospective, non-interventional real-world utilization analysis of Guardant Reveal MRD testing performed as part of routine clinical care. All analyses were descriptive. The study cohort consisted of the first 380 consecutive CRC patients with a documented cancer stage and a valid Guardant Reveal result, comprising 524 total samples collected longitudinally between July 2023 and May 2025. For analyses of ctDNA positivity, MRD status was evaluated using the result of the first MRD test per patient

(n = 380). For utilization analyses, the timing of test orders was summarized at both the sample level (all tests) and at the patient level (first test). Continuous variables were summarized using medians and ranges, and categorical variables were summarized using counts and percentages. No hypothesis testing was planned or performed; therefore, no p-values or thresholds for statistical significance were applied. Each blood draw/sample corresponds to a single clinical test result (no technical replicates). When multiple tests were available for a patient, these represent serial samples obtained at different timepoints rather than replicate measurements. Data extraction from test requisition forms and descriptive analyses were performed using a standard spreadsheet.

3. Results

3.1. Demographics

A total of 380 patients (524 samples) had MRD test results with cancer stage documented by the ordering physicians and included in the analysis. Demographic details are shown in Table 1.

Table 1. Demographics.

Patient Characteristic	**No. (n = 380) (%)**
Gender (%)	
Male	230 (60.5%)
Female	150 (39.5%)
Median Age (range)	59 (26–90 yrs)
Cancer Stage at the first MRD test	
I	3 (0.8%)
II	142 (37.4%)
III	210 (55.3%)
IV (oligometastatic)	25 (6.6%)
Median methylation TF% for MRD-positive samples per cancer stage	
I (n = 1)	0.167%
II (n = 21)	0.225%
III (n = 59)	0.196%
IV (n = 13)	0.336%

3.2. Test Utilization and ctDNA Positivity by Cancer Stage

One hundred ten out of 380 (28.9%) patients had undergone more than one MRD test; the calculation of ctDNA positivity (MRD positive status) was based on the result of the first MRD test. Overall, 17.9% of all samples were reported as ctDNA positive, regardless of the timing of the order. In their first MRD test, 17.3% of patients had ctDNA detected, 16% for those conducted post-resection, and 20% for first tests during surveillance. Based on the result of the first test alone, the proportion of patients with ctDNA detection per cancer stage based on the result of the first test alone is shown in Figure 1. As the patient number for stage I is very small, it has not been included in the further analysis to avoid erroneous conclusions.

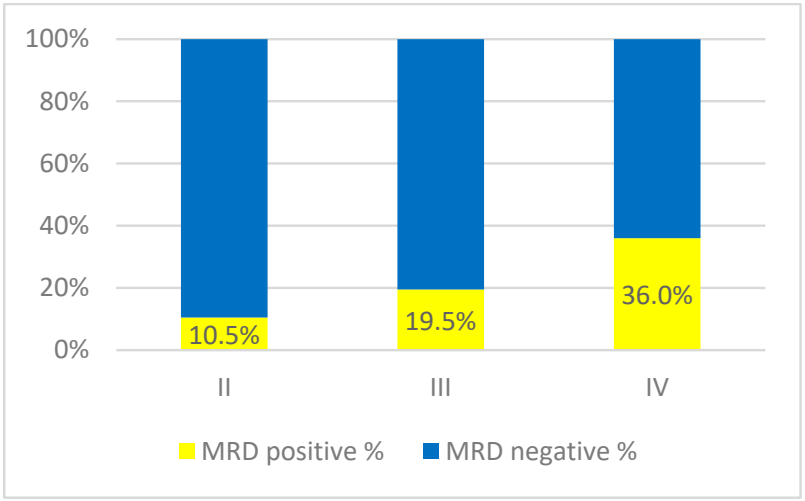


Figure 1. ctDNA positivity rate at first MRD test by cancer stage. Positive MRD samples for stage II, $n = 15$; stage III, $n = 41$; and stage IV (oligometastatic), $n = 9$.

3.3. Stratification of MRD Test Order Timing by Cancer Stage

Among all tests for patients with stage II disease, 57.69% (105/182) were ordered within the first 12 weeks after surgery. For patients with stage III and IV disease, the majority of tests were ordered during surveillance (stage III 192/302, 63.58%; stage IV 27/35, 77.14%) (Figure 2).

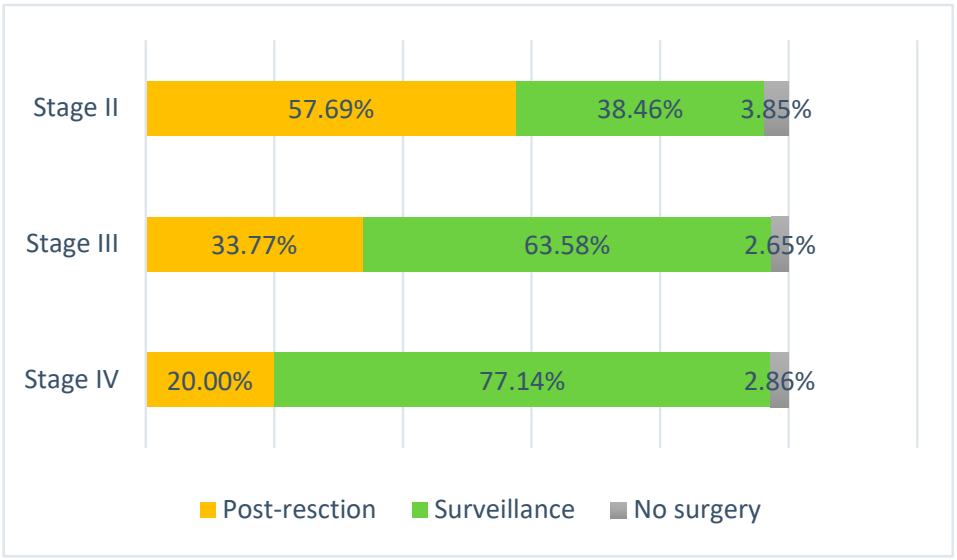


Figure 2. Timing of MRD test order for stage II ($n = 182$), stage III ($n = 302$), and oligometastatic stage IV ($n = 35$).

3.4. Timing of the First MRD Test Order by Cancer Stage

Focusing on the timing of the first MRD test for patients with stage II disease, the majority of the first MRD tests were ordered within the first 12 weeks after surgery (102/142, 71.83%). For patients with stage III disease, about half of the first MRD tests were ordered beyond 12 weeks after surgery (105/210, 50%). For patients with stage IV oligometastatic cancer, the majority of the first MRD tests were ordered during surveillance (18/25, 72%) (Figure 3).

