EVIDENCE-BASED GI
AN ACG PUBLICATION

Multi-Target Stool RNA Test for CRC Screening: When Should You Use It?

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This summary reviews Barnell EK, Wurtzler EM, La Rocca J, et al. Multitarget stool RNA for colorectal cancer screening. JAMA 2023;330:1760-68 .

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Keywords: colorectal cancer screening, stool test, fecal immunochemical test

STRUCTURED ABSTRACT

Question: What is the sensitivity and specificity of a multi-target stool RNA test (ColoSense; Geneoscopy, St. Louis, MO) for colorectal cancer (CRC) screening for detection of stage I, II, and III CRC and advanced adenomas in average-risk individuals aged 45 years and older?

Design: Prospective, blinded, cross-sectional observational diagnostic test study using colonoscopy as the gold standard for detection of CRC and precancerous lesions: CRC-PREVENT study.

Setting: The United States.

Patients: Asymptomatic individuals ≥ 45 years old were first recruited using social media and completed a survey to ensure eligibility for CRC screening. Key exclusion criteria included: (a) history of inflammatory bowel disease (IBD); (b) prior history of adenomas or gastrointestinal (GI) cancers; (c) medical or family history of inherited polyposis syndromes; and, (d) currently up-to-date with CRC screening (e.g., had a normal screening colonoscopy ≤9 years or negative fecal immunochemical test [FIT] within previous year). Individuals with family history of CRC in a first-degree relative were also included.

Interventions/Exposure: Stool specimens for next-generation multi-target stool RNA test were obtained prior to colonoscopy bowel preparation and mailed for processing. The multi-target stool RNA test consists of FIT and concentration of 8 RNA transcripts in stool plus self-reported smoking history (never vs prior or current use of tobacco products). A software program generated the multi-target stool RNA binary result (positive or negative) based on a predetermined threshold value.

After providing the stool specimen, patients were "navigated" using a decentralized nursing call center to have screening colonoscopy prescribed by their health care provider and performed by a local endoscopist.

Outcomes: Primary outcome was sensitivity for CRC and advanced adenomas, defined as adenomas $\geq$ 10 mm, adenoma with villous histology or high-grade dysplasia, and specificity for all other findings. Secondary outcome was sensitivity for advanced adenomas and comparison of FIT and multi-target stool RNA test for CRC and advanced precancerous lesions.

Data Analysis: Sensitivity (percentage of individuals with the disease who have a positive test) and specificity (percentage of individuals without the disease who have a negative test) with corresponding 95% confidence intervals (CIs) were calculated with standard formulas.*

Funding: Geneoscopy, manufacturer of multi-target stool RNA test, ColoSense.

Results: Between June 2021 and June 2022, 11,034 patients provided an adequate stool sample and met enrollment criteria with 85% completing an adequate colonoscopy. Among these individuals, approximately 514 were withdrawn due to inadequate records or being found to meet exclusion criteria, leaving 8,920 patients for evaluation. Demographic data for these patients included: mean age 55 years old, 59% female, 83.5% White, 6.5 % had family history of CRC in first-degree relative, and prior/current user of tobacco products was 34%. In this group, 0.4% (36 out of 8,920) had CRC stage I-III and 6.8% (606 out of 8,920) had advanced adenomas. Overall, adenoma detection rate was 40.1%.

For CRC Stage I-III, 94.4% (34 out of 36) had a positive multi-target stool RNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced adenomas, 45.9% (278 out of 606) had a positive multi-target stool RNA test (**Table 1**). FIT had 77.8% sensitivity for Stage I-III CRC and 28.9% sensitivity for advanced adenomas (**Table 1**). The multi-target stool RNA test was significantly better than FIT for both comparisons by McNemar's test. Among 5,345 patients with no adenomas on colonoscopy, specificity of multi-target stool RNA test was 86.9%; 95% CI: 86%-88% (4,647 out of 5,345 had negative test) and specificity for FIT was 95.4%; 95% CI: 95%-96% (5,100 out of 5,345 had negative test).

*Note: Based on US Food and Drug Administration (FDA) guidance provided to study investigators, a test was considered acceptable if sensitivity for CRC was 90% with the lower boundary of the 95% CI for CRC sensitivity was ≥80% and if sensitivity for advanced adenomas was at least 45% with the lower boundary of the 95% CI for advanced adenoma sensitivity was ≥40%, and if specificity for all other findings was ≥80%.

