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Emerging stool-based and blood-based non-invasive DNA tests for colorectal cancer screening: The importance of cancer prevention in addition to cancer detection

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Abstract

Colorectal cancer (CRC) screening can be undertaken utilizing a variety of distinct approaches, which provides both opportunities and confusion. Traditionally, there has often been a trade-off between the degree of invasiveness of a screening test and its ability to prevent cancer, with fecal occult blood testing (FOBT) and optical colonoscopy (OC) at each end of the spectrum. CT colonography (CTC), although currently underutilized for CRC screening, represents an exception since it is only minimally invasive yet provides accurate evaluation for advanced adenomas. More recently, the FDA approved a multi-target stool DNA test (Cologuard) and a blood-based test (Epi proColon) for average-risk CRC screening. This commentary will provide an overview of these two new non-invasive tests, including the clinical indications, mechanism of action, and diagnostic performance. Relevance to radiology practice, including a comparison with CT colonography, will also be discussed.

Introduction

Colorectal cancer (CRC) remains the second-leading cause of cancer death in the U.S and worldwide.[1,2] To a large degree, this represents a failure of programmatic screening in that CRC is almost entirely preventable through screening options that effectively target advanced neoplasia (ie, high-risk adenomas and invasive cancer). The ACS guidelines for CRC screening, derived in conjunction with the three major US gastrointestinal societies and the American College of Radiology, placed a strong emphasis on preventive tests, which include optical and virtual endoscopic modalities.[3] Both CT colonography (CTC) and optical colonoscopy (OC) are effective for detecting advanced adenomas, which are seen about 25 times more frequently than invasive cancer in a typical screening cohort.[4,5] The fecal occult blood tests (FOBT) in current use, guaiac-based FOBT and fecal immunochemical tests (FIT), are moderately effective in terms of cancer detection, but with

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large trade-offs between sensitivity and specificity, as well as very low positive predictive values.[3,6] Perhaps more importantly, neither is sensitive enough for advanced adenomas to be considered an effective preventive test for CRC.[3] This lack of cancer prevention is a critical omission when the target screening population is largely composed of otherwise healthy 50–75 year-old adults, where most of the screening value is derived from cancer prevention over cancer detection.

The FDA recently approved two new non-invasive tests for CRC screening. In August 2014, Cologuard (Exact Sciences) became the first multi-target stool DNA approved by the FDA for general CRC screening.[7] On that very same day, through an unprecedented parallel review process, CMS announced that Cologuard would also be a covered benefit for Medicare beneficiaries (a regulatory "coup" that was never available to CTC). Medicare agreed to cover the Cologuard test every three years at a reimbursement cost of $502 per test. In April 2016, Epi proColon (Epigenomics) became the first blood test approved by the FDA for CRC screening. To date, however, Medicare does not cover this blood test for screening purposes. According to the company's website, the blood test currently costs about €99–€161 (~$112–$182) in Germany. The clinical indication, mechanism of action, diagnostic performance, and the relevance of these two non-invasive CRC screening tests to radiology practice are discussed below.

Cologuard (multi-target stool DNA test for CRC)

Cologuard is indicated for CRC screening in "typical average-risk" adults, at a screening interval of three years. The basic rationale behind stool DNA (sDNA) testing is that invasive cancers, and presumably advanced benign neoplasms, exfoliate enough material to allow for their detection in stool through amplification techniques. A stool sample is collected from the patient at home in a process that requires a number of active steps. The patient is first sent a collection kit that requires defecation into a plastic container, manual scraping of the stool specimen with a small handheld probe, pouring a preservative over the entire sample, and bagging and sealing of the kit. The entire box is then returned to Exact Sciences via overnight shipping.

Initial screening results from sDNA testing demonstrated an improved sensitivity for CRC detection compared with gFOBT (52% versus 13%), but no improvement for detecting large (≥10 mm) adenomas (10.7% versus 10.3%).[8] The current iteration of this stool test actually combines a multi-target stool DNA test with FIT. As such, the Cologuard test evaluates for 11 distinct molecular biomarkers in the stool sample, including seven DNA mutation biomarkers, two DNA methylation biomarkers, hemoglobin, and also β-actin as a control for human DNA. Although quantitative analysis is possible, the test is reported out as a qualitative binary "positive" or "negative" result, derived using thresholds that presumably optimize sensitivity and specificity.

A large multi-center CRC screening trial of nearly 10,000 adults using Cologuard showed a sensitivity for CRC that was at the high end of the reported FIT range (92%), but at the low end of the typical FIT range for specificity (87%).[9] The prevalence for cancer in this study group (0.7%) was somewhat higher than what is typically encountered in an asymptomatic

screening cohort (0.2%).[4,5] Unfortunately, Cologuard detected fewer than half of all large advanced adenomas (42%), limiting its preventive role. By comparison, the reported ranges of sensitivity and specificity for FIT in detecting CRC are roughly 60–90% and 85–95%, respectively.[3,6] Sensitivity of FIT for advanced adenomas is typically much lower but ranges up to 40%, which is similar to Cologuard but much lower than truly preventive tests such OC or CTC.[10–14]

Epi proColon (blood-based test for methylated SEPT9 DNA)

The Epi proColon blood test (also referred to as the mSEPT9 assay) is indicated for average-risk CRC screening adults, to be performed annually. This test utilizes a 10 ml blood sample, out of which about 3.5 ml of plasma is extracted for free circulating DNA. Plasma methylated SEPT9 DNA (mSEPT9) is amplified via PCR analysis, along with β-actin as an internal control. Aberrantly methylated genes such as SEPT9 are attractive candidate markers for CRC detection, as such methylation occurs early in tumorigenesis, appears to be stable, and yields an amplifiable signal that can be assayed with high accuracy.[15] From the patient perspective, this screening test simply requires a blood draw, which could be performed in conjunction with other routine laboratory testing.

