ASGE POSITION STATEMENT

ASGE Position on Blood-Based Colorectal Cancer Screening

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States.[1]

Screening for early detection of CRC and prevention (through removal of precancerous polyps) is the best and most effective way to reduce the incidence and mortality of CRC.[2] There are multiple screening modalities available, including colonoscopy, fecal immunochemical testing (FIT), multi-target stool DNA tests, and blood-based tests.[3]

Among these, colonoscopy remains the gold standard due to its dual role in detection and prevention. Non-invasive stool-based methods provide alternative options for individuals hesitant about colonoscopy. Meanwhile, blood-based screening, which has recently been FDA approved, expands non-invasive options but bring certain limitations in terms of sensitivity and specificity, particularly with respect to advanced precancerous lesions (APL).

While the American Society for Gastrointestinal Endoscopy (ASGE) recognizes the potential for the blood-based test to improve screening participation, particularly among those who are unwilling to undergo other screening modalities, ASGE does not recommend the blood test as a first line screening tool. ASGE has determined that blood-based tests are inferior to established screening options (i.e., colonoscopy and stool-based tests), especially concerning APL detection.

ASGE's Position on Blood-Based Test is Based on Scientific Evidence

Despite the increased availability and public interest in blood-based CRC screening, the scientific evidence does not support its use as a first line screening tool.

A clinical study on the Guardant Shield blood-based test demonstrated that it detects CRC with an overall sensitivity of 83%, sensitivity for stage I CRC of 55%, and sensitivity for detecting APLs of just 13.2% with an overall specificity of 90%.[4] However, colonoscopy offers the highest sensitivity (96%) for all stages of CRC and 92% for APLs. Moreover, as noted above, colonoscopy offers the advantage of allowing for polypectomy at the time of screening, thereby reducing the risk of future CRC.[2]

FIT and multi-target stool DNA tests are non-invasive CRC screening alternatives that also offer higher sensitivity for CRC and advanced adenomas than blood-based tests. For example, a multi-target stool DNA test, which is performed every three years, has an overall sensitivity of 92.3% sensitivity for CRC and 42.4% for advanced adenomas with one time

testing.[2] While the FIT, which is performed on annual basis, has a sensitivity for CRC of 73.8%, sensitivity for APL of approximately 24%, and nearly 95% specificity with one time testing.[2, 3]

There are currently no prospective studies evaluating the clinical effectiveness of blood-based tests. Therefore, the best available comparative effectiveness studies come from computer simulation models comparing various screening strategies.[5] These models demonstrate that substitution of screening by colonoscopy or stool-based tests with blood-based tests would result in increased CRC incidence and mortality. This finding is primarily driven by the low sensitivity of blood-based tests for APLs.[5] However, blood-based tests are anticipated to be more effective than no screening. Therefore, if individuals who decline to be screened with colonoscopy or stool-based tests are willing to undergo blood-based screening (and complete follow-up colonoscopy when the blood test is abnormal), then their overall CRC outcomes would improve.

Based on this data, ASGE recommends that blood-based tests should only be recommended for patients who are otherwise unwilling to get screened for CRC with colonoscopy or stool-based tests.

In order for the patient to make informed decisions about the appropriate screening modality, ASGE firmly believes that it is imperative for patients to receive credible information about the limitations of blood-based tests to detect early-stage CRC and polyps.[6]

Blood-Based CRC Tests Are Not US Preventive Services Task Force Recommended

While some blood-based CRC screening tests are FDA approved and are reimbursable by Medicare[7] [8], none are currently recommended by the U.S. Preventive Services Task Force (USPSTF) CRC screening guidelines. Indeed, the most recent USPSTF recommendation (2021) outlines accepted screening modalities, including colonoscopy, FIT, multi-target stool DNA testing, and flexible sigmoidoscopy.[9] Yet, blood-based tests were not included in the 2021 USPSTF CRC screening recommendations due to insufficient evidence of their effectiveness, particularly when it comes to detecting advanced adenomas. Subsequently, this exclusion affects insurance coverage and reinforces the importance of prioritizing proven screening methods in clinical practice.

