# ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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## Beyond the Scope: The Promise and Limitations of Blood-Based Colorectal Cancer Screening

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**G&H** Could you describe blood-based colorectal cancer screening in the United States, test availability, and accuracies?

**JD** Currently, there is only one blood-based colorectal cancer (CRC) screening test available in the United States. Shield (Guardant Health) received approval from the US Food and Drug Administration (FDA) and a coverage decision from the Centers for Medicare and Medicaid Services (CMS) for CRC screening in asymptomatic average-risk adults aged 45 years and older. The approval was based on the results of the ECLIPSE study, which found that the overall sensitivity for cancer was 83.1% (95% CI, 72.2%-90.3%), with a specificity of 89.6% (95% CI, 88.8%-90.3%). Sensitivity for stage I, II, or III CRC was 87.5% (95% CI, 75.3%-94.1%) but was only 65% for stage I cancer (95% CI, 41%-83%) and 13.2% for advanced precancerous lesions (95% CI, 11.3%-15.3%). Results from the PREEMPT CRC study, which evaluated the Freenome blood test, have been reported in abstract form, but the test is not currently FDA approved. These preliminary results demonstrate a sensitivity for CRC of 79.2% (95% CI, 68.4%-86.9%) and a sensitivity for advanced adenomas of 12.5% (95% CI, 11.3%-13.8%) at a specificity of 91.5% (91.2%-91.9%). It would not be appropriate to compare the 2 tests based on these data, as the populations were different and the proportion of early cancers in each study can have a significant impact on these results.

**G&H** What is the mechanism of action of the blood-based CRC screening tests?

**JD** As CRC is, by definition, invasive, tumor DNA may be freely circulating in the bloodstream. Blood-based CRC screening tests capitalize on this by using polymerase chain reaction assays and DNA sequencing to assess cell-free DNA fragment lengths, sequences, and methylation patterns to identify changes associated with CRC or advanced precancerous lesions. For example, the Shield test incorporates information about methylation status, aberrant fragmentation patterns, and somatic genetic variants in the *APC* and *KRAS* genes into a logistic regression model to calculate a score to determine normal vs abnormal results.

**G&H** Could you summarize the clinical studies evaluating blood-based CRC screening tests to date?

**JD** Unfortunately, we do not have any prospective, or even retrospective, studies that demonstrate the effectiveness of screening with these blood tests to reduce cancer incidence or mortality, unlike with colonoscopy and the fecal immunochemical test (FIT). Although the studies evaluating the sensitivity and specificity of the Shield test and Freenome test compared with screening colonoscopy are an important first step, there are many unanswered questions.

One important question is whether the availability

of a new CRC screening test option will impact participation in screening. Approximately 42% of Americans aged 45 to 75 years are not up-to-date with screening. Therefore, there is a significant need to boost screening participation to reduce the burden of CRC, which is currently the second leading cause of cancer death in the United States. Coronado and colleagues recently compared screening participation among 2004 patients randomized to usual care vs offering blood draw for CRC screening. All patients had previously been offered but did not complete FIT screening in the prior 3 to 9 months and had an upcoming clinic appointment. One group received an introductory study letter followed by up to 3 phone calls inviting them to be screened with the Shield blood test. Over the ensuing 3 months, 17.5% more patients were screened in the blood-test group than the usual care group (30.5% vs 13.0%, respectively; odds ratio, 2.94). It is not clear how much of this increased screening resulted from availability of the blood test vs the telephone outreach for screening. Importantly, the increase in overall screening was comprised of a somewhat lower proportion completing colonoscopy or FIT in the blood-test group than in the usual care group. Thus, there was some substitution of the new blood test for these traditional and proven tests.

Of course, neither blood-based nor stool-based screening will be effective if the patient opts not to have a colonoscopy to evaluate abnormal results.

**G&H** How does blood-based CRC screening compare with stool-based tests and colonoscopy?

**JD** Although there are no published comparative effectiveness research studies, decision-analytic models have examined this question. In brief, models demonstrate that, assuming equal adherence, both stool-based screening and colonoscopy are superior to blood-based screening in terms of reducing CRC incidence and mortality. The major reason for this finding is that blood-based screening has essentially no ability to detect advanced precancerous polyps beyond chance discovery (13%), whereas FIT has approximately 24% sensitivity for these polyps. This makes biologic sense because advanced precancerous polyps are not invasive and would not be expected to shed their DNA into the bloodstream; however, these polyps do shed DNA and/or blood into the lumen of the colon. Also, FIT is recommended annually, and the blood-based test is recommended by the manufacturer (and covered by CMS) only every 3 years. Colonoscopy has much higher sensitivity for these lesions (approximately 90%). Thus, finding and removing these lesions during colonoscopy prevents future CRC incidence and, therefore, cancer deaths.

