Minimal Residual Disease Detection using a Plasma-Only Circulating Tumor DNA Assay in Colorectal Cancer Patients

Aparna R. Parikh1, Emily E. van Seventer1, Giulia Siravegna1, Anna V. Hartwig2, Ariel Jaimovich2, Yupeng He2, Katie Kanter1, Madeleine G. Fish1, Kathryn D. Fosbenner1, Benchun Miao3, Susannah Phillips3, John H. Carmichael3, Nihaarika Sharma3, Joy Jarnagin1, Islam Baiev1, Yojan S. Shah1, Isobel J. Fetter1, Heather A. Shahzade1, Jill N. Allen1, Lawrence S. Blaszkowsky1, Jeffrey W. Clark1, Jon S. Dubois1, Joseph W. Franses1, Bruce J. Giantonio1, Lipika Goyal1, Samuel J. Klempner1, Ryan D. Nipp1, Eric J. Roeland1, David P. Ryan1, Colin D. Weekes1, Jennifer Y. Wo4, Theodore S. Hong4, Liliana Bordeianou5, Cristina R. Ferrone5, Motaz Qadan3, Hiroko Kunitake5, David Berger5, Rocco Ricciardi5, James C. Cusack3, Victoria M. Raymond5, AmirAli Talasaz2, Genevieve M. Boland3, Ryan B. Corcoran1

1 Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital Cancer Center & Harvard Medical School, Boston, Massachusetts, USA;

2 Guardant Health, Inc, Redwood City, CA, USA;

3 Department of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA;

4 Department of Radiation Oncology, Massachusetts General Hospital Cancer Center & Harvard Medical School, Boston, Massachusetts, USA;

5 Department of General and Gastrointestinal Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA

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Corresponding Author:
Dr. Ryan B. Corcoran
Massachusetts General Hospital Cancer Center, 149 13th St., 7th floor
Boston, MA 02129
Phone: 617-726-8599
Fax: 617-724-9648
Email: rbcorcoran@partners.org

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Statement of Translational Relevance

Detection of persistent circulating tumor DNA (ctDNA) after curative-intent surgery to identify patients with minimal residual disease (MRD) who will ultimately recur has emerged as a potentially transformative approach in oncology. Early identification of patients with MRD through ctDNA detection could identify patients in whom additional therapy might salvage the chance of cure. To date, ctDNA MRD assays have employed a tumor-informed approach, requiring initial sequencing of tumor tissue to guide ctDNA detection, and thus cannot be used when a patient has insufficient tumor tissue for analysis. Here, we evaluate the first tumor-uninformed, plasma-only ctDNA assay integrating genomic and epigenomic signatures to detect MRD in post-operative colorectal cancer (CRC) patients, without requiring parallel tumor sequencing, which produced favorable sensitivity and specificity, comparable to tumor-informed approaches. These data highlight the feasibility and potential clinical utility of plasma-only ctDNA-guided MRD detection.
Abstract

Purpose: Detection of persistent circulating tumor DNA (ctDNA) after curative-intent surgery can identify patients with minimal residual disease (MRD) who will ultimately recur. Most ctDNA MRD assays require tumor sequencing to identify tumor-derived mutations to facilitate ctDNA detection, requiring tumor and blood. We evaluated a plasma-only ctDNA assay integrating genomic and epigenomic cancer signatures to enable tumor-uninformed MRD detection.

Experimental Design: 252 prospective serial plasma specimens from 103 colorectal cancer (CRC) patients undergoing curative intent surgery were analyzed and correlated with recurrence.