The Role of Primary Care and Need for Credible Patient Communication

Primary care providers play a pivotal role in facilitating CRC screening, as they are frequently the first point of contact for individuals considering their screening options.

ASGE is concerned about the blood-based CRC test marketing campaigns that might influence primary care professionals' recommendations. ASGE believes that it is essential for gastroenterologists to discuss the evidence with primary care providers so that they can

provide their patients with evidence-based information on the sensitivity and specificity of various CRC screening tests,[10] especially as it relates to the limits of current blood-based tests to detect advanced adenomas and early-stage cancers.

Additionally, patients should be given clear and concise information about the CRC screening options so they can make informed decisions. Messaging that suggests blood-based CRC tests are comparable to the other, more reliable CRC screening options, misleads patients and may result in worse outcomes.

Finally, ASGE believes that it is important for primary care professionals to inform patients who are considering blood-based or other non-invasive CRC screening options that they will need a follow-up colonoscopy if they have an abnormal test result (which is expected in approximately 5%, 11% and 13% of patients undergoing FIT, blood-based testing, or multi-target stool DNA, respectively for each round of screening). Therefore, a significant proportion of individuals electing non-invasive tests are expected to have an abnormal result over the course of repeated rounds of screening.

Adherence and Follow-Up Concerns

Similar to stool-based CRC tests, every patient who has a positive or abnormal blood-based CRC test result will require a follow-up colonoscopy to determine why the initial screening test was abnormal. Unfortunately, adherence to follow-up colonoscopy after a positive non-invasive test is consistently suboptimal.

Studies have shown that only 56% of patients with a positive stool-based test complete the recommended colonoscopy within one year.[11] This will likely be the case for patients who have abnormal blood-based tests as well, which will undermine the efficacy of the entire CRC screening process.

Subsequently, ASGE believes that there is a tremendous need for more effective systems and processes to ensure that patients who have an abnormal blood-based or other non-invasive CRC screening test have a follow-up colonoscopy. Without follow-up colonoscopy, the benefits of screening are lost.

ASGE recommends that a follow-up colonoscopy should be performed within 90 days of an abnormal non-invasive CRC screening test result to ensure there is a timely diagnosis and to optimize clinical outcomes.[6] Colonoscopies performed more than seven months after an abnormal FIT are associated with more advanced stage CRC diagnoses and reduced survival.[11-14]

Effectiveness, Cost-Effectiveness and Accessibility

A recent cost-effectiveness study found that screening with either colonoscopy or FIT is more effective and less costly than no screening.[15] While blood-based screening is

expected to reduce CRC mortality compared to no screening, alternative screening tests are less costly and more effective. Therefore, if individuals who are willing to undergo colonoscopy or stool-based screening shift to blood-based screening, CRC deaths would increase. To overcome these excess deaths, 2 more individuals who otherwise would not be screened would have to complete blood-based screening for every 3 individuals who switch from colonoscopy or stool-based tests to blood-based screening. Thus, blood-based screening could result in net harms or benefits depending on the balance of shifting screening from more effective tests like colonoscopy versus increasing screening participation.

It is imperative that screening tests be accessible to all, regardless of insurance status. By reducing financial and logistical barriers to screening, healthcare systems can bolster access and support the overall success of CRC screening programs.

Conclusions

One of ASGE's primary missions is to promote high-quality, evidence-based CRC screening. Therefore, ASGE believes:

- Colonoscopy is the most effective test to detect and prevent CRC.[17]

- Stool-based tests are effective, lower-cost alternatives for patients seeking non-invasive CRC screening options.

- While they may be convenient and increase CRC screening rates, blood-based tests should be reserved for individuals who are not otherwise willing to undergo established screening tests.

- Insurers and policymakers could help create systems that streamline access to a follow-up colonoscopy while minimizing delays.

- Advances in CRC screening technology must be accompanied by efforts to ensure equitable access and affordability for all patient populations. This includes addressing disparities in healthcare access, particularly for underserved communities, to maximize the potential benefits of innovations in CRC screening.

ASGE will continue to monitor, evaluate, and weigh in on new CRC screening options and technologies. ASGE will assess ongoing research and update its position as more data becomes available.

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