There are several timely, important, and novel aspects to colorectal cancer (CRC) screening that are highlighted in the study by Aziz et al.\textsuperscript{1} Despite good evidence to illustrate the reduction in CRC mortality associated with screening,\textsuperscript{2} adherence to screening still falls short of the goal of 80% across all populations.\textsuperscript{3} For this reason, it makes sense to develop more acceptable tests that avoid the colon cleansing or sedation associated with colonoscopy, obtaining the specimen for fecal immunochemical testing (FIT), or other barriers to completion of CRC screening. Moreover, prior studies have demonstrated differential preferences and uptake of CRC screening tests that contribute to the racial and ethnic disparities in health care outcomes. Compared with White people, people of other races and ethnicities (eg, Asian, Black, and Hispanic or Latinx people) adhere more often to noncolonoscopy tests.\textsuperscript{4} Studies have demonstrated that blood tests for cancer screening may be more acceptable than other screening tests, such as FIT that detects human blood in stool or colonoscopy that requires a cathartic to cleanse the bowel to allow direct visualization of the colon lining.\textsuperscript{5} Thus, this study by Aziz and colleagues\textsuperscript{1} examines an important step in the dissemination of new technologies to improve cancer screening and possibly reduce racial and ethnic disparities in CRC outcomes.

Aziz and colleagues\textsuperscript{1} report that the strategy that yielded the greatest number of life-years (ie, the most effective strategy) was offering blood-based biomarker screening to individuals who refused to undergo colonoscopy; however, this was expensive ($377 538 per life-year gained) and greatly exceeded the accepted threshold of $100 000 per life-year gained. Colonoscopy screening was the most cost-effective strategy ($28 071 per life-year gained), meaning that this yielded the greatest benefit within the limits of willingness to pay.\textsuperscript{1} Screening with blood-based biomarkers alone was dominated, meaning that it was both less effective and more costly than colonoscopy screening. Among individuals without elevated risk for development of CRC and who declined to be screened by FIT or colonoscopy, testing with blood-based biomarkers would have to cost two-thirds less than currently priced to become a cost-effective option to reduce cancer mortality.\textsuperscript{1}

This study by Aziz and colleagues\textsuperscript{1} illustrates the potential downside of screening with blood tests: it is hoped that these increase screening among people who are not up to date with screening; however, they may also entice people who are currently screened with colonoscopy to undergo a less invasive test. In this case, we need to assess the trade-offs in effectiveness, harms, and costs among the competing screening strategies. For example, compared with other available strategies, such as annual FIT or colonoscopy every 10 years, Aziz et al\textsuperscript{1} found that blood-based biomarkers for CRC screening is not cost-effective. In some cases, this is defined as exceeding the $100 000 per quality-adjusted life-year gained limit, but in other scenarios it means that blood-based screening is both less effective and more expensive than currently recommended strategies.

What would make blood-based CRC screening more effective and cost-effective? Interestingly, it is more likely to depend on the ability to detect precancerous polyps than on the detection of CRC itself. Despite the widely held belief that FIT is a cancer detection strategy compared with colonoscopy, which is a cancer prevention strategy, FIT screening achieves much of its effectiveness from the detection of advanced neoplasia and subsequent prevention of CRC through colonoscopy and polypectomy.\textsuperscript{6} The specificity of a screening strategy reflects the false-positive rate, or, in the case of CRC screening, the proportion of people in whom a positive test result does not lead to a
finding of CRC or precancerous polyp. The Centers for Medicare & Medicaid Services has provided a determination of coverage that includes a specificity of 90%, which equates to a false-positive rate of 1 − specificity or 10%. This means that if a test is able to detect more than 10% of CRC or advanced polyps, this is not due to chance alone. FIT sensitivity for detection of advanced polyps is approximately 20%, while stool multtarget tests for blood and DNA or RNA detect 40% to 45% of advanced polyps. This is compared with blood-based tests that have been reported to detect 12% to 16% of advanced polyps, which is close to probability of a false-positive test. Because of their high cost, blood-based CRC screening will not be cost-effective unless they detect a greater proportion of advanced polyps than FIT.

An important concept that is not emphasized enough in clinical practice is the necessity of the follow-up colonoscopy in the case of a positive noncolonoscopy CRC screening test result. The mere performance of a FIT or stool DNA test does not confer protection against CRC: it is the follow-up colonoscopy after a positive screening test to detect curable CRC or remove advanced polyps (high-grade dysplasia, villous histology, large [>1 cm] adenomas, or multiplicity of adenomas) that reduces CRC mortality. Unfortunately, only 40% to 80% of people with positive noncolonoscopy screening test results follow-up with the requisite colonoscopy. Clinicians need to emphasize the necessity of the follow-up colonoscopy when discussing CRC screening options and adherence. Little information is known about the difference in rates of follow-up colonoscopy after positive stool-based vs blood-based CRC screening results.

Additional limitations of blood-based biomarker tests include potential differential effectiveness based on age of the individual undergoing screening. There is a cohort effect of younger adults experiencing an increasing risk of CRC, and it is not known how blood-based tests will perform in people younger than 50 years. Relatedly, there is an alternative mechanism for CRC development outside of the adenoma-carcinoma pathway that involves BRAF and CIMP polymorphisms that lead to sessile serrated polyps. These polyps are more common in the proximal colon, more difficult to detect due to their flat or nonprotruding profile, and more likely to be incompletely removed even after detection. It is not clear how well blood-based biomarker tests will be able to detect sessile serrated polyps. Both limitations may make the effectiveness and cost-effectiveness of blood-based CRC screening less effective than modeled in this study by Aziz et al.

Finally, in our attempts to increase access to screening, we may inadvertently increase the barrier to screening in certain populations, especially individuals for whom the cost of screening is greater with blood-based tests due to the retail price (for those without insurance) or copayments (for those with high-deductible insurance). Access to blood-based tests may be limited to individuals covered by insurance plans with low out-of-pocket costs, since these tests will likely be commercially priced at $500 or more. Similarly, access to follow-up colonoscopy may be restricted to individuals with insurance. Since Black people and Latinx people have been shown to have lower access to insurance, it is possible that racial and ethnic disparities in CRC outcomes may actually increase with large-scale introduction of blood-based CRC screening tests because this may proportionally increase uptake of screening among insured people.
REFERENCES