Results: Of 103 patients, 84 (stage I (9.5%), II (23.8%), III (47.6%), IV (19%)) had evaluable plasma drawn post-completion of definitive therapy, defined as surgery only (n=39) or completion of adjuvant therapy (n=45). In “landmark” plasma drawn one-month (median 31.5 days) post-definitive therapy and >1 year follow up, 15 patients had detectable ctDNA, and all 15 recurred (positive predictive value (PPV) 100%, hazard ratio 11.28 (p<0.0001)). Of 49 patients without detectable ctDNA at the landmark timepoint, 12 (24.5%) recurred. Landmark recurrence sensitivity and specificity were 55.6% and 100%. Incorporating serial longitudinal and surveillance (drawn within 4-months of recurrence) samples, sensitivity improved to 69% and 91%. Integrating epigenomic signatures increased sensitivity by 25-36% versus genomic alterations alone. Notably, standard serum carcinoembryonic antigen (CEA) levels did not predict recurrence (hazard ratio 1.84 (p=0.18); PPV=53.9%).
**Conclusions:** Plasma-only MRD detection demonstrated favorable sensitivity and specificity for recurrence, comparable to tumor-informed approaches. Integrating analysis of epigenomic and genomic alterations enhanced sensitivity. These findings support the potential clinical utility of plasma-only ctDNA MRD detection.
**Introduction**

Colorectal cancer (CRC) is the third most commonly diagnosed and 2\textsuperscript{nd} leading cause of cancer death in the United States in men and women. While a majority of patients are diagnosed with early-stage disease, 5-year survival for patients with regional disease is only 71%.\textsuperscript{1} Surgery alone is often curative for stage I and II disease, and in higher risk disease, adjuvant chemotherapy can reduce the risk of recurrence.\textsuperscript{2} However, aside from risk stratification by tumor stage, clinical criteria and CEA, there are no effective clinical tools to identify patients with post-operative minimal residual disease (MRD) who may be at highest risk for recurrence.\textsuperscript{2} An effective clinical tool to identify patients with MRD following completion of curative-intent therapy could identify patients who may benefit from additional systemic therapy or allow avoidance of unnecessary and potentially toxic therapy for lower risk patients with no evidence of MRD.\textsuperscript{2-5}

tDNA is a promising non-invasive biomarker for MRD detection following curative intent treatment in CRC and other cancer types. Detection of persistent ctDNA after surgery or adjuvant treatment effectively identifies CRC patients with MRD who will ultimately recur without additional therapy.\textsuperscript{6-12} Accordingly, several prospective clinical trials of ctDNA-guided adjuvant therapy are currently underway to evaluate whether patients with evidence of MRD through ctDNA detection following surgery and/or adjuvant therapy may benefit from additional or more intensive systemic therapy to reduce recurrence risk.\textsuperscript{13-21}

To date, most ctDNA assays designed for MRD detection rely on initial genomic profiling of tumor tissue to identify tumor-derived alterations specific for each individual patient, so that these precise alterations can be evaluated in ctDNA.\textsuperscript{6,9,22,23} The rationale behind such “tumor-
informed” approaches is that prior knowledge of the tumor-specific mutations may allow increased sensitivity for ctDNA detection and may improve specificity by enabling determination of which alterations are tumor-derived versus potential false positives arising from non-tumor origins, such as clonal hematopoiesis of indeterminate potential (CHIP).\textsuperscript{24-26} However, a tumor-informed approach may pose several limitations. Importantly, in many cases, tumor cellularity may be limited, which would preclude the use of a tumor-informed approach. In one series, up to 9\% of molecular analysis may be inadequate for tissue sequencing given low tumor cellularity, DNA yield, or quality.\textsuperscript{27} This issue is particularly relevant alongside the increasing use of neoadjuvant therapy in many tumor types, where surgical specimens may have insufficient tissue for molecular analysis due to treatment response. By contrast, a plasma-only ctDNA assay for MRD detection could offer several advantages, including more rapid turn-around time due to the need to analyze a single plasma sample, potential cost savings, and decreased logistical complexity. However, no studies have evaluated if a plasma-only MRD assay can detect ctDNA with clinically meaningful specificity and sensitivity.

