

ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

Section Editor: John Baillie, MB ChB, FRCP

Noninvasive Tests for Colorectal Cancer Screening

Deborah A. Fisher, MD, MHS
Assistant Professor of Medicine
Center for Health Services Research
in Primary Care
Durham Veterans Affairs Medical Center
Division of Gastroenterology
Duke University School of Medicine

G&H Could you explain why there is a need for colorectal cancer screening options other than colonoscopy, being that colonoscopy is so highly recommended by all of the screening guidelines?

DF An ideal screening test, for any disease, is one that is widely available, noninvasive, inexpensive, engenders minimal risk, and is easily accessible to both patients and physicians. Of course, it also must be effective at identifying disease prior to the presentation of symptoms, in an earlier and more treatable stage. Colonoscopy is one of the potential modalities recommended by all current colorectal cancer screening guidelines, and there is certainly nothing wrong with using this procedure as a primary screening option. Colonoscopy is, by far, the most sensitive test for identifying cancer prior to symptoms and, additionally, for identifying precancerous lesions (ie, adenomatous polyps). Colonoscopy also allows for the opportunity for removal of these polyps, which may decrease the incidence of cancer in the future.

However, colonoscopy is also the most expensive and invasive modality currently recommended. It carries a measurable risk of complications, even death, and it is not necessarily easily accessible or widely available. Even patients who have health insurance often have out-of-pocket costs (eg, copayments) in addition to the cost of missing work and having someone else potentially miss work to drive them to and from the colonoscopy (since sedation is commonly used for colonoscopy in the United States).

A screening test is, by definition, targeted toward an asymptomatic, average-risk population. The entire colorectal cancer screening population (those who are asymptomatic and 50 years of age or older) is exposed to the risk and expense of colonoscopy, but only a minority will benefit via reduced cancer death rates and perhaps a reduced risk of developing cancer.

Furthermore, few regions in the United States have the resources or a sufficient number of endoscopists to screen every person with colonoscopy. The expense, limited access, invasiveness, and risk are significant barriers to colorectal cancer screening participation. The colorectal cancer screening rate in the United States is still only around 50%. Ideally, we would have a screening test that could triage people who need to undergo colonoscopy and save those who do not need this procedure from the risk and expense that accompany it. Because colonoscopy is not an ideal first-line screening test, there is interest in new screening tests that minimize risk, and are inexpensive, more accessible, and more widely available.

G&H How significant of a problem is inappropriate colonoscopy screening in terms of morbidity, financial burden, and use of resources?

DF Use of colonoscopy as the primary screening modality is certainly not, in and of itself, inappropriate. However, there are individuals who should not undergo any colorectal cancer screening such as individuals with advanced age or severe comorbidities who have a reduced life expectancy and are, therefore, unlikely to benefit from screening. Screening is generally recommended if a patient has at least 5 years of life expectancy, though the real benefit of screening lies with patients who have a life expectancy of at least 10 years. If the patient is unlikely to live that long, they are unlikely to benefit from screening, even if they have a cancerous or precancerous lesion, as they are more likely to die from their comorbidity or advanced age than from colorectal cancer. Furthermore, it is unlikely that these patients would be able to tolerate treatment for colorectal cancer.

Another category of inappropriate screening is average-risk and higher-risk individuals who undergo colonoscopy too frequently. There is growing evidence that gastroenterologists and referring primary-care physicians are recommending that patients undergo repeat colonoscopy sooner than is recommended by screening and polyp surveillance guidelines. Having a repeat colonoscopy is not inappropriate, but doing so sooner than is necessary may result in several extra, unnecessary colonoscopies. For example, if a patient is not due for a colonoscopy for 10 years, but a physician sends them for colonoscopy every 3 years, in a 10-year period, the patient will undergo 3 follow-up colonoscopies instead of 1. These additional colonoscopies are unlikely to offer any benefit, yet they still carry the risk of complications related to perforation, bleeding, and sedation. On a population level, overuse of repeat colonoscopy results in a lost opportunity to screen someone who has never been screened.

G&H Can the use of precolonoscopy screening with noninvasive tests help encourage colonoscopy in appropriate patients and improve general screening compliance?

DF That is certainly the hope. Currently, only half of all individuals eligible for colorectal cancer screening in the United States are being screened. This rate includes all screening modalities, not just colonoscopy. Over the past few years, the use of colonoscopy for screening has increased quite a bit and has driven the overall increase in the proportion of people screened. Use of flexible sigmoidoscopy has decreased in an almost mirror image of the increase in colonoscopy, and use of fecal occult blood tests (FOBT) has also decreased. Double-contrast barium enema has always had low utilization rates, which are now even lower. We do not yet have data as to how the newly recommended modalities from the most recent screening guidelines may affect adherence.

Unfortunately, each of these procedures and tests has potential barriers for patients. Those associated with colonoscopy have been discussed above. FOBT, whether guaiac- or immunohistochemical-based, has the difficulty and inconvenience of having patients collect stool at home and mail in their cards, which may impact adherence. Computed tomography (CT) colonography has access and affordability issues because it is largely unreimbursed by government and private insurance. CT colonography also shares the problem of bowel preparation with colonoscopy and sigmoidoscopy. As with FOBT, stool-based DNA testing has the problem of stool collection, which is cumbersome and burdensome to many patients. In addition, there is the disconcerting factor for the recommending physician of an unclear follow-up interval. These are all potential barriers to screening adherence.