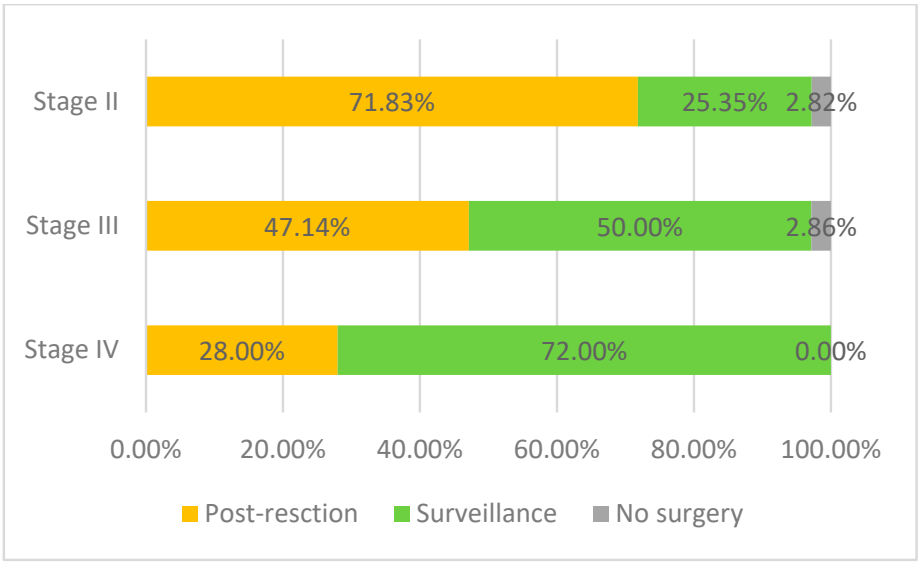


Figure 3. Timing of the first MRD test order for stage II (n = 142), stage III (n = 210), and oligometastatic stage IV (n = 25).

3.5. Median Timing of the MRD Test Order by Cancer Stage

The median time for ordering a post-resection MRD test was 5 weeks (range of 2 to 5 weeks) after surgery for both stage II and stage III patients, while the median time for ordering the first surveillance MRD test was 32 weeks (range of 13 to 388 weeks) after resection for stage II patients and 44 weeks (range of 13 to 737 weeks) after resection for stage III patients. For patients with oligometastatic stage IV disease, 72% (18/25) of the first MRD tests were ordered beyond the first 12 weeks after surgery. The median time for ordering a post-resection MRD test was 5 weeks (range 4 to 11 weeks) after surgery, and the median time for ordering the first surveillance MRD test was 46 weeks (range 16 to 138 weeks) after resection (Table 2). The median turnaround time (TAT), from sample receipt in the laboratory to report release, was 7 days (range 4 to 26).

Table 2. Median time for ordering the MRD test.

CRC Stage	Median Time for Ordering Post-resection MRD Test Weeks	Median Time for Ordering the First Surveillance MRD Test
II	5 (range 2–5)	32 (13–388)
III	5 (Range: 3–5)	44 (13–737)
IV (oligometastatic)	5 (Range: 4–11)	46 (16–138)

4. Case Reports

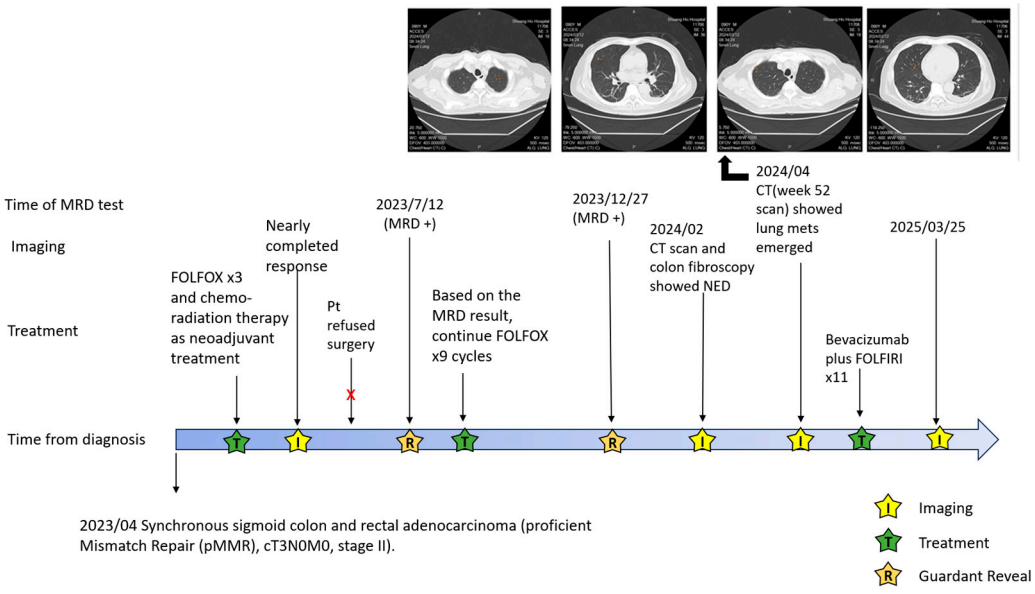
We also present 10 cases of selected patients with CRC where the MRD test (version available at the time of order) was ordered in routine clinical care, and results were included in treatment decisions. All the patients were treated at various academic tertiary care oncology centers across the AMEA region.

The objective is to describe the insights that such assays can provide throughout the treatment journey of patients with CRC, emphasizing the need to integrate this information comprehensively for appropriate clinical decision-making.

4.1. Case 1: Persistent MRD Positivity Led to Early Detection of the Recurrence

A 90-year-old male patient diagnosed with synchronous sigmoid colon and rectal adenocarcinoma (proficient Mismatch Repair (pMMR), cT3N0M0, stage II). The patient re-

ceived three cycles of the FOLFOX chemotherapy regimen, along with concurrent chemoradiation therapy as neoadjuvant treatment. After completion of the neoadjuvant treatment, the CT scan showed a nearly complete response; however, the patient refused to have curative-intent surgery. Based on this, the physician advised the patient to continue with FOLFOX, and a Reveal test was ordered (July 2023), which reported a ctDNA-positive status. In consultation with the patient, the physician decided to extend FOLFOX. After another nine cycles of FOLFOX, the second Reveal test was ordered (December 2023), and the result showed a persistent ctDNA-positive status (Figure 4b). Follow-up (F/U) re-staging CT scan and colon fibroscopy in February 2024 showed no evidence of disease (NED). However, a follow-up CT scan in April 2024 (week 52 CT scan) reported emerging solitary lung metastasis. The patient received bevacizumab plus FOLFIRI for eleven cycles and continues to show stable disease as of the last follow-up in March 2025 (Figure 4a).



