Prospective study using virtual enrollment to assess an RNA-FIT assay for non-invasive detection of colorectal neoplasias

Geneoscopy
Reinventing Gastrointestinal Health

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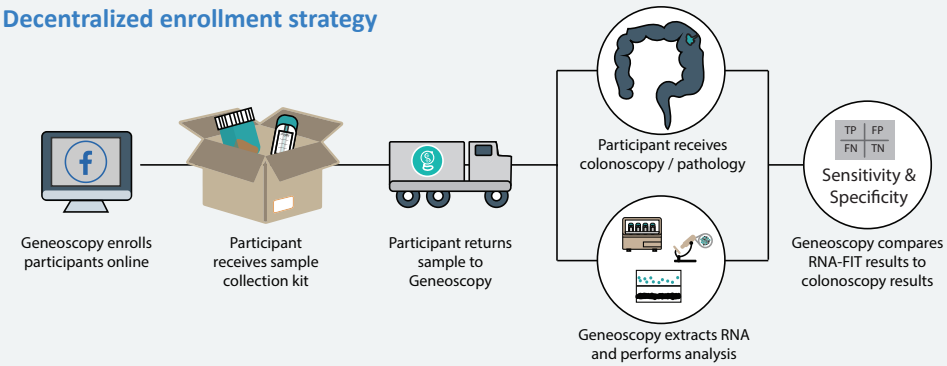
Introduction

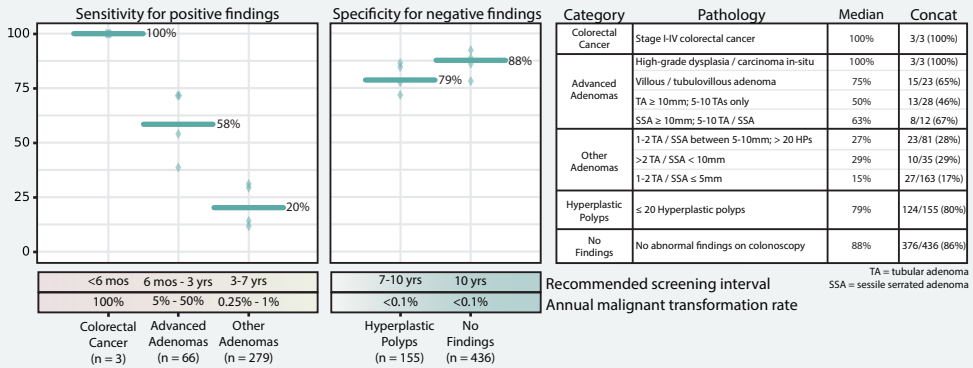
Non-invasive screening for colorectal neoplasms has focused on detection of early-stage colorectal cancer (CRC). However, meaningful reduction in CRC mortality requires cancer prevention through adenoma detection. Here we describe the performance of a noninvasive multi-target RNA-FIT assay, which consists of nine stool-derived biomarkers. This assay was shown to accurately detect both CRC and precancerous adenomas in a 1,305-patient prospective cohort.

Decentralized enrollment strategy



Participants were recruited using social media platforms and eligible participants were sent a sample collection kit. Stool samples were shipped to Geneoscopy's laboratory and analyzed with the RNA-FIT assay. Subsequently, participants received a colonoscopy. RNA-FIT results were compared to colonoscopy results to determine RNA-FIT accuracy. A 939-patient training set was used for model development and a 366-patient hold out testing set was used for model assessment.

