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Blood-based detection of early-stage colorectal cancer using multiomics and machine learning

Girish Putcha, Tzu-Yu Liu, Eric Ariazi, Marvin Bertin, Adam Drake, Michael Dzamba, Greg Hogan, Steven Kothen-Hill, Jeffrey Liao, Kang Li, Shivani Mahajan, Krishnan K. Palaniappan, Poonam Sansanwal, John St. John, Peter Ulz, Nathan Wan, Hayley Warsinske, David Weinberg, Rui Yang and C. Jimmy Lin

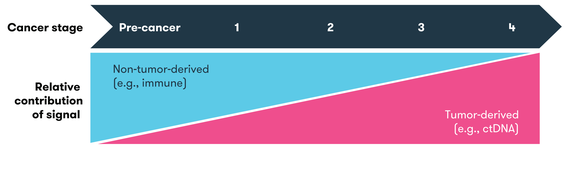
Freenome, South San Francisco, CA

All correspondence to authors@freenome.com

BACKGROUND

- Approximately one-third of age-appropriate adults are not up to date with recommended colorectal cancer (CRC) screening[1]
- A non-invasive, blood-based screening test with high sensitivity and specificity in early-stage CRC should improve adherence and ultimately reduce mortality; however, tests based on tumor-derived biomarkers alone 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 signals is required for effective early detection (**Figure 1**)
- Here we used a multiomics, machine learning platform to discover, refine, and combine tumor- and non-tumor-derived signals to develop a blood test for the detection of early-stage CRC

Figure 1. Biological signals change as cancer evolves[2,3]



- Non-tumor-derived signal complements tumor-derived signal to enable earlier detection of disease

OBJECTIVE

- The objective of this study was to assess the performance of our multiomics blood test in prospectively collected CRC samples and colonoscopy-confirmed negative controls by combining tumor- and non-tumor-derived (e.g., immune) signals from cfDNA, epigenetic, and protein biomarkers

METHODS

- Samples from a statistically-driven subset of subjects enrolled in a multi-center prospective study (AI-EMERGE®) including average-risk screening and case-control cohorts were included in this analysis (**Figure 2**)
- Forty-three subjects with CRC and 548 colonoscopy-confirmed negative controls were analyzed across assays, including 17 analyte training samples (**Table 1**)
- Plasma was analyzed by whole-genome sequencing, bisulfite sequencing, and protein quantification methods
- Four-fold cross-validation was done, and performance based on the model was reported
- The multiomics blood test was compared to FIT, plasma ctDNA, and plasma CEA. The multiomics blood test performance was calculated for each comparison using only the samples for which paired data was available

Figure 2. AI-EMERGE® Study Design (NCT03688906)

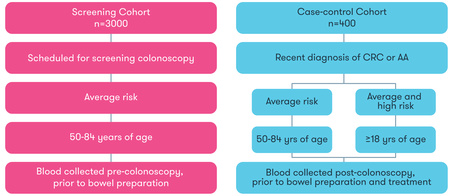
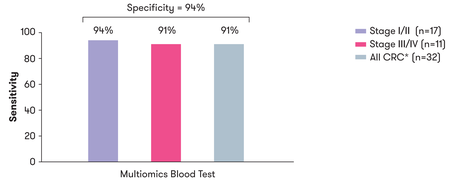


Table 1. Clinical characteristics and demographics of subjects with CRC and colonoscopy-confirmed negative subjects

	Samples* (n=574)	
	CRC† n=32	Colonoscopy-confirmed negative subjects n=539
Gender: n (%)		
Male	18 (56%)	292 (54%)
Female	14 (44%)	247 (46%)
Age: median (IQR)	62 (45-83)	59 (53-67)
Stage: n (%)		
1	11 (34%)	N/A
2	6 (19%)	N/A
3	7 (22%)	N/A
4	4 (12.5%)	N/A
Unknown	4 (12.5%)	N/A

*Excludes analyte training set (n=17).
†Excludes 3 non-adenocarcinoma cases: 1 squamous cell carcinoma (stage III) and 2 neuroendocrine tumors (stage II).

