EVIDENCE-BASED GI
AN ACG PUBLICATION

Multi-Target Stool DNA Test for CRC Screening: How Accurate is the New Version?

Dr Philip Schoenfeld
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI.

This summary reviews Imperiale T, Porter K, Zella J, et al. Next-generation multitarget stool DNA test for colorectal cancer screening. N Engl J Med 2024; 390: 984-93.

Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Chief. Email: EBGI@gi.org

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

STRUCTURED ABSTRACT

Question: What is the sensitivity and specificity of a new version of a multi-target stool DNA test (mt-sDNA) for colorectal cancer (CRC) screening for detection of stage I, II, and III CRC and advanced precancerous lesions in average -risk individuals aged ≥40 years old?

Design: The BLUE-C study is a prospective, observational diagnostic test study using colonoscopy as the gold standard for detection of CRC and precancerous lesions.

Setting: One-hundred eighty-six sites in the United States.

Patients: Asymptomatic individuals ≥40 years old scheduled for CRC screening colonoscopy. Key exclusion criteria included: (a) history of inflammatory bowel disease; (b) prior history of advanced adenomatous polyps or CRC; (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 6

months). Individuals with family history of CRC in first-degree relatives were also included.

Interventions/Exposure: Stool specimens for next-generation mt-sDNA test and FIT were obtained prior to colonoscopy bowel preparation and mailed for processing. The next-generation mt-sDNA test analyzes DNA abnormalities in colonic mucosal cells sloughed from the colon wall into stool. The new molecular panel encompasses additional methylated DNA markers compared to the current version of mt-sDNA test while continuing to test for fecal hemoglobin. Separate FIT was considered positive based on threshold of 100ng/ml of hemoglobin.

Outcome: Primary outcome was sensitivity for CRC and specificity for advanced neoplasia, defined as CRC plus advanced precancerous lesions, which were defined as adenomas ≥10mm, adenoma with villous histology or high grade dysplasia, carcinoma in situ, or serrated lesion ≥10mm. Secondary outcome was sensitivity for advanced precancerous lesions and comparison of sensitivity of FIT and next-generation mt-sDNA 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. For previous FDA-approved CRC screening tests, a test was considered acceptable if the lower boundary of the 95% CI for CRC sensitivity was >65% and if the lower boundary of 95% CI for specificity of advanced precancerous lesions was >85%.

Funding: Exact Sciences, manufacturer of Cologuard and next generation Cologuard/Cologuard 2.0.

Results: Between November 2019 and January 2023, 20,176 individuals had full data from colonoscopy and stool tests completed. Overall, mean age was 63 years old, 53% were female, 60% were White, 5.2% with family history of CRC in a first-degree relative, and 13.4% had positive next-generation mt-sDNA test. Among the individuals with full data, 0.5% (98/20,176) had CRC and 10.6% (2,144/20,176) had advanced precancerous lesions. Among individuals with CRC, 84% (82/98) had stage I-III CRC.

For CRC stages I-III, 92.7% (76/82) had a positive next generation mt-sDNA test. Per the study, sensitivity did not vary substantially based on disease stage or location in the colon. For advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas or adenomas with high-grade dysplasia or carcinoma in situ), 43.4% (931/2,144) had a positive next generation mt-sDNA test and

sensitivity rose to 74.6% when limited to lesions with high-grade dysplasia (85/114) (**Table 1**). Approximately 7% of participants had a false positive test, defined as positive stool DNA test but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Since FIT had only 64.6% sensitivity for stages I-III CRC and 23.3% sensitivity for advanced precancerous lesions (Table 1), the mt-sDNA test was significantly better for both comparisons. The stool DNA test was positive for 79% (23/29) of stage I-III CRC where FIT was negative, and stool DNA was positive for 34% (555/1644) of advanced precancerous lesions where FIT was negative. However, only 4.3% of participants had a false positive FIT, which was defined as positive FIT but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Disease	Sensitivity of stool DNA	Sensitivity of FIT
Stage I-III CRC	92.7% (95% CI: 85-97)	64.6% (95% CI: 53-75)
Advanced precancerous lesions	43.4% (95% 41-45)	23.3% (95% CI: 22-25)
High-grade dysplasia lesions	74.6% (95% 66-82)	47.4% (95% CI: 38-57)

Table 1. Sensitivity of next generation multi-target stool DNA test and fecal immunochemical test

COMMENTARY

Why Is This Important?

