Background

Approximately one-third of age-appropriate adults are not up to date with recommended colorectal cancer (CRC) screening. A non-invasive, blood-based screening test with high sensitivity and specificity in early stage CRC should improve adherence and ultimately reduce mortality. Current tests rely on tumor-derived biomarkers alone and have limited sensitivity, especially in early-stage disease.

Given the biological heterogeneity of CRC and its evolution over time, a multiomics approach wherein non-tumor-derived signals complement tumor-derived signal to enable earlier detection of disease should improve adherence and ultimately reduce mortality; however, tests based on tumor-derived biomarkers alone have limited sensitivity, especially in early-stage disease. A multiomics blood test demonstrated higher sensitivity for CRC (91% vs. 91%) at comparable specificity. Our prospective, multi-center study (AL-EMERGE) that included screening and axis-control cohorts, an expanded multi-omics approach (including both tumor-derived and extra-tumoral signals) and an initial range of complementary tests was included in this analysis.

Methods

Samples from a statistically driven subset of subjects enrolled in a multi-center prospective study (AL-EMERGE) involving average risk screening and colonoscopy cohorts were included in this analysis (Figure 2). Four-tumor subgroups with CRC and CRC-only colorectal adenocarcinoma-negative controls were analyzed across scoring, including 7 scoring training samples (Table 1). Plasma was analyzed by whole exome sequencing, bisulfite sequencing, and protein quantification methods. Four-fold cross-validation was done, and performance based on the model was reported. Four-fold cross-validation was done, and performance based on the model was reported.

Objective

The objective of this study was to assess the performance of our multiomics blood test in preoperatively collected CRC samples and corresponding colorectal adenocarcinoma-negative control subject blood samples using tumor- and non-tumor-derived (e.g., inflammatory) signals from ctDNA, epigenetics, and proteomics.

Results

CRC sensitivity was higher for the multiomics blood test versus plasma ctDNA (91% vs. 55%), plasma CEA (91% vs. 87%), and stool-based FIT (80% vs. 55%) (Table 1). CRC sensitivity was higher for the multiomics blood test versus plasma CEA (91% vs. 87%), whereas a CEA-only classifier achieved 31% sensitivity and 94% specificity, consistent with previous reports (91% sensitivity and 93% specificity).

Conclusions

When compared to other blood-based tests, our multiomics blood test demonstrated higher sensitivity for CRC (91% vs. 91%) at comparable specificity. Our prospective, multi-center study (AL-EMERGE) that included screening and axis-control cohorts, an expanded multi-omics approach (including both tumor-derived and extra-tumoral signals) and an initial range of complementary tests was included in this analysis.

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References

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3. Imperiale et al. NEJM 2015;373;1568-76

Figure 1. Biologic signals change as cancer evolves.

Figure 2. AL-EMERGE Study Design (NCT03688906)

Figure 3. CRC sensitivity was higher for the multiomics blood test versus plasma CEA.

Figure 4. CRC sensitivity was higher in distal and proximal tumors.

Figure 5. CRC sensitivity was higher for the multiomics blood test versus FIT.

Figure 6. CRC sensitivity was higher for the multiomics blood test versus plasma ctDNA.

Figure 7. Table 1. Clinical characteristics and demographics of subjects with CRC and colorectal adenocarcinoma-negative subjects.

*Four samples with unknown stage were tested. Two were correctly classified by CEA and 3 were correctly classified by the multiomics blood test.