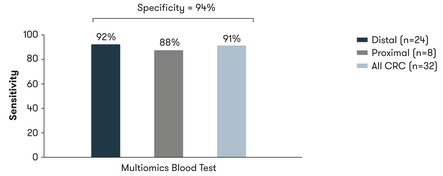
Figure 3. Sensitivity was high in both early (I/II) and late (III/IV) stage CRC† for the multiomics blood test



†Only results for colorectal adenocarcinoma, which represents >95% of CRC, are shown. Three non-adenocarcinoma subtypes were tested: The single squamous cell carcinoma (stage III) was correctly classified but both neuroendocrine tumors (stage II) were misclassified.
*4 samples with unknown stage were tested, 3 were classified correctly

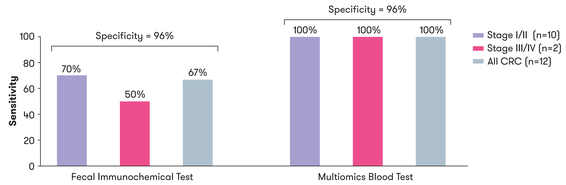
- In early stage CRC (I/II), 16/17 samples were correctly classified, with a sensitivity of 94% and specificity of 94%
- In late stage CRC (III/IV), 10/11 samples were correctly classified, with a sensitivity of 91% and specificity of 94%

Figure 4. CRC sensitivity is high in distal and proximal tumors



- Seventy-five percent of tumors were distal and 25% were proximal

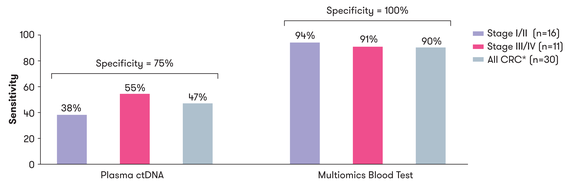
Figure 5. CRC sensitivity was higher for the multiomics blood test versus FIT



Polymedco OC-Auto® FIT results are reported per manufacturer's specification at a cutoff of 100 ng/ml[5].

- In AI-EMERGE®, stool collection was optional. Only 52% of subjects who provided a blood sample provided stool for FIT
- The multiomics blood test demonstrated 100% sensitivity and 96% specificity for CRC, whereas FIT achieved 67% sensitivity and 96% specificity, consistent with previous reports (74% sensitivity and 95% specificity)[6]

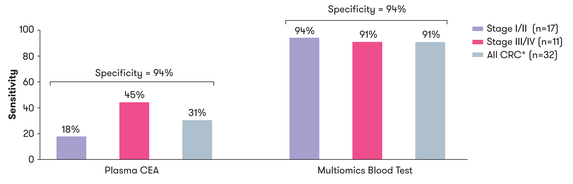
Figure 6. CRC sensitivity was higher for the multiomics blood test versus plasma ctDNA



*Three samples with unknown stage were tested for both plasma ctDNA and the multiomics blood test, and 2 were classified correctly. Plasma ctDNA results are reported per manufacturer's specification.[7]

- The multiomics blood test demonstrated 90% sensitivity and 100% specificity for CRC, whereas plasma ctDNA achieved 47% sensitivity and 75% specificity

Figure 7. CRC sensitivity was higher for the multiomics blood test versus plasma CEA



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

- The multiomics blood test demonstrated 91% sensitivity and 94% specificity for CRC, whereas a CEA-only classifier achieved 31% sensitivity and 94% specificity, consistent with previous reports (47% sensitivity and 80% specificity)[8]

CONCLUSIONS

- In our prospective, multi-center study (AI-EMERGE®) that included screening and case-control cohorts, we achieved high sensitivity (94%) and high specificity (94%) for early-stage (I/II) colorectal adenocarcinoma
- Our multiomics approach combines tumor- and non-tumor-derived (e.g., immune) signals from cfDNA, epigenetic, and protein biomarkers to detect early-stage CRC
- When compared to a leading stool-based FIT, our multiomics blood test demonstrated higher sensitivity for CRC (100% vs. 67%) at comparable specificity
- When compared to other blood-based tests, our multiomics blood test demonstrated higher sensitivity for CRC vs plasma ctDNA (90% vs. 47%) or plasma CEA (91% vs 31%) at comparable or better specificity
- These results will be validated in a prospective, multi-center registrational study

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