(**a**)

Guardant Reveal Results Summary

Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result	Tumor Fraction#
2	DEC-27-2023	+39 weeks	ctDNA Detected	0.954%
1	JUL-12-2023	+15 weeks	ctDNA Detected	0.105%

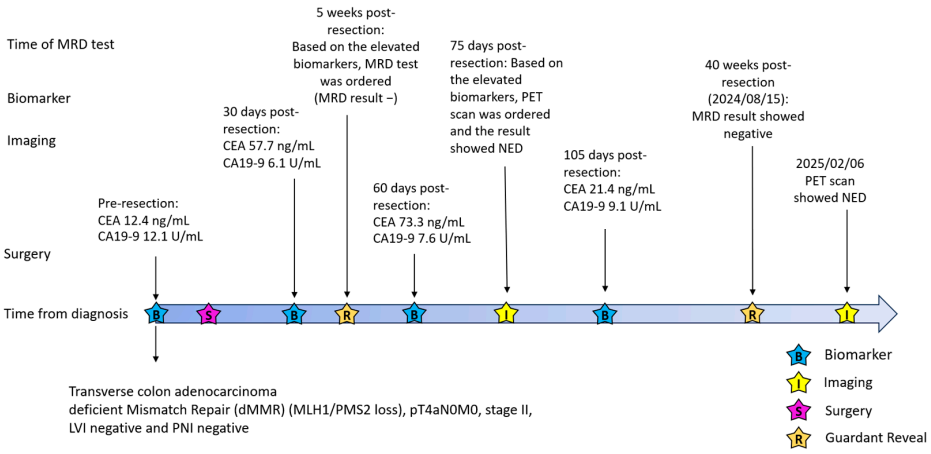
(**b**)

Figure 4. (**a**) Chronological timeline capturing Case 1 patient's treatment journey. (**b**) Case 1 MRD test results. Tumor fraction increased from July 2023 to December 2023. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

4.2. Case 2: Post-Surgery ctDNA Is More Specific than CEA

A 56-year-old female diagnosed with transverse colon adenocarcinoma underwent right hemicolectomy. The preliminary pathology report from tumor tissue testing indicated deficient Mismatch Repair (dMMR) (MLH1/PMS2 loss), pT4aN0M0, stage II, LVI negative, and PNI negative. The pre-operative CEA was 12.4 ng/mL, and at 30 days, CEA was elevated to 57.7 ng/mL, and the pre-operative cancer antigen 19-9 (CA19-9) was 12.1 U/mL, and at 30 days, CA19-9 was 6.1 U/mL. Based on these elevated biomarkers, the physician suggested observation with MRD monitoring. The 5-week post-resection

MRD test was negative (Figure 5b). However, the 60-day post-resection CEA further increased to 73.3 ng/mL, and CA19-9 went up to 7.6 U/mL; these continued increases in biomarkers prompted a follow-up scan. A 75-day post-operation PET scan showed NED. Continued CEA monitoring reported a reduction to 21.4 ng/mL at day 105. Dynamic change of CEA/CA19-9 is shown in Figure 5c. A 40-week post-resection MRD test and repeat PET scan done at 64 weeks continued to report NED. MRD-negative status had a better correlation with NED on PET than CEA/CA19-9 (Figure 5a).

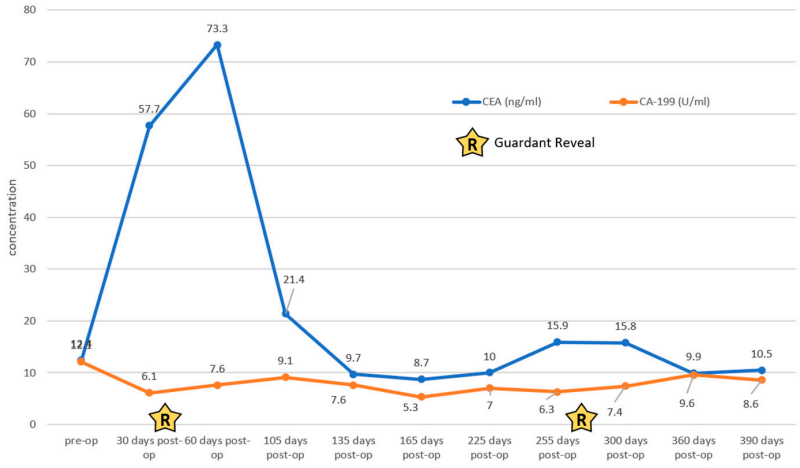


(**a**)

Guardant Reveal Results Summary

Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result†	Tumor Fraction#
2	AUG-15-2024	+40 weeks	ctDNA Not Detected	0%
1	DEC-12-2023	+5 weeks	ctDNA Not Detected	0%

(**b**)