We report results from a prospective, observational study in stage I to IV CRC patients treated with curative-intent therapy to assess the ability of a plasma-only ctDNA assay to identify patients with MRD who would ultimately recurr. In addition to standard detection of tumor-derived genomic alterations employed by most MRD assays, this tumor-uninformed assay (Guardant Reveal, Guardant Health) also integrates epigenomic signatures related to aberrant DNA methylation facilitating detection of ctDNA without requiring parallel assessment of tumor tissue.
Methods

Study population

This single-institution prospective study recruited patients with stages I-IV CRC treated with curative intent from 8/2016-5/2019 at the Massachusetts General Hospital Cancer Center. The study was approved by the Dana-Farber/Harvard Cancer Center IRB and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. All patients received treatment according to standard-of-care as per the treating medical oncology and surgical oncology teams. Data on neoadjuvant therapy, adjuvant therapy, and clinicopathological information was collected from the electronic health record (EHR).

Sample collection

We collected 20mL of peripheral blood in two 10mL Streck tubes pre-operatively (when available), approximately four weeks post-surgery and approximately four weeks post-completion of adjuvant therapy for patients who received additional treatment. “Landmark” timepoint was defined as the plasma specimen drawn approximately one month after completion of definitive therapy (surgery alone or completion of adjuvant therapy for patients who received adjuvant treatment). Longitudinal timepoints were defined by patients who had subsequent draws after their “landmark” timepoint, and, using the methods employed by Reinert et al, we also assessed performance in patients with evaluable “surveillance” draws, defined as a draw obtained within 4 months of clinical recurrence. Due to the variability of follow up, a window of up to 6 weeks post-recurrence scan was allowed for some serial draws to allow them to be collected at the patient’s scheduled visit, provided that no intervening therapy was received. Carcinoembryonic antigen (CEA) at the landmark timepoint (+9 days) was obtained from the
EHR. The timing of CEA draws was not mandated by the study and was performed according to the treating physician’s discretion according to appropriate standard-of-care guidelines. Abnormal CEA was defined as >3.4 ng/ml. Serial blood collections from eleven patients who recurred but were negative at their landmark timepoint were analyzed. Plasma was separated within 1-4 days of collection through two different centrifugation steps (the first at room temperature for 10 minutes at 1,600 \( \times \) g and the second at 3,000 \( \times \) g for the same time and temperature). Plasma was isolated and stored at -80 degrees until extraction. In a subset of samples (N=72), cell-free DNA was extracted from plasma using QIAamp Circulating Nucleic Acid Kit (QIAGEN) with 60 minutes of proteinase K incubation at 60 degrees Celsius.

**Plasma Genomic and Epigenomic Based Analysis of Cell-Free DNA**

Plasma (N=180 samples; median 4mL, range 1-4mL) and extracted cfDNA (N=72 samples; median 60ng, range 4.4–100ng) were transferred to a single site for analysis (Guardant Health, Redwood City, CA). cfDNA was extracted from plasma as previously described. Extracted cfDNA was analyzed using the plasma-only Guardant Reveal test (formerly called LUNAR-1), which is a single sample next generation sequencing test validated in early stage CRC that integrates assessment of somatic alterations with an epigenomic cancer signature to identify the presence of methylation signatures associated with cancer vs. normal DNA (Figure 1A). The Guardant Reveal assay was designed to detect the presence of MRD without prior knowledge of the specific molecular alterations present in an individual patient’s tumor.

For analysis ctDNA fragments are partitioned and individual molecules within each partition are barcoded and then pooled and processed together through the rest of the library preparation. The libraries are enriched with a ~500kb panel targeting both somatic and epigenomic regions using
biotinylated bait oligonucleotides and sequenced on a NovaSeq 6000 System. Enriched samples are then amplified and sequenced. Sequencing data files containing raw data are analyzed using a proprietary bioinformatics pipeline software, trained to detect the presence of ctDNA based on multiple analytical features, including genomic variation (single nucleotide variants and insertion-deletion alterations) and epigenomic signals, and to exclude common sources of interference such as CHIP. Based on this analysis, the plasma-only ctDNA test returns a result of either ctDNA detected or ctDNA not detected. For the current study, ctDNA analysis was performed blinded to the clinical data. Neither treating physicians nor patients were informed regarding the results of the ctDNA analyses.

