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Development of a second-generation multi-target stool RNA test (ColoSense 2.0) for colorectal cancer screening

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REFERENCES

[1] Barnell EK, Wurtzler EM, La Rocca J, Fitzgerald T, Petrone J, Hao Y, Kang Y, Holmes FL, Lieberman DA. Multitarget Stool RNA Test for Colorectal Cancer Screening. JAMA. 2023 Nov 14;330(18):1760-1768. doi: 10.1001/jama.2023.22231. Erratum in: JAMA. 2024 Mar 12;331(10):888. PMID: 37870871; PMCID: PMC10594178.

INTRODUCTION

The multi-target stool RNA test (mt-sRNA, ColoSense) was evaluated though a pivotal prospective cross-sectional study (CRC-PREVENT).[1] ColoSense was recently approved by the FDA for average-risk CRC screening in subjects 45 years and older. The original assay (ColoSense 1.0) consisted of 8 RNA transcripts, a fecal immunochemical test (FIT), and smoking status. ColoSense 1.0 demonstrated 94% sensitivity for colorectal cancer (CRC), 46% sensitivity for advanced adenomas (AA), and 86% specificity for all other findings, with 88% specificity for no findings on a colonoscopy.[1]

STUDY AIMS

We conducted feasibility research using residual samples from the CRC-PREVENT clinical trial to ascertain if novel RNA biomarkers could be used to improve ColoSense sensitivity and specificity. Study aims are provided below:

Aim 1: Identify novel biomarkers that improve sensitivity for ColoSense using RNA sequencing from stool samples and biopsy samples.

Aim 2: Determine preliminary improvement in accuracy of ColoSense 2.0 using novel, differentially expressed transcripts.

METHODS

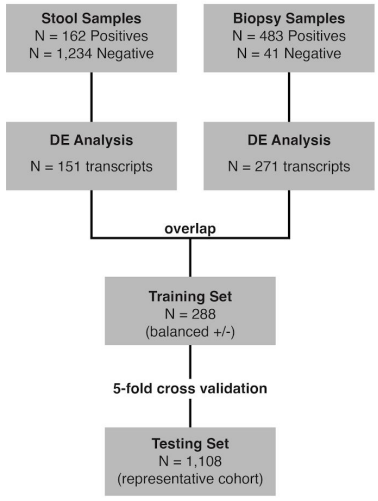
Banked CRC-PREVENT stool samples underwent RNA extraction and sequencing. RNA sequencing data from biopsy samples (CRC and normal tissue) were also obtained. Differential expression (DE) was assessed for both cohorts. Overlapping DE transcripts were used to build a random forest model. The training set leveraged 288 stool samples balanced between positive and negative samples. The testing set leveraged 1,108 stool samples with disease states that represented an average-risk cohort.

CONCLUSIONS

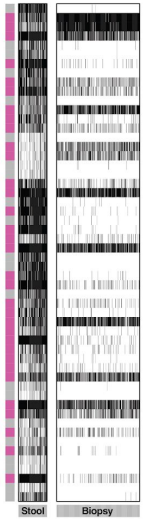
Using stool samples and biopsy data, DE transcripts were used to develop a machine learning model. The model was employed on a hold out testing set which achieved 100% sensitivity for CRC, 54% sensitivity for AA, and 90% specificity for all other findings. Additional analyses and biomarker discovery are ongoing.

Using novel RNA transcripts and key demographic features, ColoSense 2.0 showed a **14%** improvement in sensitivity for colorectal neoplasia (colorectal cancer and advanced adenomas) with a **4%** improvement in specificity for all other findings, relative to ColoSense 1.0.

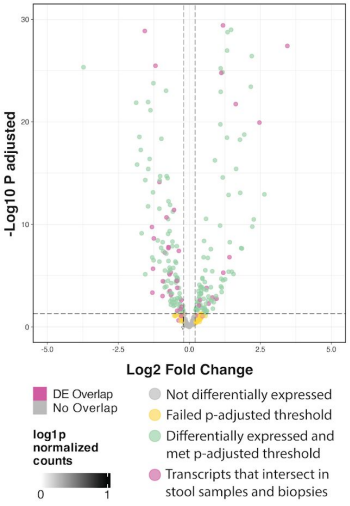
Methodology overview



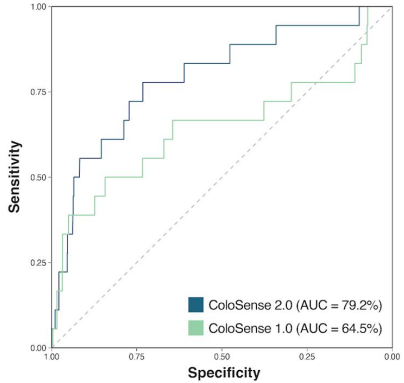
Heatmap showing DE transcripts



Volcano Plot showing DE transcripts



ROC AUC for stool samples in the testing set



Random forest machine learning model performance on the testing set (N = 1,108) showed:

- 100% sensitivity for CRC
- 54% sensitivity for AA
- 90% specificity for all other findings