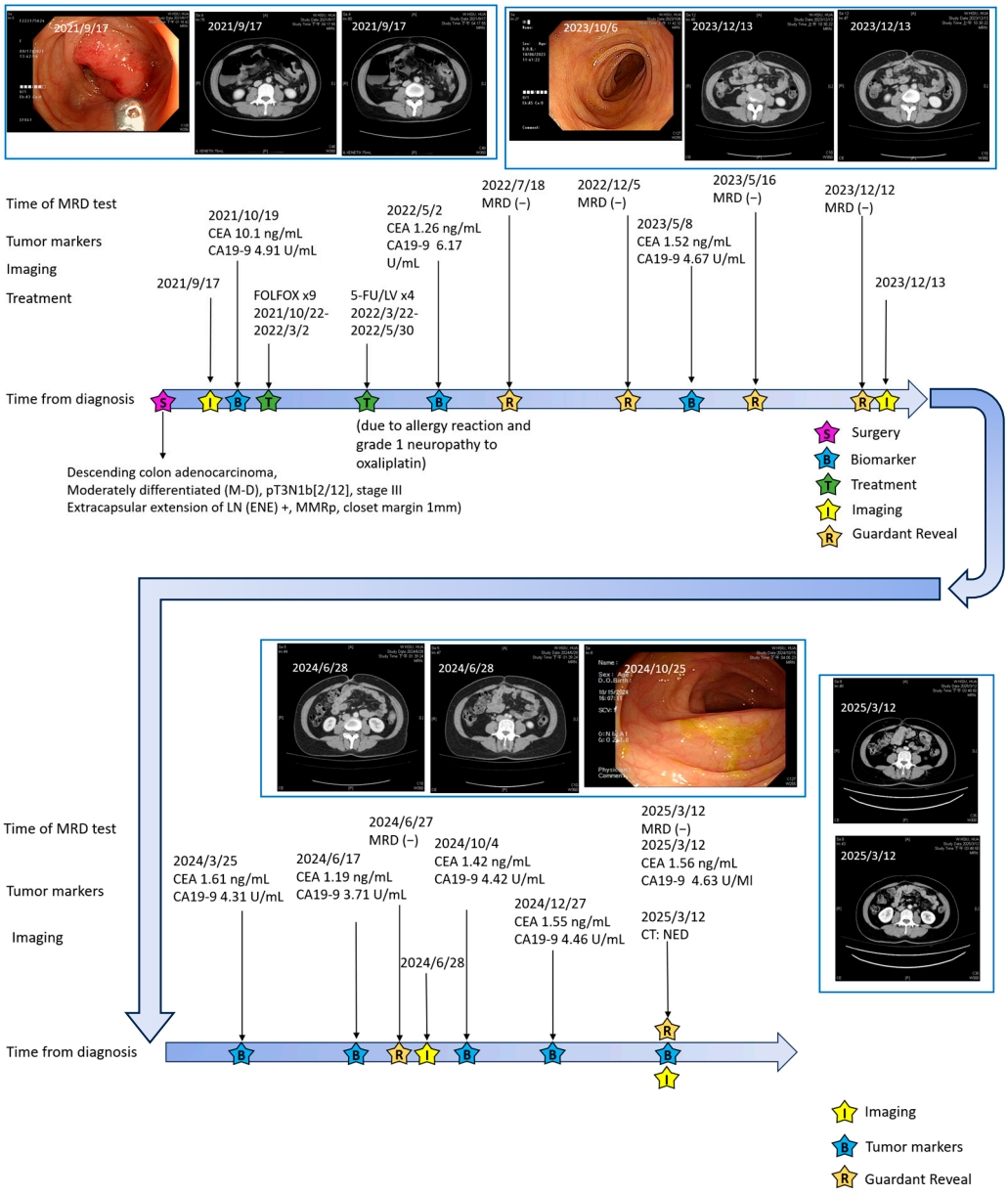


(**c**)

Figure 5. (**a**) Chronological timeline capturing Case 2 patient's treatment journey. (**b**) Case 2 MRD test results. (**c**) Case 2 Dynamic change of CEA/CA19-9. † Guardant Reveal Result is based on analysis of >2000 differentially methylated regions (DMR) in individuals with cancer compared to individuals without cancer. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

4.3. Case 3: Persistent Negative MRD Indicates Low Risk of Recurrence

A 50-year-old female diagnosed with descending colon adenocarcinoma. The patient received curative surgery, and the final pathology report from tumor tissue testing indicated moderately differentiated, pT3N1b [2/12], stage III, extracapsular extension of lymph node (ENE) positive, and pMMR. The patient then received nine cycles of the FOLFOX adjuvant chemotherapy and shifted to four cycles of 5-FU/LV treatment alone due to allergic reaction and grade 1 neuropathy to oxaliplatin. After completing adjuvant chemotherapy, the patient was monitored by tumor markers (CEA and CA19-9) and MRD tests for more than 2 and a half years and reported no evidence of recurrence. Six consecutive MRD tests did not detect ctDNA (Figure 6b) and correlated with the NED on the periodic scans. The patient continued to be NED as of the last follow-up in March 2025 (Figure 6(a-1,a-2)).



(a-1,a-2)

Figure 6. *Cont.*

Guardant Reveal Results Summary

Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result†	Tumor Fraction#
6	MAR-12-2025	+180 weeks	ctDNA Not Detected	0%
5	JUN-27-2024	+143 weeks	ctDNA Not Detected	0%
4	DEC-12-2023	+115 weeks	ctDNA Not Detected	0%
3	MAY-16-2023	+85 weeks	ctDNA Not Detected	NR##
2	DEC-05-2022	+62 weeks	ctDNA Not Detected	NR##
1	JUL-18-2022	+42 weeks	ctDNA Not Detected	NR##

(**b**)

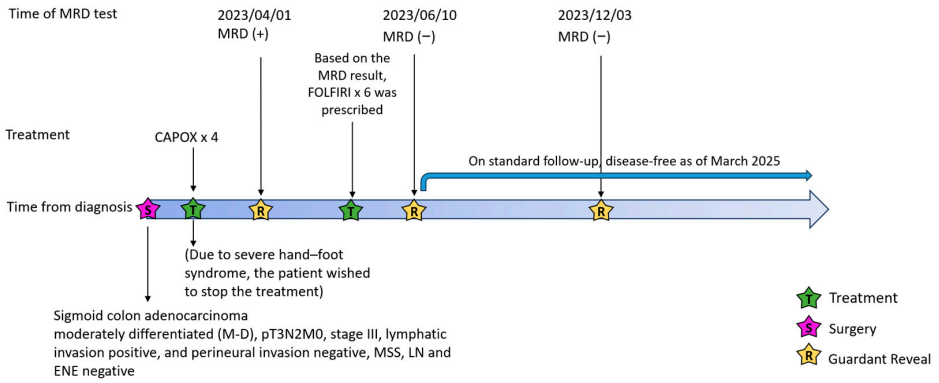
Figure 6. (**a-1**,**a-2**) Chronological timeline capturing Case 3 patient's treatment journey. (**b**) Case 3 MRD test results. NR indicates that the early version of this test did not report Tumor Fraction, whereas the current version now includes it. † Guardant Reveal Result is based on analysis of >2000 differentially methylated regions (DMR) in individuals with cancer compared to individuals without cancer. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals. ## Tumor fraction is a feature available on all Reveal tests processed after July 2023. Reveal tests processed before this date will have NR (Not Reported) listed in the Tumor Fraction column.

4.4. Case 4: MRD Positive Result Leading to the Escalation of Adjuvant Chemotherapy

A 64-year-old male diagnosed with sigmoid colon adenocarcinoma underwent R0 resection. The preliminary pathology report from tumor tissue testing indicated moderately differentiated (M-D), pT3N2M0, stage III, lymphatic invasion positive, perineural invasion negative, MSS, LN, and ENE negative. The patient received 3 months of adjuvant CAPOX (four cycles, q3w); however, due to severe hand–foot syndrome (HFS), the patient wished to stop the treatment. Based on the initial results of the PEGASUS study [16], the physician decided to order an MRD test after 3 months of CAPOX (17 weeks from surgery), and the MRD result was positive. In consultation with the patient, the physician decided to escalate therapy to FOLFIRI for 3 months (six cycles, q2w). After completion of this therapy, MRD status was reassessed, and the status seroconverted to negative (Figure 7b). The patient was on follow-up as per the routine clinical plan and continues to have NED for the last 2 years, with the most recent follow-up being March 2025.

4.5. Case 5: MRD Positive Result Leading to Escalation of Adjuvant Chemotherapy in Stage IV Oligometastatic Rectal Adenocarcinoma

A 54-year-old male diagnosed with mid-rectal adenocarcinoma, with approximately 1 cm solitary right middle lobe lung metastasis. The results showed that the patient was wild-type for RAS and BRAF with MSS. The patient was given four cycles of neoadjuvant FOLFOX q2w and underwent R0 resection (robotic) for both the rectal tumor and lung metastasis. The pathology report showed moderately differentiated adenocarcinoma, pT3N2M1G2, LN positive, perineural invasion positive, ENE positive, and tumor regression grade (TRG) 3. An MRD test was ordered 5 weeks after surgery and reported positive (Figure 8b). Adjuvant chemotherapy was therefore changed to FOLFIRI for 4 months (eight cycles, q2w). After completing the therapy, MRD status was reassessed, and it seroconverted to negative. The patient was followed up as per the routine clinical plan and has continued to be NED over the last 26 months, with the most recent follow-up in March 2025 (Figure 8a).



