Abstract # 43

Evaluation of a sensitive blood test for the detection of colorectal advanced adenomas in a prospective cohort using a multiomics approach

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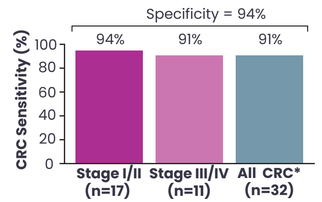
INTRODUCTION

- Blood tests for colorectal cancer (CRC) with high sensitivity and specificity can improve adherence, facilitate early detection, and ultimately reduce mortality from CRC
  - As previously reported, our multiomics blood test detects early-stage (I/II) CRC at a sensitivity of 94% and specificity of 94%[1] (**Figure 1**)
- The detection and subsequent removal of adenomas, especially advanced adenomas (AA), saves lives[2]
  - ~ 60× greater impact on CRC-specific mortality for adenoma vs CRC sensitivity[3,4,5] (**Figure 2**)
- Current stool-based tests, such as FIT and FIT-DNA, have AA sensitivities of 24% and 42%, and specificities of 95% and 87%[6], respectively
- To date, blood tests that rely on tumor-derived cell-free DNA (cfDNA) methylation signatures alone have shown limited sensitivity for AAs[7]

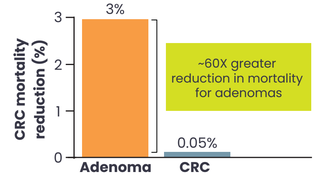
Figure 1. Multiomics blood test detects early-stage CRC[1]

Previously presented data



*14 samples with unknown stage were tested, 3 were classified correctly

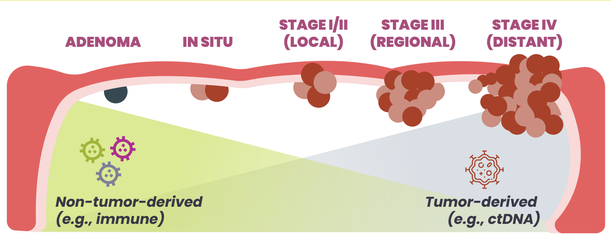
Figure 2. CRC-specific mortality reduction is impacted far more by adenoma sensitivity than by CRC sensitivity



OBJECTIVES

- To demonstrate that AAs can be detected from blood using a multiomics approach combining both tumor- and immune-derived signatures from cell-free nucleic acids and plasma proteins in prospectively collected colonoscopy-confirmed advanced adenoma samples and colonoscopy-confirmed negative controls
- To compare the multiomics blood test to other single assay approaches (e.g., cfDNA methylation or CEA)

Figure 3. Biological signals change as cancer evolves

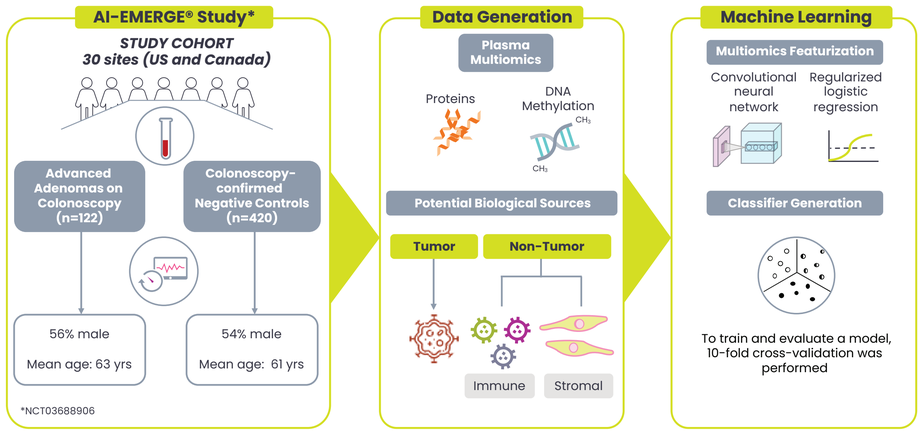


- While tumor-derived signals are abundant in later-stage disease, signals from non-tumor sources (e.g., the immune system) predominate in earlier stages
- A multiomics approach that complements tumor-derived signals with non-tumor-derived signals can better address the inherent limitations of a strategy focused on only a single assay

STUDY DESIGN AND METHODS

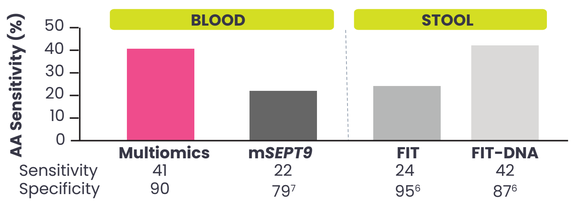
Figure 4. Study design and methods

- Blood samples were collected from participants enrolled in AI-EMERGE®, a prospectively collected, multi-center study that included average-risk screening patients
- Plasma from colonoscopy-confirmed AAs and negative controls were analyzed and signatures were generated for cell-free nucleic acids based on next-generation sequencing and for plasma proteins based on high-throughput multiplexed assays
- Modeling involving a combination of convolutional neural networks and regularized logistic regression was performed
- To train and evaluate a model, 10-fold cross-validation was performed. Each sample was tested once in a hold-out test set, and assessed by a model that had never seen that sample in training.



RESULTS

Figure 5. Multiomics blood test achieved 41% AA sensitivity at 90% specificity



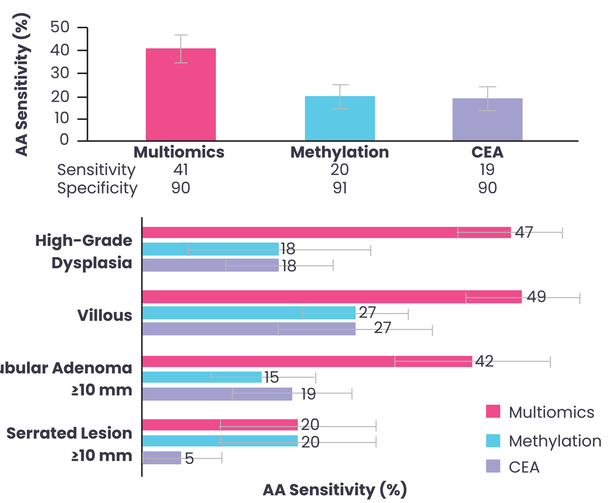
- AA sensitivity was greater than m*SEPT9*, the only blood test for CRC screening currently available
- AA sensitivity was much higher than FIT and comparable to FIT-DNA

Figure 6. AA sensitivity was similar across size, histology, and location

Whiskers show 95% confidence interval for sensitivity

- AA sensitivity increased with increasing size, similar to fecal tests[6]
- Performance was similar across histological subtypes, with the exception of sessile serrated lesions
- Higher sensitivity was observed for proximal versus distal lesions

Figure 7. Multiomics detected twice as many AAs as cfDNA methylation or CEA only



Whiskers show 95% confidence interval for sensitivity

CONCLUSIONS

- Our novel multiomics blood test detected colorectal AAs from a predominantly average-risk, prospectively collected study and achieved sensitivity of 41% at a specificity of 90%
  - This AA performance is comparable to that of existing stool-based tests
- AA sensitivity improved with increasing lesion size and was consistent across location and histology (except for serrated lesions)
- By combining signatures from both tumor- and non-tumor (e.g., immune) derived sources, our multiomics test detected approximately twice as many AAs as methylation-only or single-protein approaches
- Sensitive AA detection at levels similar to or better than currently available stool tests is achievable in blood, which is necessary for effective early detection and prevention of CRC

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