In initial retrospective case-control studies, the mSEPT9 test showed great promise, with a sensitivity of about 70% and specificity of 90% for CRC detection.[16–18] A subsequent prospective trial in an asymptomatic screening cohort reported a sensitivity of 48.2% and specificity of 91.5% for CRC, as well as a sensitivity of 11.2% for advanced adenomas.[15] Relative to Cologuard, the Epi proColon test appears to be less sensitive for both CRC and advanced adenomas in actual practice, but with a higher specificity for cancer.

Discussion and comparison with CT colonography

How do these two FDA-approved non-invasive CRC screening tests fit in with the currently available screening options? To answer this question, it is critical to understand the importance of prevention in CRC screening. Among average-risk screening adults, one invasive cancer will be found for every 500 or so individuals screened, whereas at least one large benign polyp will be found for every 20 individuals screened, on average. Unfortunately, both of these new tests currently fall well short of expectations in terms of their preventive ability to detect advanced adenomas. Pursuing such a noninvasive test that will miss most advanced neoplasia in average-risk 50-year-olds makes little sense, regardless of patient adherence. This setback is regrettable, especially for the blood-based test, since this approach ultimately represents the “holy grail” for CRC screening. Perhaps a case could be made for such a cancer-detection test in frail elderly adults, where precancerous lesions are of less clinical concern.

When screening is focused on a relatively low-prevalence entity such as CRC, specificity must not be overlooked at the expense of high sensitivity. To illustrate this concept, it can be useful to consider the positive predictive value (PPV) of these non-invasive cancer tests. Assuming a typical 0.2% prevalence of CRC in an average-risk screening population and inserting the best available performance data for CRC accuracy (ie, 92% sensitivity and 87%

specificity for Cologuard; 48% sensitivity and 92% specificity for Epi proColon), the PPV is 1.4% for Cologuard and 1.2% for Epi proColon. Given that "positive" tests would all be referred to colonoscopy, CRC will not be found in nearly 99% of cases. Except for the minority of cases where a large adenoma is detected, the vast majority will represent false-positives, calling into question both clinical efficacy and cost-effectiveness. Many patients and providers may be understandably confused as to which test was "correct" – the DNA-based test or a challenging physical scope that augers from below? Concern over missed cancers at OC related to these "genetically-positive" test results may lead to inappropriate additional testing, such as repeat colonoscopy or even PET/CT to search for other aerodigestive cancers that may give rise to a positive DNA test.[19] Such a sequence of events could undermine the desired benefits of a non-invasive screening test.

At the other end of the spectrum, the message of CRC prevention can be taken too far, as is sometimes the case with optical colonoscopy, the most invasive and expensive CRC screening test.[20,21] While there is no doubt that OC provides cancer prevention through polyp detection and removal, this concept is now being taken to the extreme, with universal polypectomy for adenoma detection rates (ADR) that approach 50%.[22] The ADR was initially intended as a quality measure for screening OC, but is now driving endoscopic technology to find and resect more and more diminutive lesions of little or no clinical relevance. Given that the lifetime risk of CRC is about 5%, it stands to reason that the vast majority of diminutive tubular adenomas will never transition to cancer, let alone grow to a large polyp size.[23] Perhaps an apt skin cancer analogy would be to remove all moles regardless of size or concerning features. CRC risk is highly dependent upon polyp size, as even a large 1–2 cm colorectal polyp has only a 1% or less likelihood of harboring cancer.[4,24] Furthermore, the prevalence of large polyps closely mirrors the lifetime CRC risk of 5%.

In my opinion, CTC occupies a veritable "Goldilocks Zone" within the spectrum of available CRC screening tests.[25] Unlike the non-invasive CRC tests that lack cancer prevention at one end of the modality spectrum (including the new DNA tests), and overly invasive, aggressive, and expensive colonoscopy at the other end, CTC is "just right" in terms of balancing invasiveness and prevention. In fact, no other test can claim to be both minimally-invasive and highly preventive for CRC. CTC matches OC for the detection of advanced neoplasia with almost no risk for the serious complications associated with physical endoscopy and sedation.[11,20,26] Furthermore, additional screening benefit can be gained from the extracolonic evaluation at CTC, including osteoporosis and AAA screening, among others.[27,28]

In summary, to remain a relevant participant in CRC screening, it is important to understand the strengths and weaknesses of the various screening options, including those that are just now emerging. Although the new stool-based and blood-based non-invasive DNA tests are conceptually appealing at face value, they generally lack the preventive benefit that should be considered essential for effective CRC population screening.

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