Diagnostic Tests

What Physicians Need to Know

m*SEPT9* Blood Test (Epi proColon) for Colorectal Cancer Screening

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Epi proColon is a blood test used for the detection of the methylated septin 9 (m*SEPT9*) gene. It is approved by the U.S. Food and Drug Administration (FDA) for colorectal cancer screening in people at average risk who have declined first-line screening tests.

Test	Indication	Population, age range, and frequency	Cost*
Methylated *SEPT9* (Epi proColon)	Screening for colorectal cancer in people who decline first-line tests	Average-risk adults 50 years and older Optimal screening interval is uncertain	$192

*—Payment rate according to the Centers for Medicare and Medicaid Services' Clinical Laboratory Fee Schedule.[8]

Accuracy

In a prospective study of 7,941 asymptomatic, average-risk adults 50 years and older who underwent screening colonoscopy at 32 clinical sites in the United States and Germany, the m*SEPT9* test was 48% sensitive for colorectal cancer and 11% sensitive for advanced adenomas.[1] Specificity was higher: 92% of people without colorectal cancer had a negative test result. Two meta-analyses of case-control studies of m*SEPT9* tests (including Epi proColon [most common], Quest's ColoVantage, and others) using optical colonoscopy as the reference standard produced summary estimates of sensitivity and specificity for colorectal cancer of 62% to 71% and 91% to 92%, respectively.[2,3] However, this approach of comparing the test in patients with known disease and in healthy controls will overestimate accuracy.

One prospective multicenter study compared the m*SEPT9* test with the fecal immunochemical test (FIT) in 102 adults with colorectal cancer identified on optical colonoscopy prior to surgery and in 199 average-risk adults scheduled for screening colonoscopy.[4] The sensitivity of the m*SEPT9* test for detecting colorectal cancer was 73% (95% CI, 64% to 81%), which was noninferior to the FIT sensitivity of 68% (95% CI, 58% to 77%). However, the specificity of m*SEPT9* was lower than that of FIT (82% compared with 97%), leading to a lower area under the receiver operator characteristic curve for m*SEPT9* (0.82) than for FIT (0.86).

In the prospective study that resulted in FDA approval for the FIT plus multitargeted stool DNA (FIT-DNA) test (Cologuard), the sensitivity of FIT-DNA for colorectal cancer and advanced adenomas was 92% and 42%, respectively.[5] Including nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy, FIT-DNA was 87% specific.

Benefit

The m*SEPT9* test requires no preparation and is potentially more convenient for patients than fecal tests. In a randomized trial of 413 average-risk adults 50 to 75 years of age who were due for colorectal cancer screening in two integrated U.S. health systems, 99.5% of participants in the m*SEPT9* arm completed the test within six weeks, compared with 88.1% of participants in the FIT arm.[6]

To benefit from m*SEPT9*, patients with positive test results must undergo diagnostic colonoscopy. No studies have been conducted to determine whether screening with m*SEPT9* reduces colorectal cancer or all-cause mortality. In comparison, flexible sigmoidoscopy and fecal occult blood testing have reduced mortality in randomized trials.

Harms

Like FIT and FIT-DNA, the m*SEPT9* test is noninvasive and has fewer direct harms than flexible sigmoidoscopy, optical colonoscopy, or computed tomographic colonography. However, its low sensitivity for colorectal cancer and advanced adenomas could result in delays in diagnosis of colorectal cancer because of false reassurance provided by a negative test result. Its lower specificity compared with FIT and FIT-DNA suggests that it could lead to more false positives and unnecessary colonoscopies.

Although the FDA approved the m*SEPT9* test only for persons who have declined recommended screening tests, it

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is not known if patient uptake will increase the percentage of eligible adults completing any colorectal cancer screening test or if it will end up substituting for others, potentially reducing the number who use first-line screening tests.[7]

Cost

The payment rate for the m*SEPT9* test is $192 in the Centers for Medicare and Medicaid Services' 2019 Clinical Laboratory Fee Schedule.[8] Some private insurers consider m*SEPT9* to be investigational and may not reimburse for the test.

Bottom Line

The m*SEPT9* test is a noninvasive option for colorectal cancer screening in patients who have declined first-line screening tests. Limited data suggest that its test characteristics are comparable with FIT, and it may be more likely to be completed by this patient population. However, the m*SEPT9* test is not recommended in the U.S. Preventive Services Task Force or the U.S. Multi-Society Task Force guidelines.[9,10] Most importantly, there is no research showing a morbidity or mortality benefit.

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References

1. Church TR, Wandell M, Lofton-Day C, et al.; PRESEPT Clinical Study Steering Committee, Investigators and Study Team. Prospective evaluation of methylated *SEPT9* in plasma for detection of asymptomatic colorectal cancer. *Gut*. 2014;63(2):317-325.
2. Li B, Gan A, Chen X, et al. Diagnostic performance of DNA hypermethylation markers in peripheral blood for the detection of colorectal cancer: a meta-analysis and systematic review. *PLoS One*. 2016;11(5):e0155095.
3. Nian J, Sun X, Ming S, et al. Diagnostic accuracy of methylated *SEPT9* for blood-based colorectal cancer detection: a systematic review and meta-analysis. *Clin Transl Gastroenterol*. 2017;8(1):e216.
4. Johnson DA, Barclay RL, Mergener K, et al. Plasma septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. *PLoS One*. 2014;9(6):e98238.
5. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal cancer screening. *N Engl J Med*. 2014;370:1287-1297.
6. Liles EG, Coronado GD, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: a randomized trial. *Cancer Treat Res Comm*. 2017;10:27-31.
7. Parikh RB, Prasad V. Blood-based screening for colon cancer: a disruptive innovation or simply a disruption? *JAMA*. 2016;315(23):2519-2520.
8. Centers for Medicare and Medicaid Services. Clinical laboratory fee schedule. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html. Accessed May 6, 2019.
9. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement [published corrections appear in *JAMA*. 2016;316(5):545 and *JAMA*. 2017;317(21):2239]. *JAMA*. 2016;315(23):2564-2575.
10. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterol*. 2017;153(1):307-323. ■