Internal cross-validation of the training set

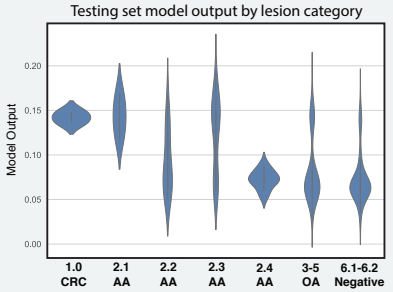


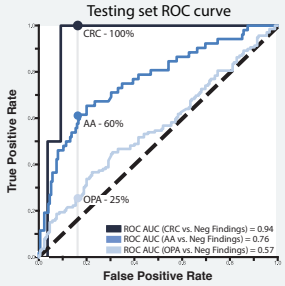
Category	Pathology	Median	Concat
Colorectal Cancer	Stage I-IV colorectal cancer	100%	3/3 (100%)
Advanced Adenomas	High-grade dysplasia / carcinoma in-situ	100%	3/3 (100%)
	Villous / tubulovillous adenoma	75%	15/23 (65%)
	TA ≥ 10mm; 5-10 TAs only	50%	13/28 (46%)
	SSA ≥ 10mm; 5-10 TA / SSA	63%	8/12 (67%)
Other Adenomas	1-2 TA / SSA between 5-10mm; > 20 HPs	27%	23/81 (28%)
	>2 TA / SSA < 10mm	29%	10/35 (29%)
	1-2 TA / SSA ≤ 5mm	15%	27/163 (17%)
Hyperplastic Polyps	≤ 20 Hyperplastic polyps	79%	124/155 (80%)
No Findings	No abnormal findings on colonoscopy	88%	376/436 (86%)

TA = tubular adenoma
SSA = sessile serrated adenoma

Five-fold internal cross validation was employed on the training set (n = 939). For each lesion category, the accuracy metric for the sub-testing set in each validation fold is reported using a green diamond and the accuracy metric for the median fold is reported with a green bar. Recommended screening intervals and malignant transformation rates for the five lesion categories are also reported. The index provides lesion categories / pathology, median accuracy (Median), and concatenated accuracy (Concat) for each lesion category in the training set.

Model performance of the hold out testing set



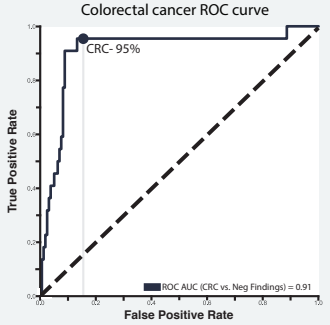


Category / Pathology	Concat
1.0: Stage I-IV colorectal cancer	2/2 (100%)
2.1: High-grade dysplasia / carcinoma in-situ	3/3 (100%)
2.2: Villous / tubulovillous adenoma	9/15 (60%)
2.3: TA ≥ 10mm; 5-10 TAs-only	15/22 (68%)
2.4: SSA ≥ 10mm; 5-10 TA / SSA	3/10 (30%)
3.0: 1-2 TA / SSA between 5-10mm; > 20 HPs	11/42 (26%)
4.0: >2 TA / SSA < 10 mm	6/27 (22%)
5.0: 1-2 TA / SSA ≤ 5mm	18/70 (26%)
6.1: ≤ 20 Hyperplastic polyps	59/74 (80%)
6.2: No abnormal findings on colonoscopy	86/101 (85%)

A final model was built using the training set (n = 939) and was employed on the hold out testing set (n = 366). The violin plot shows model output parsed by lesion category. Mean output for all advanced adenomas (mean score = 0.103), and for other adenomas (mean score = 0.079), was significantly higher than for no findings on a colonoscopy (mean score = 0.068). ROC curves show model performance for colorectal cancer (n = 2), advanced adenomas (n = 50), and other adenomas (n = 139) when compared to hyperplastic polyps and no findings on colonoscopy (n = 175). The index provides categories, pathology, and concatenated accuracy (Concat) for each lesion category in the testing set.

Incremental assessment of retrospectively collected CRC samples

To demonstrate the RNA-FIT assay performance on patients with colorectal cancer, 17 samples were collected from patients after diagnosis of cancer but prior to treatment or surgical resection. These samples, in addition to the 5 prospectively collected samples, were evaluated with the RNA-FIT assay. The test was positive for 21 of the 22 samples derived from patients with CRC (95% sensitivity; 95%CI = 77% to 100%). The ROC curve shows model performance for colorectal cancer (n = 22) when compared to patients with negative findings from the hold out testing set (n = 175).



The RNA-FIT assay can prevent colorectal cancer development through advanced adenoma detection

The RNA-FIT assay demonstrated clinically relevant detection of all advanced neoplasms, including early carcinomas, advanced adenomas, and other precancerous lesions. This test could provide a comprehensive method to prevent colorectal cancer through precancerous adenoma detection, which is the primary goal of screening. Ongoing clinical trials are underway to confirm analytical verification and clinical validation of the RNA-FIT assay.

Conflicts of interest and affiliations

EKB, YK, ARB, KRK, JF, and EMW are employees of and own equity / intellectual property in Geneoscopy. EKB and ARB are board members of Geneoscopy. No other authors are conflicted.

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