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Performance of Colon and Rectal Cancer Detection With a Multi-Cancer Early Detection (MCED) Blood Test

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Matthew Margolis, MS[1]; Kathryn N. Kurtzman, MD[1]; Cheng Chen, PhD[1]; Jordan J. Karlitz, MD[1] | [1]GRAIL, LLC, Menlo Park, CA, USA

INTRODUCTION

- A blood-based MCED test intended to complement, but not replace, United States Preventive Services Task Force (USPSTF)-recommended screening has detected a shared cancer signal across multiple cancers simultaneously at a specificity of 99.5% (low false positive rate)[1]
- In the case-control Circulating Cell-free Genome Atlas substudy 3 (CCGA3),[1] MCED test performance across multiple cancer types, including gastrointestinal (GI) and non-GI cancers, was evaluated in participants with known cancer/non-cancer status (N = 4077)
  - Overall sensitivity across 50+ cancer types was 51.5% (95% confidence interval [CI]: 49.6%-53.3%)[1]
  - Sensitivity was 76.3% (74.0%-78.5%) in 12 pre-specified cancers that account for approximately two-thirds of annual US cancer deaths[1]
  - **Table 1** shows sensitivity of cancer signal detection in GI cancers detected in CCGA3[1]
- If a cancer signal is detected, the MCED test provides a cancer signal origin (CSO) prediction; overall CSO prediction accuracy was 89% in CCGA3[1]
- Sensitivity of cancer signal detection for colorectal cancer (CRC) was 82.0% (**Table 1**)[1]

Table 1. The MCED Test Detected Multiple GI Cancers (All Stages) in CCGA3.

Cancer Type	Total N	Sensitivity % (95% CI)
Liver/Bile-duct	46	93.5 (82.5 - 97.8)
Esophagus	100	85.0 (76.7 - 90.7)
Pancreas	135	83.7 (76.6 - 89.0)
Colon/Rectum*	206	82.0 (76.2 - 86.7)
Anus	22	81.8 (61.5 - 92.7)
Gallbladder	17	70.6 (46.9 - 86.7)
Stomach	30	66.7 (48.8 - 80.8)

Sensitivity of cancer signal detection by GI cancer with 95% CI. The full list of cancer types detected and corresponding cancer signal detection sensitivity was previously reported in Klein et al. 2021.[1]
*CRC subanalysis of CC and RC was performed on this group.
CC, colon cancer; CCGA3, Circulating Cell-free Genome Atlas substudy 3; CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; MCED, multi-cancer early detection; RC, rectal cancer.

- Although staged together in American Joint Committee of Cancer (AJCC) guidelines, colon cancer (CC) and rectal cancer (RC) can be clinically distinct
  - Importantly, CC is more common, more likely to present with no/minimal symptoms, and more likely to present as an interval cancer between colonoscopy or stool-based screenings than RC[2,3]
  - Thus, it is clinically relevant to investigate the MCED test detection rates of CC and RC independently

OBJECTIVE

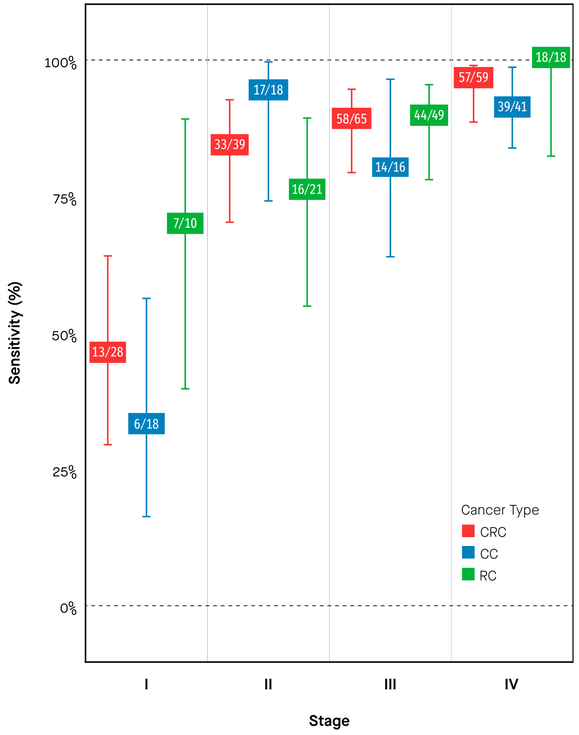
- To provide a subanalysis of MCED test performance in CC and RC from CCGA3
- To provide a survival analysis of participants with CC and RC from CCGA3

METHODS

- The MCED test uses a targeted methylation assay and machine learning classifier to detect a cancer signal in cell-free DNA and predict its CSO
- We evaluated 199 CCGA3[1] participants with CRC. Participants with neuroendocrine carcinomas or multiple primaries were excluded from analysis
  - Pathology reports were used to determine tumor location (CC vs RC)
  - Rectosigmoid junction cancers were classified as RC and appendiceal adenocarcinomas were classified as CC
- Sensitivity of cancer signal detection, stratified by stage and cancer type (CC vs RC), and overall survival were assessed
  - Sensitivities across cancer stages or between CC and RC were compared using Fisher's exact test with pairwise comparisons
  - Kaplan-Meier curves were produced for the observed survival of participants with a cancer signal detected/not detected and for the expected survival based on Surveillance, Epidemiology, and End Results (SEER) data[4]

KEY RESULTS: HIGH SENSITIVITY OF THE MCED TEST ALLOWS DETECTION OF BOTH CC AND RC, WHILE ALSO DETECTING MULTIPLE OTHER CANCER TYPES

Figure 1. The MCED Test Detected CC and RC When Considered Together or Separately.