On the other hand, the models also show that blood-based screening could approximate the effectiveness of stool-based screening or colonoscopy if screening participation is higher with the blood-based test, despite lower sensitivity. For example, if we assume colonoscopy is 99% sensitive for cancer, but only 60% of individuals agree to undergo screening colonoscopy, the effective sensitivity is 59%. Likewise, if a blood test has 83% sensitivity and 80% agree to be screened, the effective sensitivity is 66%. However, it is not yet known how the availability of these tests will impact screening participation.

One major concern with the blood-based tests is that their simplicity and convenience may result in patients choosing this test over colonoscopy or stool-based screening and not following up when results are abnormal. Most of the benefits of CRC screening are attributable not to the early detection of cancer, but to the detection and removal of precancerous polyps. Given the lack of sensitivity of current blood tests for advanced precancerous lesions, substitution for colonoscopy or stool-based tests would be expected paradoxically to lead to worse CRC outcomes for the population undergoing screening. Therefore, blood-based screening tests would only be helpful if they lead to the addition of new individuals participating in CRC screening, without significantly diverting individuals away from more effective screening tests.

Of course, neither blood-based nor stool-based screening will be effective if the patient opts not to have a colonoscopy to evaluate abnormal results. This is a critically important point because patients with abnormal results from screening who do not complete colonoscopy have been demonstrated to have significantly increased risk of CRC death. Therefore, all patients with abnormal results need to be informed about the importance of timely colonoscopy to realize the benefits of screening.

**G&H** What has been the response from the major US gastroenterology societies on the use of blood-based CRC screening?

**JD** As I mentioned, there is a significant need to improve participation in CRC screening to reduce morbidity and

mortality. Although blood-based testing has been sought as a means to boost screening uptake, there is concern that some may incorrectly view blood-based screening as a replacement for colonoscopy when, in fact, currently available blood tests would not be effective at preventing CRC. The American Society for Gastrointestinal Endoscopy (ASGE) recommends that blood-based tests should only be offered to patients who have declined both screening colonoscopy and stool-based tests because the blood tests are unable to detect precancerous lesions. Patients should be informed of the limitations of blood-based screening tests.

**G&H** What thresholds for sensitivity and specificity need to be reached before blood-based testing can be considered as a sensible alternative to colonoscopy?

**JD** This is a complicated question. The CMS specified that it would cover a test that met certain specifications, including FDA approval, 74% sensitivity for cancer, and 90% specificity. The FDA-approved Shield test has met these specifications and, thus, has received a positive coverage determination from the CMS. However, given the limitations of blood-based tests with respect to the detection of precancerous polyps and the results of the models I mentioned, it would be better for patients to be screened with colonoscopy or stool-based tests. According to models, blood tests would need to demonstrate sensitivity for advanced precancerous lesions over 70% to compete with colonoscopy with respect to cost-effectiveness.

**G&H** Should gastroenterologists expect their colonoscopy volumes to change significantly over the next 5 to 7 years as a result of these tests?

**JD** This is hard to predict. Blood-based CRC screening tests are not currently covered by many insurers, as they are not recommended by any major professional organizations, including the US Preventive Services Task Force. However, that may change in the coming years. It is certainly conceivable that fewer patients will choose to have a screening colonoscopy in favor of the blood test. On the other hand, this would result in referrals for diagnostic colonoscopy for the 13% or so with abnormal blood-test results. Given that 42% of Americans are not up-to-date with screening, overall demand for colonoscopy could be increased if enough individuals come off the sidelines and agree to be screened. There is no doubt that a blood test is more convenient than a colonoscopy. Nonetheless, patients who prioritize cancer prevention and test accuracy over convenience would be more likely to choose colonoscopy.

Overall, the development of blood-based tests for CRC screening is a tremendous scientific achievement. My hope is that patients and providers do not incorrectly assume that blood-based tests are as effective as colonoscopy or other proven screening tests. Perhaps future advances will improve the ability of the blood-based tests to detect advanced precancerous lesions. Until that time, I would follow the ASGE guidance and reserve blood-based CRC screening for individuals who refuse colonoscopy or stool-based tests, and who understand that timely colonoscopy is needed if the results are abnormal.

***Disclosures***

*Dr Dominitz has received grant funding from the Department of Veterans Affairs for studies comparing the effectiveness of screening colonoscopy with annual FIT screening for reducing mortality from CRC. He is currently president-elect of the ASGE.*

***Disclaimer***

*The views expressed herein do not represent the US Department of Veterans Affairs or the US Government.*

## Suggested Reading


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