Disease	Sensitivity of Stool DNA	Sensitivity of FIT
Stage I-III CRC	94.4% (95% CI: 81-99)	77.8% (95% CI: 61-90)
Advanced adenomas	45.9% (95% CI 42-50)	28.9% (95% CI: 25-33)

Table 1. Sensitivity of next generation multi-target stool RNA test and FIT.

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test

COMMENTARY

Why Is This Important?

As discussed in prior commentaries,[1-2] about 60% of the eligible US population are up-to-date with CRC screening. This equates to more than 40 million individuals who are not up-to-date with this preventable cancer.[3] Given the desire of some patients to avoid colonoscopy with the associated bowel preparation, sedation, and time missed from work, stool-based tests for CRC screening are a viable option. Although annual FIT is inexpensive for healthcare systems, the sensitivity for stage I-III CRC is 65%-75% (i.e., approximately 25%-35% of individuals with stage I-III CRC will have a negative test). The limited sensitivity of FIT could be overcome by performing it annually, but multiple studies demonstrate that adherence to annual FIT is at best 75% and then decreases to approximately 30%-35% in subsequent years.[3-4] Therefore, stool-based tools with improved sensitivity and higher adherence would be beneficial, and multi-target stool DNA tests fit this need. Although they are more expensive than FIT, the out-of-pocket cost to eligible patients with Medicare, Medicaid, or most commercial insurers is zero since multi-target stool DNA tests are endorsed by the US Preventive Services Task Force and covered as an approved cancer screening test under the Affordable Care Act.

In the study by Barnell et al, new technology examining concentrations of 8 RNA transcriptions in stool are combined with FIT and smoking history to produce a positive or negative test.

These investigators[5] have proposed that eukaryotic RNA derived from stool may be an ideal biomarker to detect CRC and adenomas because it provides an assessment of cellular activity. This is a timely topic since the FDA approved the multitarget stool RNA test in May 2024. However, out-of-pocket cost to patients will probably be substantial unless the US Preventive Services Task Force endorses this test for CRC screening, leading to it being covered as an approved cancer screening test under the Affordable Care Act. Stay tuned.

Key Study Findings

For CRC stage I-III, 94.4% (34 out of 36) had a positive multi-target stool RNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced adenomas, 45.9% (278 out of 606) had a positive multi-target stool RNA test (**Table 1**). FIT had 77.8% sensitivity for stage I-III CRC and 28.9% sensitivity for advanced adenomas.

Caution

A substantial proportion of patients completed the stool collection but didn't complete colonoscopy during the study, which creates some uncertainty. The study results are similar to results achieved with multi-target stool DNA, but these tests were not studied head-to-head. Appropriate intervals between multi-target stool RNA tests will need to be better defined by longitudinal data.

My Practice

Again, per prior commentaries,[1-2] colonoscopy is my primary tool for CRC screening since it's also a CRC prevention tool. Nevertheless, some average-risk individuals are fearful of colonoscopy, sedation, or simply doing the bowel preparation and want a non-invasive alternative. What's the best option for these individuals? Again, the best option is the one that the patient actually completes! At my Veteran's Affairs institution, I'm limited to offering annual FITs as a stool-based screening test. Multi-target stool DNA tests clearly produce higher sensitivity than FIT for stage I-III CRC and advanced precancerous lesions,[2] are essentially free to most patients, and only have to be completed once every 3 years. Until multi-target stool RNA tests are covered by insurance, I'd stick with FIT or multi-target stool DNA tests if your patient is hesitant to get colonoscopy.

For Future Research

Innovations in RNA technology to improve specificity (i.e., minimizing frequency of false positive tests, which drives use of colonoscopy) while preserving high sensitivity for CRC and advanced adenomas will be beneficial. A comparative trial with multi-target stool DNA tests would define if one test is more accurate than the other. Until then, defer to stool-based tests that are covered with no out-of-pocket costs to the patient.

Conflicts of Interest

Dr. Schoenfeld previously served as a speaker for Exact Sciences and has discontinued that relationship.

Note: The authors of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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