As discussed in prior commentaries,[1] only about 59% of the eligible US population is up to date with CRC screening, equating to more than 40 million unscreened individuals. Therefore, new interventions to improve screening are sorely needed.[2] 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% (i.e., approximately 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 FIT is at best 75% and then decreases to approximately 30%-35% in subsequent years.[2-4] Therefore, stool-based tools with improved sensitivity and higher adherence would be beneficial.

In the study by Imperiale et al, the next generation mt-sDNA test demonstrates superiority to FIT for sensitivity of stage I-III CRC (92.7% vs 64.6%) as well as for advanced precancerous lesions (43.4% vs 23.3%) while improving specificity to 92.7% for non-neoplastic or negative colonoscopy. Compared to the currently available mt-sDNA test,[5] the sensitivity remains the same, but the specificity is improved, leading to fewer false-positive tests requiring colonoscopy. Finally, based partly on quality control processes developed by Exact Sciences, adherence to completing mt-sDNA tests may be twice as high compared with standard FIT (85% vs 43%).[6]

Key Study Findings

For CRC Stage I-III, sensitivity was 92.7% (76/82) since 92.7% of individuals with stage I-III CRC had a positive next generation mt-sDNA test. Sensitivity was 43.4% (931/2144) for advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas or adenomas with high-grade dysplasia or carcinoma in situ. Approximately 7% of participants had a false positive test, defined as positive mt-sDNA test, but no adenomas, advanced precancerous lesions, or CRC found on colonoscopy.

Caution

The next-generation mt-sDNA test was not directly compared to the current version, limiting assessment of how the new DNA biomarker panel improves diagnostic test characteristics for stage I-III CRC and advanced precancerous lesions.

My Practice

As per prior commentaries,[1] colonoscopy is my primary tool for CRC screening since it's also a CRC prevention tool. Nevertheless, I do see average-risk individuals who 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? At my VA institution, we're limited to offering annual FITs as a stool-based screening test, and this is certainly an appropriate cancer detection tool. However, mt-sDNA tests clearly produce higher sensitivity than FIT for stage I-III CRC and advanced precancerous lesions. This limitation may be overcome if patients get FIT annually, but adherence to annual FIT may be less than 40% in repeated years and adherence to mt-sDNA is considerably better.

Of course, mt-sDNA tests are significantly more expensive than FIT as a CRC screening test, but this cost is borne by insurers instead of individual patients, since mt-sDNA tests are covered under the Affordable Care Act as an approved CRC screening test. Therefore, the out-of-pocket cost for a vast majority of CRC screen-eligible individuals will be zero.

For Future Research

Future efforts to improve specificity (i.e., minimizing frequency of false positive tests, which drives use of colonos-

copy) while preserving high sensitivity for CRC will be beneficial. Since mt-sDNA tests are recommended for use every 3 years, additional longitudinal data will also be helpful.

Conflict 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.

@DrJohnKisiel
John Kisiel

@limberg_paul
Paul Limberg

REFERENCES

1. Schoenfeld P. Cell-free DNA blood test for CRC screening: a promising development won't "eclipse" current tools. Evidence-Based GI. Published April 24, 2024. Accessed May 10, 2024. https://gi.org/journals-publications/schoenfeld_April2024/
2. Carethers J. Improving noninvasive colorectal cancer screening. N Engl J Med 2024; 390: 1045-46.
3. Fisher DA, Princic N, Miller-Wilson LA, et al. Adherence to FIT screening among adulats at average risk for CRC. Int J Colorectal Dis 2022; 37: 719-21.
4. van der Vlught M, Grobbee EJ, Bossuyt P, et al. Adherence to CRC screening: four rounds of faecal immunochemical test-based screening. Br J Cancer 2017; 116: 44-49.
5. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 370: 1287-97.
6. Finney Rutten LK, Jacobson DJ, Jenkins GD, et al. CRC screening completion: an examination of differences in screening modality. Prev Med Rep 2020; 20: 101202.