**Statistical Analysis**

The primary outcomes of the study were detection of ctDNA and recurrence-free survival (RFS) as assessed by standard radiographic imaging. RFS was measured from the day of completion of definitive treatment to first radiographic recurrence or death from CRC. For patients whose only treatment was surgery or surgery was the final intervention, definitive treatment was defined as day of surgery. For patients who received adjuvant chemotherapy, RFS was measured from the day of completion of adjuvant therapy. Patients were censored at the date of last follow-up or non-CRC-related death. Patients without clinical follow-up available were excluded from the study. Analysis was completed for patients with at least one year of follow-up and for the overall eligible cohort. The Kaplan-Meier method was used to describe survival outcomes. A log rank test was used for Hazard Ratios and all $P$ values were based on 2-sided testing with statistically significant differences at $p \leq 0.05$. Statistical analysis was performed using Graphpad PRISM version 8.0 for Windows, GraphPad Software, San Diego, CA, USA.
Results

We evaluated the feasibility of tumor-uninformed MRD detection with a plasma-only MRD ctDNA assay in 103 patients with stage I-IV CRC undergoing curative-intent surgery. This assay (Guardant Reveal, Guardant Health) evaluates epigenomic signatures related to aberrant DNA methylation in addition to “standard” detection of tumor-derived genomic alterations employed by most MRD assays, without requiring parallel assessment of tumor tissue (Figure 1A). Genomic alterations detected are filtered to remove variants of likely benign origin (e.g. CHIP). Overall, 84 patients were evaluable (Figure 1B), and patient characteristics (9.5% Stage I, 23.8% Stage II, 47.6% Stage III, and 19% Stage IV) are shown (Table 1, Supp. Tables S1 and S2). 45% of patients received neoadjuvant therapy and 53.6% received adjuvant therapy. 16/84 (19%) had surgery alone with no neoadjuvant or adjuvant therapy. Overall, 30/84 (35.7%) patients recurred with a median time to recurrence from surgery of 348.5 days (range 35-887) and median time to recurrence from completion of definitive treatment of 211 days (range 7-887). Blood was drawn a median of 30 days (range 11-148) post-operatively and median of 32 days (range 0-193) post-completion of definitive therapy (Table 1). Four patients were excluded from the landmark analysis as they did not have an appropriate blood draw at post-completion of definitive therapy. Of the 80 remaining patients, 10 patients were excluded from the primary analysis as post-curative intent specimens yielded extracted cfDNA that was of insufficient quantity or failed to pass sequencing quality control thresholds, leaving 70 (88% success rate) patients evaluable for the primary landmark analysis. Timing and receipt of neoadjuvant therapy, surgery, adjuvant therapy, and serial blood collections for each patient are shown (Figure 2).
Primary “Landmark” Analysis

For the primary analysis, a single “landmark” plasma specimen drawn approximately one month after completion of definitive therapy (median 31.5 days) was assessed, as early MRD detection is critical to enable therapeutic decisions during the standard window for adjuvant therapy initiation. Of 70 landmark evaluable patients, 17/70 (24%) patients had detectable ctDNA post-completion of definitive therapy and 15/17 (88%) of these patients recurred (specificity 95.4%) (Supp. Figure S1A; Supp. Table S3). However, the two patients with detectable ctDNA but no recurrence both had clinical follow-up of less than one year. In patients with at least one year of clinical follow-up available at the data cutoff, 15/15 patients with detectable ctDNA (“ctDNA-detected”) recurred at a median of 162 days post-definitive therapy (positive predictive value (PPV) of recurrence of 100% (95% confidence interval 78.2-100%); hazard ratio 11.28 (p<0.0001)) (Figure 3A). Of the 49 patients without detectable landmark ctDNA, 12/49 (24%) recurred (median time to recurrence not reached). Sensitivity and specificity for recurrence was 55.6% (95% confidence interval 35.3-74.5%) and 100% (95% confidence interval 90.5-100%). Negative predictive value (NPV) was 75.5% (95% confidence interval 61.1-86.7%). ctDNA detection predicted recurrence regardless of stage, neoadjuvant, or adjuvant therapy (Supp Table S4).