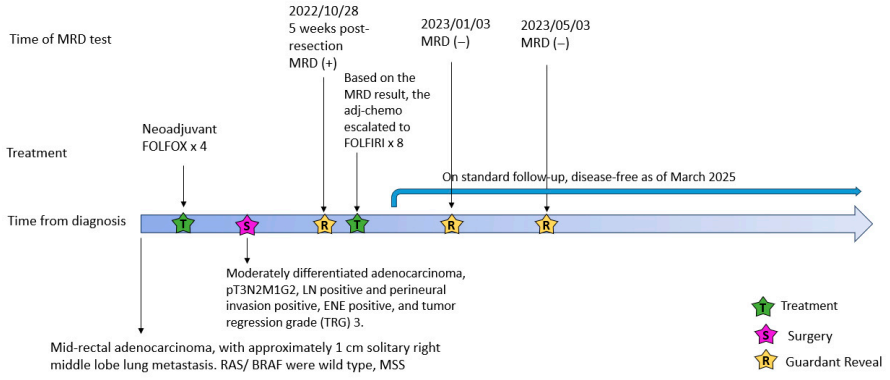
(**a**)

Guardant Reveal Results Summary

Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result	Tumor Fraction#
3	DEC-03-2023	+52 weeks	ctDNA Not Detected	0%
2	JUN-10-2023	+27 weeks	ctDNA Not Detected	NR##
1	APR-01-2023	+17 weeks	ctDNA Detected	NR##

(**b**)

Figure 7. (**a**) Chronological timeline capturing Case 4 patient's treatment journey. (**b**) Case 4 MRD test results. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals. ## Tumor fraction is a feature available on all Reveal tests processed after July 2023. Reveal tests processed before this date will have NR (Not Reported) listed in the Tumor Fraction column.



(**a**)

Timeline

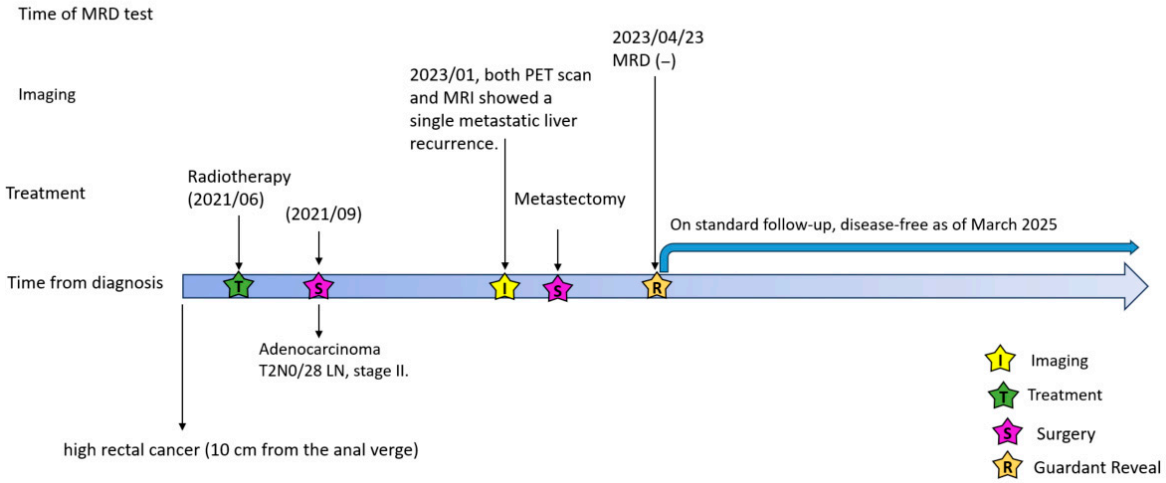
Time Elapsed Since Surgery*	+4 weeks	+14 weeks	+31 weeks
Guardant Reveal™ Result	ctDNA Detected	ctDNA Not Detected	ctDNA Not Detected
Collection Date	OCT-28-2022	JAN-03-2023	MAY-03-2023

(**b**)

Figure 8. (**a**) Chronological timeline capturing Case 5 patient's treatment journey. (**b**) Case 5 MRD test results. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form.

4.6. Case 6: Negative MRD Test Supported Sparing of Adjuvant Chemotherapy

A 74-year-old female diagnosed with high rectal cancer (10 cm from the anal verge). She received short-term radiation therapy in June 2021 and underwent surgery after 3 months of radiation therapy. The pathology showed adenocarcinoma T2N0/28 LN, stage II. No adjuvant therapy was given as per the institutional practice and physician judgment. In January 2023, both the PET scan and MRI showed a single metastatic liver recurrence. The patient underwent metastasectomy, and the pathology result showed adenocarcinoma compatible with colon origin. Post-resection, the physician ordered an MRD test in April 2023 and received an MRD-negative result (Figure 9b). The MRD result was considered along with other clinical factors, and a decision was made to spare the patient from the adjuvant therapy. The patient was followed up closely over the last 2 years and is still NED as of the last follow-up in March 2025 (Figure 9a).



(**a**)

Timeline

Time Elapsed Since Surgery*	+9 weeks
Guardant Reveal™ Result	ctDNA Not Detected
Collection Date	APR-24-2023

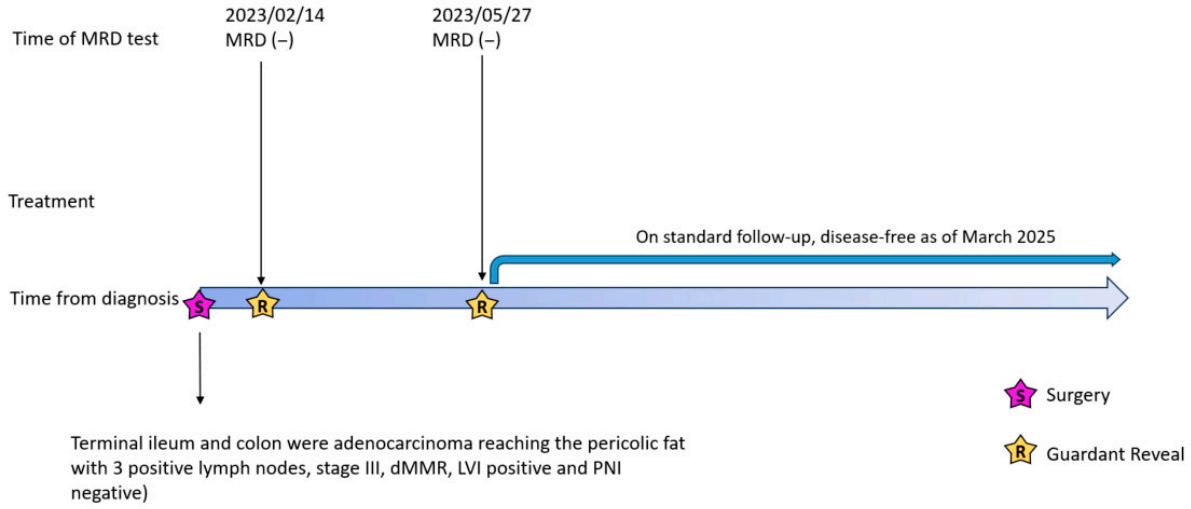
(**b**)

Figure 9. (**a**) Chronological timeline capturing Case 6 patient's treatment journey. (**b**) Case 6 MRD test results. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form.

