On April 13, 2016, the US Food and Drug Administration (FDA) approved the first blood-based screening test for colon cancer. The assay (Epi proColon) relies on qualitative detection of the methylated septin 9 gene (SEPT9) and has been considered an innovation in screening. Despite multiple accepted options for colorectal cancer screening—including stool-based tests, such as the fecal occult blood test (FOBT) and lower endoscopy—handling, storing, and returning stool tests or prepping and undergoing an invasive procedure have limited adherence. Approximately one-fourth of eligible individuals aged 50 to 75 years have never been screened for colon cancer, and half are inadequately screened. Blood-based cancer screening has the potential to address this gap. Yet physicians must question how this newly approved assay might be incorporated in routine clinical practice, and, most important, whether use of the test will reduce colorectal cancer mortality.

The new blood-based screening test was approved on the basis of clinical data regarding the sensitivity and specificity of the test for detecting colon cancer. Although case-control studies reported an estimated sensitivity and specificity for cancer detection approaching 90%, in a clinical trial the assay’s sensitivity and specificity (68% and 79%, respectively) did not meet 1 of 2 prespecified goals (65% and 85%). A subsequent clinical trial found that, compared with fecal immunohistochemistry testing (FIT), SEPT9 testing significantly improved sensitivity (68% vs 73%) but markedly decreased specificity (97% vs 81%). The area under the receiver operator characteristic curve was greater for FIT than for SEPT9 testing (0.86 vs 0.82), suggesting worse overall test performance for the blood test. Poorer performance would increase false-positive results, with all the attendant anxiety, downstream procedures, and cost.

Important, no evidence has shown that this new assay improves disease-specific or overall mortality compared against no screening or against accepted screening methods. Sigmoidoscopy and FOBT have both demonstrated these benefits in randomized trials, while colonoscopy and FIT have not. Yet practically, colonoscopy includes sigmoidoscopy, and the rationale for FIT is more closely analogous to FOBT. Thus, in both cases, extrapolation may be more reasonable than blood-based screening, an entirely novel method.

The advantage of blood testing is the opportunity to expand the number of individuals who undergo colon cancer screening. Even among existing noninvasive tests for colon cancer, adherence is low: for annual FOBT, on average only half of participants return stool cards appropriately. Evidence suggests that some patients who are reluctant to undergo screening would be receptive to a blood test. In one survey, 97% (106/109) who refused colonoscopy accepted a noninvasive screening test, and 83% (90/109) of those preferred a blood test.

Nevertheless, 4 concerns may limit the potential benefits of the blood-based screening test and thereby limit its clinical use. First, the adequacy of the end point for approval should be questioned. In cancer screening, proof a test can detect cancer is not the same as proof that the test can reduce disease-specific mortality. For instance, ovarian cancer screening with transvaginal ultrasound and a CA-125 measurement clearly increases cancer detection; however, there is no good evidence that acting on these findings improves disease-specific mortality, with at least 2 randomized trials failing to find such a benefit in the primary analysis. In contrast with imaging-based screening, the blood-based screening test for colon cancer was accepted without demonstrating an improvement in survival for colorectal cancer.

Why does disease-specific mortality matter? Not all colon cancer is biologically similar and amenable to mortality reduction through early detection. For instance, there is persistent debate as to whether colonoscopy improves disease-specific mortality beyond the benefits from sigmoidoscopy, even though only colonoscopy is able to screen the right-sided colon. Multiple observational studies suggest that the benefit of colonoscopy is limited to a reduction in death from left-sided but not right-sided colon cancer. One putative biological explanation for this is that right-sided cancers have more aggressive early genetic events and are more difficult to detect and resect with endoscopy.

For this reason it is unclear if the cancers detected by blood-based screening are ones for which identification and removal will yield real mortality gains. Secondary data suggest that this blood-based screening is more sensitive at detecting advanced-stage cancer
detect advanced adenomas,7 which are considered precancerous because the assay appears to only have a 10% sensitivity to as gains in colon cancer mortality are related to removal of pre-opportunity to further investigations, likely including endoscopy. The prospect of such a lengthy discussion becoming routine seems unlikely. Moreover, SEPT9 blood testing raises concerns that like prostate-specific antigen testing, it may be ordered without specific patient consent, as part of routine blood work.

Questions about comparative efficacy may explain the test’s approval history. In March 2014, the FDA’s Molecular and Clinical Genetics Panel evaluating Epi proColon voted 9-0 (1 abstention) in favor of adequate evidence of safety, but voted 4-5 against adequate evidence of efficacy (1 abstention).9 The panel recommended further testing showing benefit. The manufacturer of this test proposed including a warning to address the low sensitivity, specifying that a negative result “does not guarantee absence of cancer” and that patients should still pursue other screening methods.2 This warning along with further prospective evidence that SEPT9 blood testing improved detection of colon cancer led to the FDA’s eventual approval in 2016.

As more molecular ways to detect cancer are discovered, the medical community must consider the standard for integrating these markers as screening tests. For imaging, the bar has been randomized trials demonstrating improved disease-specific mortality, though some in the research community favor even higher standards.6 The standard for blood screening tests should be no lower. While there may be value to enhanced population-wide cancer screening, physicians and policy makers must be objective about the comparative efficacy of novel blood-based screening tests. As the experience with SEPT9 blood testing shows, blood-based testing must balance convenience against the risk of inadequate screening, underdiagnosis, and reluctance to pursue further testing. Allowing blood-based screening tests for colon cancer to have a lower standard than that of other screening tests risks prioritizing convenience over patient safety and health care value.

ARTICLE INFORMATION
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REFERENCES