Longitudinal and surveillance ctDNA Analyses

Prior studies have shown that sensitivity for recurrence prediction can be improved with longitudinal plasma monitoring. Overall, 9/14 (64%) of patients who recurred despite no detectable landmark ctDNA or who lacked landmark draws had at least one evaluable
longitudinal specimen at a later timepoint (median 3 per patient). Integrating longitudinal specimens increased sensitivity from 55.6 to 69.0% (hazard ratio of 12.26 (p<0.0001)), with specificity remaining 100% (Figure 3B; Supp Figure S1B). Using the methods employed by Reinert et al\textsuperscript{6}, we assessed performance in patients with evaluable “surveillance” draws, defined as a draw obtained within 4 months of clinical recurrence, and observed that sensitivity improved to 91%.

\textit{Integration of genomic and epigenomic assessment of ctDNA}

Since this is the first MRD assay to leverage ctDNA methylation analysis in addition to genomic alterations, compared to other ctDNA MRD assays that detect genomic alterations only, we assessed the relative contributions of integrating genomic and epigenomic signatures for ctDNA detection. ctDNA methylation and other epigenomic markers, such as ctDNA fragmentation, show promise in ctDNA-based early cancer detection approaches, which are tumor-uninformed, and thus might also improve MRD detection\textsuperscript{30-32}. Across all ctDNA-positive specimens, 47% of samples were positive by both epigenomic and genomic calls, while 28% and 25%, respectively, were positive by either genomic or epigenomic calls alone (Figure 3C). For the landmark analysis, using genomic calls alone, recurrence sensitivity would have been only 40.7%, and 48.2% using epigenomic calls alone. By integrating genomic and epigenomic calls, sensitivity improved to 55.6%. Similarly, in the longitudinal and surveillance analyses, respectively, sensitivity would have been only 55.2% and 72.7% with genomic calls alone or 48.3% and 63.6% with epigenomic calls alone, but sensitivity improved to 69.0% and 90.9% by integrating genomic and epigenomic calls. Thus, incorporating epigenomic calls with standard genomic calls
increased relative MRD detection sensitivity by 25-36% across analysis groups, suggesting ctDNA methylation may be an effective modality for MRD detection.

*Analysis of CEA levels and recurrence*

As a basis of comparison, we evaluated the ability of the standard-of-care CRC serum tumor marker CEA to predict recurrence in this same cohort. CEA values post-definitive therapy were available for 56 patients at their landmark timepoint. Notably, CEA values failed to predict recurrence (Figure 4; Supp. Figure S2).

**Discussion**

In this prospective cohort study, we report initial findings for one of the first plasma-only assays designed for tumor-uninformed ctDNA-based MRD detection, which demonstrated favorable sensitivity and specificity, comparable to previously reported tumor-informed approaches. This study also represents one of the first assessments of a ctDNA assay incorporating both genomic and epigenomic markers for MRD detection which also increased sensitivity.

One of the primary concerns with plasma-only assays is that specificity and sensitivity might be limited if the assay is not guided by specific alterations identified in the resected tumor. Notably, the loss of specificity is a critical concern, as non-cancer derived mutations are frequently present in the blood which could lead to false positives.\(^{24}\) In the current study, specificity was 100\% in patients with at least one-year minimum clinical follow-up, which aligns with specificity of other tumor-informed MRD approaches for CRC.\(^{6,8}\) In the overall cohort, two patients with ctDNA detected had not yet recurred by the cutoff date. However, both patients had
clinical follow-up under one year. Further analysis of larger cohorts is needed as high specificity of MRD detection will remain critical if MRD assays are to be used to select patients for additional or more intensive therapy. This would avoid situations in which patients who are cured are erroneously identified as MRD positive and subjected to potentially unnecessary therapy.