4.7. Case 7: Persistent MRD Negative Results Supported Sparing of Adjuvant Therapy in an Elderly Patient

An 85-year-old male diagnosed with Crohn's disease at the age of 24 underwent an ileocecectomy and started treatment for Crohn's disease around age 40 with a very indolent disease. In January 2024, the patient underwent elective surgery due to narrowing of the anastomosis. The pathology result showed the terminal ileum and colon had developed adenocarcinoma reaching the pericolic fat with three positive lymph nodes out of 36,

leading to a diagnosis of stage III, dMMR, LVI positive, and PNI negative. According to NCCN guidelines [17], the recommended treatment was CAPEOX (3 months) or FOLFOX (3–6 months). However, considering the patient's age, the physician decided to spare the patient from the adjuvant chemotherapy and monitoring by MRD tests. Two Reveal tests were ordered, in Feb 2024 and May 2024; both were negative (Figure 10b). The patient has no evidence of recurrence as of March 2025 (Figure 10a).



(**a**)

Guardant Reveal Results Summary

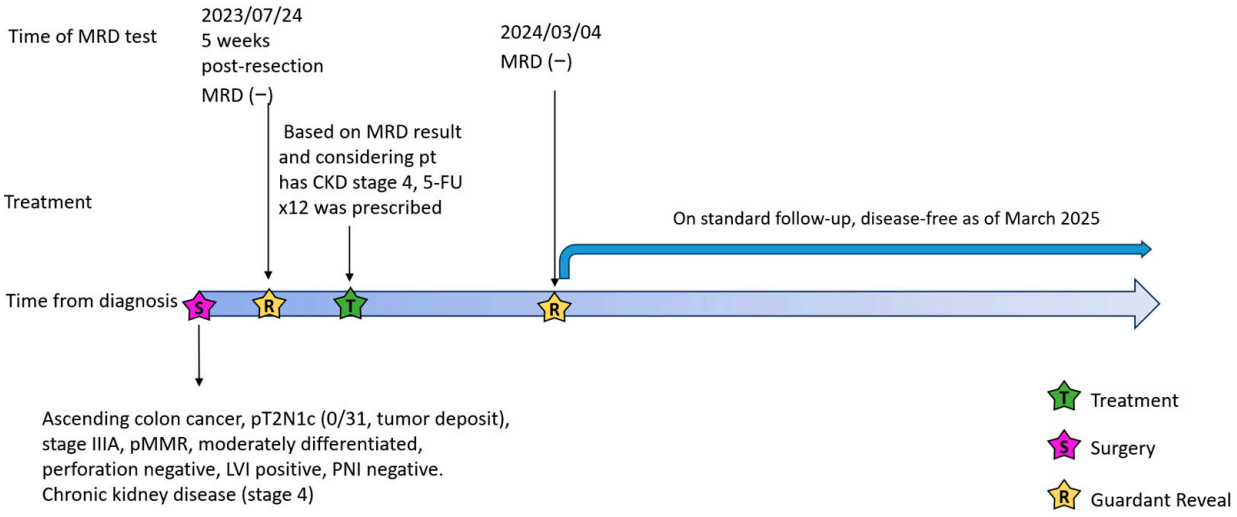
Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result	Tumor Fraction#
2	MAY-27-2024	+20 weeks	ctDNA Not Detected	0%
1	FEB-14-2024	+5 weeks	ctDNA Not Detected	0%

(**b**)

Figure 10. (**a**) Chronological timeline capturing Case 7 patient's treatment journey. (**b**) Case 7 MRD test results. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

4.8. Case 8: MRD Negative Results Leading to De-Escalation of Adjuvant Chemotherapy

A 59-year-old female with chronic kidney disease (stage 4) was diagnosed with ascending colon cancer and underwent hemicolectomy in June 2023. The pathological result showed pT2N1c (0/31, tumor deposit), stage IIIA, pMMR, moderately differentiated, perforation negative, LVI positive, and PNI negative. The patient's first MRD test was done 5 weeks after surgery, which reported MRD negative status. Based on the CKD stage 4 and negative MRD status, the physician chose a low-intensity chemotherapy regimen of twelve cycles of 5-FU. To reassess the risk of recurrence after this therapy, another MRD test after 37 weeks post-surgery was ordered, which reported a persistent MRD negative status (Figure 11b). A routine surveillance CT scan around 57 weeks showed NED and continues to be NED as of the last follow-up in March 2025 (Figure 11a).



(**a**)

Guardant Reveal Results Summary

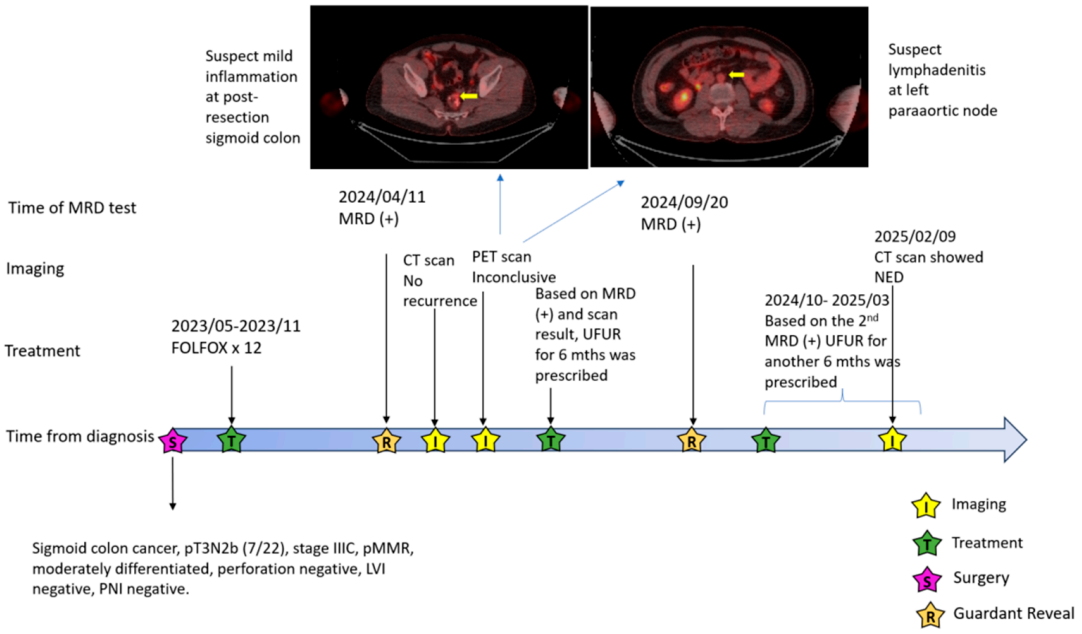
Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result	Tumor Fraction#
2	MAR-04-2024	+37 weeks	ctDNA Not Detected	0%
1	JUL-24-2023	+5 weeks	ctDNA Not Detected	0%