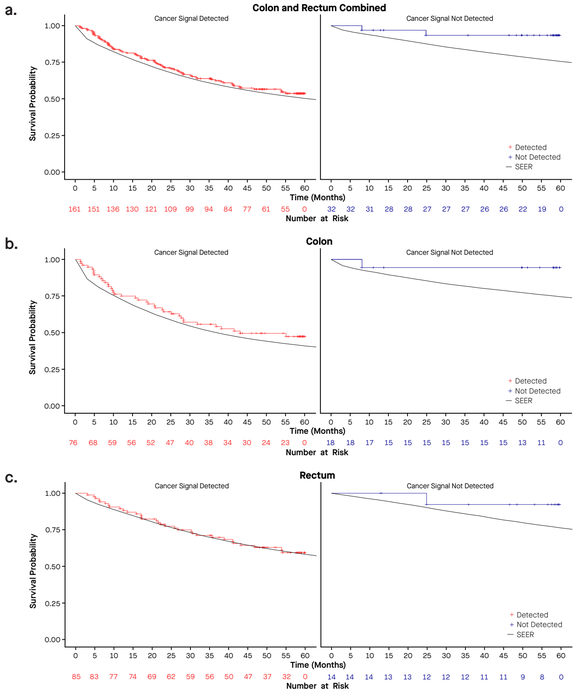


MCED test sensitivity for CRC (red), CC (blue), and RC (green) across cancer stages. Of the 199 CCGA3 participants with CRC that were evaluated, 7 were excluded due to lack of staging information, and 1 was excluded because the cancer was non-invasive. Fractions indicate the number of cases with 'cancer signal detected' out of the total number of cases, and interval markers indicate 95% confidence interval.

CC, colon cancer; CCGA3, Circulating Cell-free Genome Atlas substudy 3; CRC, colorectal cancer; MCED, multi-cancer early detection; RC, rectal cancer.

- The MCED test detected both CC and RC, including earlier-stage disease (ie, I-III, before metastases) (**Figure 1**)
- The MCED test was equally sensitive between CC and RC within each stage ($p \geq 0.05$) (**Figure 1**)

Figure 2. Cancers Not Detected by the MCED Test Had Better Prognosis Than What Would Be Expected From SEER Data.



Kaplan-Meier survival curves for CCGA3 participants with cancer signal detected (left, red) and not detected (right, blue) by the MCED test compared to SEER-expected survival (black). Overall survival was determined across all stages for CC and RC cases together (a: CRC) and separately (b: CC and c: RC). Of the 199 CCGA3 participants with known cancer/non-cancer status evaluated for this study, 193 were included in the overall survival analysis. Two participants with non-invasive cancer were excluded, and 4 participants were censored at time of blood draw because of missing follow-up information.

CC, colon cancer; CCGA3, Circulating Cell-free Genome Atlas substudy 3; CRC, colorectal cancer; MCED, multi-cancer early detection; RC, rectal cancer; SEER, Surveillance, Epidemiology, and End Results.

- CRC, CC, and RC cases without detectable circulating tumor DNA–and thus not detected by the MCED test–had better prognosis than what would be predicted based on SEER-expected survival (**Figure 2**)
- Although MCED test sensitivity was lower for stage I CC relative to stages II-IV (**Figure 1**), this survival analysis suggests that the CC cases missed by the MCED test may be less aggressive (**Figure 2b**)

CONCLUSIONS

- At a specificity of 99.5%, the MCED test detected both CC and RC at earlier stages (I-III), prior to metastases
- The MCED test has been shown to detect less indolent, more aggressive disease,[5] with MCED test-detected cancers having as good as or better survival than expected based on SEER. Detecting aggressive cancers earlier provides the opportunity for earlier intervention in higher-risk patients
- High sensitivity for CC is especially important as CC may be associated with fewer symptoms and be more likely to present as interval cancer (potentially asymptomatic) between standard screening intervals
- A study limitation was relatively low subgroup sizes
- Lower sensitivity for stage I CC may be explained by lower tumor fraction at this stage,[6] and test sensitivity increases significantly for stage II CC, when treatments are still highly effective
- In summary, high sensitivity of this MCED test allows detection of both CC and RC signals while also detecting multiple other cancer types, making blood-based MCED testing a promising complement to, but not replacement of, standard screening

References

1. Klein EA, et al. *Ann Oncol.* 2021;32(9):1167-1177.
2. Yang J, et al. *PLoS One.* 2016;11(12):e0167540.
3. Samadder NJ, et al. *Gastroenterology.* 2014;146(4):950-960.
4. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov).
5. Chen X, et al. *Clin Cancer Res.* 2021;27(15):4221-4229.
6. Bredno J, et al. *PLoS One.* 2021;16(8):e0256436.

Disclosures

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