Additionally, we found that sensitivity was comparable to the performance of many tumor-informed assays at the landmark timepoint. Landmark detection sensitivity is of central importance, as this assessment occurs within the time window in which treatment decisions are typically made. Previously reported “fixed panel” and “bespoke” tumor-informed MRD assays produced sensitivities of ~40%-50% when specifically assessing a single landmark timepoint obtained ~1-month post-therapy \(^6,9\), which is comparable to the landmark sensitivity of 55.6% produced by this plasma-only tumor-uninformed assay. Furthermore, recent evidence has demonstrated that serial monitoring for recurrence can increase detection sensitivity. For example, Reinert et al found that for patients with surveillance draws, defined as a at least one draw within 4 months of clinical recurrence, sensitivity improved to 88%. \(^6\) Similarly, when evaluating patients with analogous surveillance draws in our cohort, we observed that sensitivity improved to 91%. Thus, these initial data suggest that this plasma-only assay can achieve performance characteristics comparable to currently approved tumor-informed approaches.

Importantly, we also evaluated whether assessment of epigenomic markers (specifically, changes in DNA methylation patterns) in ctDNA might increase the effectiveness for MRD detection. Indeed, methylation and other epigenomic markers, and DNA fragmentation patterns show
promise in ctDNA-based early detection approaches, which are tumor-uninformed, and thus may also help with MRD detection.\textsuperscript{30-34} Our data suggest that epigenomic methylation signatures in ctDNA can allow MRD detection with high specificity and may improve performance compared to detection of genomic calls alone, which is the method utilized by most MRD assays. Interestingly, we observed that while most cases showed ctDNA positivity by both genomic and epigenomic signatures, many cases were detected as positive by genomic or epigenomic calls alone (Figure 4 A,B), suggesting that integrating these two modalities may augment sensitivity for MRD detection. Specifically, integration of epigenomic signatures for landmark MRD detection increased sensitivity by a relative 36\% compared to genomic alterations alone.

Overall, a plasma-only ctDNA assay for MRD detection may hold several advantages relative to tumor-informed approaches. These advantages include a more rapid turn-around time as only a single plasma draw is required, potential cost savings, and decreased logistical complexity. Moreover, a plasma-only assay would offer the potential for MRD detection even in situations where tumor tissue is not available or sufficient for use in tumor-informed ctDNA detection. Although sufficient tumor tissue is often available following a surgical procedure, some studies have suggested that in a subset of patients available tissue may be insufficient for molecular analysis, which would preclude the ability to utilize a tumor-informed approach for MRD detection.\textsuperscript{27} As neoadjuvant therapy becomes increasingly utilized as standard-of-care for many tumor types, a growing number of surgical specimens may yield insufficient tissue for molecular analysis post-surgery, due to low tumor cellularity following a favorable treatment response.\textsuperscript{35} Thus, in some situations, a plasma-only ctDNA assay might offer the only means of assessing for MRD in certain situations.
While this study supports the potential of plasma-only ctDNA detection of MRD, this study also has several key limitations. First, the sample size is modest, and further evaluation in larger patient cohorts will be important to better define the assay performance characteristics. Second, while this study suggests the potential for effective MRD detection across multiple stages of CRC and across different treatment pathways (neoadjuvant and/or adjuvant therapy), a more focused and in-depth analysis will be important to understand the true performance in specific patient populations. Third, while this cohort provides a potentially valuable initial assessment the study design utilizing banked, isolated plasma samples, showed that in some cases the extracted ctDNA quantity or quality was below the recommended and optimal input levels for the assay. In particular, all of our samples had plasma input volumes of 4 mL or less, versus the recommended input of 8-10 mL, which may have affected overall performance characteristics. Finally, this study focused primarily on analysis of a single landmark timepoint and did not systematically incorporate serial longitudinal draws for all patients. While effective detection of MRD at a landmark timepoint early after completion of curative intent therapy is clinically relevant, recent data suggests a potential value for serial monitoring during surveillance. Although incorporation of longitudinal and surveillance draws available for some patients did improve overall sensitivity from 55.6% to 69% and 91%, respectively, the lack of systematic longitudinal and surveillance draws across all patients precluded a comprehensive assessment.