(**b**)

Figure 11. (**a**) Chronological timeline capturing Case 8 patient's treatment journey. (**b**) Case 8 MRD test results. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

4.9. Case 9: Persistent MRD-Positive Results Leading to Extended Therapy

A 55-year-old male was diagnosed with sigmoid colon cancer and underwent post-laparoscopic low anterior resection in April 2023. The pathological result showed pT3N2b (7/22), stage IIIC, pMMR, moderately differentiated, perforation negative, LVI negative, and PNI negative. Adjuvant FOLFOX for 12 cycles was given from May to November 2023, followed by an MRD test done in April 2024, which reported ctDNA positive status (TF 0.108%) (Figure 12b). A follow-up CT scan reported NED, and the PET scan was inconclusive, as it showed suspected mild inflammation at the site of operation in the sigmoid colon and suspected lymphadenitis at the left paraaortic node, but no evidence of early metastasis. Based on the positive MRD test results and findings on the scan, the physician initiated extended adjuvant UFUR from April to October 2024. Subsequent repeat MRD tests showed persistent ctDNA-positive (TF 0.093%) status (Figure 12b). The physician continued extended UFUR treatment from October 2024 to March 2025. The most recent CT scan performed on 9 February 2025 showed NED (Figure 12a).



(**a**)

Guardant Reveal Results Summary

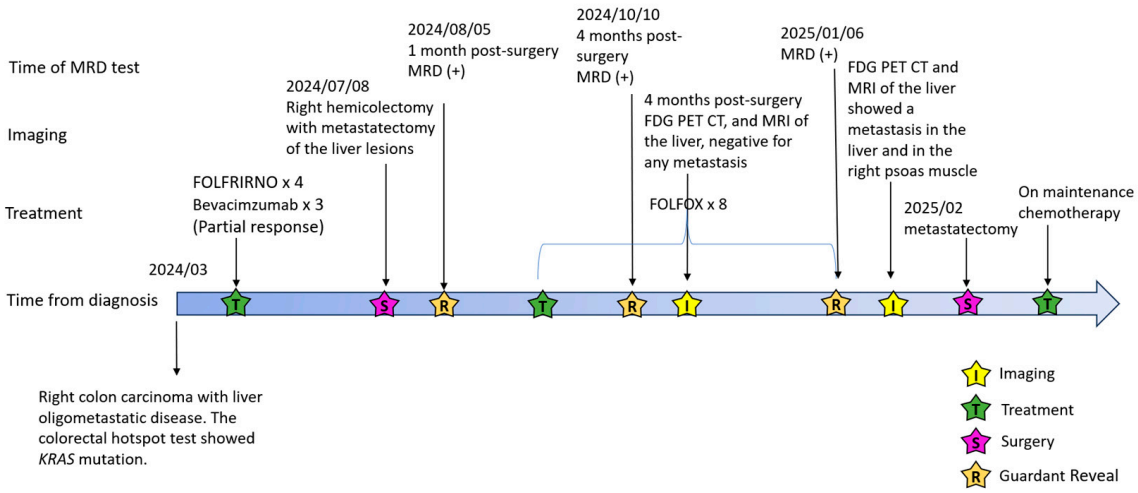
Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result†	Tumor Fraction#
2	SEP-20-2024	+67 weeks	ctDNA Detected	0.093%
1	APR-11-2024	+44 weeks	ctDNA Detected	0.108%

(**b**)

Figure 12. (**a**) Chronological timeline capturing Case 9 patient's treatment journey. (**b**) Case 9 MRD test results. † Guardant Reveal Result is based on analysis of >2000 differentially methylated regions (DMR) in individuals with cancer compared to individuals without cancer. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

4.10. Case 10: MRD Positive Report Led to Early Detection of Recurrent Oligometastasis

A 50-year-old man was diagnosed with carcinoma of the right colon with liver oligometastatic disease in March 2024. The colorectal hotspot test showed a *KRAS* mutation and a CEA of 9.4 ng/mL. The patient was given four cycles of FOLFIRINOX and three doses of bevacizumab with the intent of conversion. He had a partial response post four cycles of neoadj-chemotherapy and underwent right hemicolectomy with metastatectomy of the liver lesions in Jul 2024 (ypT3N1M1). One month after the surgery, the patient had an MRD test done; the result showed ctDNA positive (Figure 13b). The patient was given four cycles of FOLFOX as adj-chemotherapy. The 2nd MRD test (4 months post-surgery) was also positive (Figure 13b), but the FDG PET CT and MRI of the liver in the 4th month were negative for any metastasis. Upon repeating the MRD testing after completion of all the planned eight doses of chemotherapy, the 3rd MRD test was still positive (Figure 13b). Repeat FDG PET CT and MRI of the liver showed an isolated site of metastasis in the liver and another deposit in the right psoas muscle. The patient then underwent metastatectomy in February 2025 and is on maintenance chemotherapy (Figure 13a).



(**a**)

Guardant Reveal Results Summary

Draw Number	Collection Date	Time Elapsed Since Surgery or Completion of Curative-Intent Therapy*	Guardant Reveal Result†	Tumor Fraction#
3	JAN-06-2025	+26 weeks	ctDNA Detected	0.111%
2	OCT-10-2024	+13 weeks	ctDNA Detected	0.128%
1	AUG-05-2024	+4 weeks	ctDNA Detected	0.242%

(**b**)

Figure 13. (**a**) Chronological timeline capturing Case 10 patient's treatment journey. (**b**) Case 10 MRD test results. † Guardant Reveal Result is based on analysis of >2000 differentially methylated regions (DMR) in individuals with cancer compared to individuals without cancer. * Time elapsed since surgery or completion of curative intent therapy is calculated using the date of surgery or completion of curative intent therapy provided on the test requisition form. # Tumor fraction is defined as the proportion of tumor molecules present in the cfDNA within the submitted specimen and is based on epigenomic signals.

5. Discussion

CRC imposes a significant health burden worldwide and particularly across the AMEA region, where high incidence rates in nations like Japan, South Korea, and Australia reflect demographic aging and Westernized lifestyles. Despite advances in treatment, recurrence remains a substantial threat, driving urgent interest in molecular residual disease (MRD) testing to refine risk stratification and personalize therapy in CRC.

Our real-world analysis offers important insights into the utility of MRD testing in CRC management across AMEA. Among 382 patients analyzed, 17.3% showed ctDNA positivity on their first MRD test. Notably, ctDNA positivity was observed in 16% of tests performed post-resection and 20% during surveillance, suggesting persistent disease detection even long after initial therapy. Median methylation tumor fractions varied across stages, with notably higher values in stage IV disease. In addition, 92% of the total tests were ordered for stage II and III patients, reflecting the clinical need and availability of the clinical trial data. Importantly, the timing of MRD test orders varied substantially between stages, reflecting differences in surveillance strategies and perhaps differing levels of clinician confidence in incorporating MRD data into practice. Within stage II, almost 72% of the first tests were ordered within 12 weeks of surgery, presumably supporting the decision to initiate adjuvant therapy. In stages III and IV, most of the first tests were ordered during the surveillance phase, presumably for early recurrence detection. A real-world publication

involving 215 patients across CRC stages I to IV from the Asia Pacific and the Middle East region reported similar results with a 22% ctDNA positivity rate, an increasing ctDNA positivity rate with increasing stage of CRC, and differing utility by stage of CRC [18]. Almost 30% of the patients had more than one MRD test ordered, which reflects physicians' belief that MRD status needs longitudinal monitoring to improve the prognostic value and review the changing MRD status. Published data support that longitudinal testing has stronger prognostic value than a single MRD test [12,15]. The shorter TAT reported in this cohort can support decision-making within a clinically relevant timeline.

The real-world impact of MRD testing becomes particularly vivid when considering the 10 individual cases we report, which collectively illustrate how MRD results influence diverse clinical decisions across the CRC continuum.

Case 1 exemplifies how persistent MRD positivity, despite radiologic normality, anticipated eventual metastatic recurrence, highlighting MRD's potential in identifying occult disease before imaging detects changes. Similarly, Case 2 demonstrates that MRD negativity may outperform traditional tumor markers like CEA or CA19-9 in ruling out disease, avoiding unnecessary interventions despite biochemical fluctuations. Similar results have been reported in large-scale observational clinical studies [12,15].

Conversely, persistently negative MRD results provided reassurance in several patients. Case 3 shows how sustained MRD negativity over multiple tests correlated with durable remission in stage III disease, underscoring MRD's utility in potentially sparing patients from excessive imaging or interventions. Likewise, Cases 6 and 7 illustrate how negative MRD findings supported the decision to forgo adjuvant chemotherapy, even in elderly patients or those with significant comorbidities, minimizing toxicity without compromising outcomes. Case 8 presents an example of therapy de-escalation guided by MRD results. In a patient with significant comorbidities, negative MRD allowed for a less intensive chemotherapy regimen, avoiding undue toxicity while maintaining remission. Even if physicians relied on a single MRD-negative test result for de-escalation, previously reported studies highlight that persistent (more than one test result) negative MRD status is prognostic of a low risk of recurrence [11], and the impact of the dose changes based on persistent negative results is currently being assessed in PEGASUS [16].

The ability of MRD results to drive escalation of therapy is highlighted in Cases 4 and 5, where MRD positivity supported intensified adjuvant chemotherapy regimens, resulting in subsequent MRD clearance and ongoing remission. These cases underscore the transformative role MRD testing can play in tailoring therapy to the molecular evidence of residual disease rather than relying solely on clinicopathologic features. High positive predictive value (PPV) of the MRD-positive results has been consistently reported in clinical studies [12,15].

Case 9 further highlights the challenge of persistent MRD positivity despite radiologic normality. Here, ongoing ctDNA detection led to extended therapy and careful monitoring, aiming to preempt radiologic recurrence. Such cases emphasize the potential of MRD testing for early intervention, though they also highlight current uncertainties regarding how best to manage persistent MRD positivity when imaging remains negative.

Finally, Case 10 underscores that MRD tests have high sensitivity, where repeated MRD positivity ultimately predicted isolated metastases that eluded initial imaging, enabling timely surgical intervention. This case illustrates MRD's role as an early warning system capable of triggering intensified surveillance and potentially life-saving interventions. Previous reports have shown that the lead time from the ctDNA positivity to the recurrence detection scan could be ~6 months [12,15].

In the absence of guidelines, the treating physicians of these 10 patients have taken treatment decisions based on their clinical judgement, clinic-pathological factors, in consul-

tation with patients, as Guardant Reveal reports do not make recommendations on the next steps. Limitations of real-world data analysis also apply to our reported results, including a lack of standardized data collection and physicians' variable approach to modifying treatment based on MRD results. Additionally, potential selection bias exists due to the exclusive inclusion of patients who were prescribed Guardant Reveal, as the authors do not have access to the other patients who were prescribed other MRD tests.

Collectively, these real-world cases highlight MRD testing's ability to contribute to personalized CRC management across diverse clinical scenarios. As evident from some of these cases, tissue-free (tumor-agnostic) MRD assays offer logistical advantages—reducing the burden of tissue collection and handling on healthcare systems—while delivering faster turnaround times during the critical adjuvant therapy decision window, without sacrificing performance compared to the tissue-informed approach [12].

Results from the observational clinical trials [12,15,19] and interim results from the interventional trials [16] report high prognostic value and lead time for MRD-positive patients. However, we must underscore challenges, including the need for robust outcome data in the patients whose treatments are modified based on MRD status, next steps to be taken in the MRD-positive patients whose scans show NED, and how to safely de-escalate in MRD-negative patients. Some of these questions will be answered by the ongoing studies [16,20,21].

6. Conclusions

As MRD technology continues to mature, further prospective studies and health economic analyses are needed to define how to best integrate these assays into routine care across AMEA. Nevertheless, our findings suggest MRD testing as a critical tool in shifting CRC management toward a truly personalized approach.

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Informed Consent Statement: The Institutional Review Board of Advarra, which approved this protocol, also waived the need for informed consent to analyze de-identified data, as reported in Figures 1–3 (Advarra IRB Pro00034566/CR00218935, approved on 9 September 2019 and was last renewed on 7 July 2023). For the 10 case reports, written informed consent has been obtained from the patient(s) by the respective treating physicians to publish this paper.

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Conflicts of Interest: Y.-Y.H., F.-C.K., V.L., C.-T.C. and S.V. received honoraria from Guardant Health as speakers. S.J., S.S.H., H.-Y.J. and R.B. are employees of Guardant Health Pte. Ltd. and own shares in Guardant Health. G.P. declares no conflict of interest.

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