In summary, we show that plasma-only, tumor-uninformed ctDNA-based detection of MRD is feasible and can produce comparable sensitivity and specificity to previously reported tumor-informed MRD approaches. These data also suggest that integration of epigenomic markers, such
as DNA methylation analysis, may enhance detection sensitivity over standard genomic alteration detection methods alone and the integration of genomic and epigenomic assessment improves performance. The Guardant Reveal test is currently being utilized in several prospective clinical trials to assess the impact of ctDNA-guided adjuvant therapy.\textsuperscript{13,17,21} Ongoing prospective interventional studies will further evaluate the performance of this assay for MRD detection and to help guide treatment decisions.

\textbf{Acknowledgements}

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Table 1. Baseline patient and disease characteristics

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<td>Days on Adjuvant Treatment – median (range)</td>
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Figure Legends

**Figure 1.** (A) Guardant Reveal plasma-only ctDNA assay schema and (B) patient enrollment and analysis groups

**Figure 2.** ctDNA assay results and timing of treatment for each patient. Patients are ordered by total days of clinical follow up from surgery for (A) patients that received curative intent surgery alone and (B) for patients that received curative intent surgery followed by adjuvant therapy. Patients receiving neoadjuvant therapy are designated by a yellow square. Specimens obtained on the day of surgery were obtained pre-operatively.

**Figure 3.** (A) Recurrence-free survival by landmark one-month post-therapy ctDNA detection for patients with >1 year follow up. Bar graph displays recurrence rates by ctDNA detection status with Venn diagram of ctDNA detection by calling methods (epigenomic only, genomic only, or both). (B) Sensitivity analysis for landmark, longitudinal, and surveillance cohorts and Venn diagram of ctDNA detection for longitudinal and surveillance analyses by calling method. (C) Recurrence sensitivity and Venn diagram of ctDNA detection by individual calling methods.

**Figure 4.** Recurrence-free survival by landmark one-month post-therapy CEA analysis for patients with >1 year follow up. Bar graph displays recurrence rates by CEA status.
A. Landmark Analysis

- **ctDNA detected**
- **ctDNA not detected**

- ctDNA Positive mRFS = 168 days
- ctDNA Negative mRFS = Not Reached
- Log Rank: p < 0.0001
- Hazard Ratio: 11.20

B. Landmark Analysis

- Sensitivity: 55.6% (15/27)
- Longitudinal Analysis
  - Sensitivity: 69.0% (20/29)
- Surveillance Analysis
  - Sensitivity: 90.9% (20/22)

C. Sensitivity (%) by ctDNA Calling Methods

- Genomic Only
- Epigenomic Only
- Genomic & Epigenomic

- Landmark
  - Sensitivity: 40.7%
- Longitudinal
  - Sensitivity: 48.3%
- Surveillance
  - Sensitivity: 90.9%
Landmark Timepoint
(1 Year Minimum Follow Up)

Probability of Survival

CEA Abnormal

CEA Normal

CEA Abnormal mRFS = 400 days
CEA Normal mRFS = Not Reached
Log Rank: p=0.1846
Hazard Ratio: 1.840

Percentage of Patients

n = 13
n = 38

p = 0.3241

Recurred
Not Recurred

6
7
25
13

Sensitivity = 35.0%
Specificity = 80.7%
PPV = 53.9%
NPV = 65.8%
Clinical Cancer Research

Minimal Residual Disease Detection using a Plasma-Only Circulating Tumor DNA Assay in Colorectal Cancer Patients


Clin Cancer Res Published OnlineFirst April 29, 2021.

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