It is hoped that if future tests address the reasons that patients are not being screened (eg, cost, risk, inconvenience), adherence will increase. Time and time again, however, the strongest and most consistent predictor of adherence to any colorectal cancer screening test has been physician recommendation of the test.

G&H Could you summarize the recently updated guidelines for colorectal cancer screening?

DF Two of the major US guidelines were updated in 2008, the first from the US Multi-Society Task Force, which included the gastroenterological professional societies, the American Cancer Society, and the American Society of Radiologists, and the second from the US Preventative Services Task Force. Previously, these groups had issued guidelines in 2003 and 2002, respectively, that were similar. The primary difference at that time was the designation of colonoscopy as the preferred test by the US Multi-Society Task Force, whereas the US Preventative Services Task Force maintained that there are advantages and disadvantages of each test and it is not clear whether any given test is the preferred or best test.

However, in 2008, the two sets of updated guidelines differed quite a bit. The US Multi-Society Task Force guidelines were targeted toward average-risk individuals, age 50 years and older, with no upper age limit given. The guidelines recommended FOBT annually, noting its recommended sensitivity; flexible sigmoidoscopy every 5 years; colonoscopy every 10 years (which was noted to be the preferred test); double-contrast barium enema every 5 years (even though it is used quite rarely in clinical practice); CT colonography at a recommended interval of every 5 years (which was included for the first time); and stool DNA testing (though the follow-up interval was uncertain). The guidelines divided these tests into two groups: those that potentially prevent cancer by detecting precancerous lesions (the imaging studies: colonoscopy, barium enema, CT colonography, flexible sigmoidoscopy) and those that detect cancer at an earlier and more treatable stage (the stool-based tests).

Prior to this differentiation, the gold standard for any screening test was preventing death from the condition being screened. With this guideline, the Task Force promoted the idea of preventing colorectal cancer. There are growing data that prevention has real potential, though the data from polyp studies, which originally suggested that up to 90% of cancers could be prevented, may have been more optimistic than the actual impact of colonoscopy in clinical practice. There have been other studies, for example, one by Baxter and associates, suggesting that colonoscopy reduces left-sided cancers but possibly not right-sided cancers. Although this study had limitations such as the use of administrative claims data, a setting in

which the majority of colonoscopies were not performed by gastroenterologists (Canada), and a 5-year time horizon, it serves as a caution to overestimating the impact of colonoscopy on cancer prevention.

In contrast, the US Preventative Services Task Force guidelines recommended annual FOBT; flexible sigmoidoscopy every 5 years; and colonoscopy every 10 years. Unlike the US Multi-Society Task Force, they did not recommend any other tests due to insufficient evidence and noted that no test among their three recommended tests was superior. They also recommended against routine screening in adults 76–85 years of age, though these could be considered on a case-by-case basis, and against any screening after age 85.

G&H Are any of these screening tests used in combination with others?

DF As far as the recommendations, the only tests used in combination are annual FOBT and flexible sigmoidoscopy every 5 years. When using these tests together, it is recommended that FOBT be administered first because a positive FOBT would require the patient to undergo colonoscopy and thereby avoid the flexible sigmoidoscopy. It is not clear how much the combination adds to the use of each test separately. I suspect that as the use of sigmoidoscopy continues to decrease, this combination will also be used less and less frequently. There are far fewer primary-care physicians who are offering sigmoidoscopy. Access to sigmoidoscopy is likely reduced in many healthcare settings; the majority of gastroenterologists are not set up for large-volume sigmoidoscopy because they are performing large-volume colonoscopy. Healthcare systems that use flexible sigmoidoscopy as one of their primary screening tools have maintained their capacity for flexible sigmoidoscopy and often have nongastroenterologists (in some cases, nonphysicians) perform the procedure.

G&H Is there an optimal time for follow-up colonoscopy from a positive screening test?

DF Sporadic colorectal cancer, as we understand it, has a time horizon of 7–10 years from precancerous lesion to cancer. Any time interval from the initial test to colonoscopy will be dwarfed in impact by the much longer time horizon of the condition's natural history. None of the data so far have consistently demonstrated that the time from the initial test to colonoscopy impacts the stage at diagnosis for colorectal cancer or mortality. There is, however, a sense that for patient satisfaction, as well as for qualitative considerations of what constitutes good patient care, a delay is not optimal. In particular, there is concern that a long delay may impart the message to the patient that the colonoscopy is not important, thereby decreasing

adherence to the follow-up colonoscopy. A variety of studies have shown that only 50–60% of patients with a positive FOBT undergo colonoscopy within a 6–12 month period. This is quite concerning; noninvasive tests are effective for screening colorectal cancer only if patients with positive tests undergo a full colonoscopy.

The lack of data to inform follow-up intervals can result in recommendations or requirements based upon subjective determinations of good care. These requirements can overwhelm a system already working at capacity. An unintended result could be a lack of access to colonoscopy for symptomatic patients without necessarily improving outcomes for patients with a positive screening test. Allowing additional time for follow-up colonoscopy could lead to better triage of all patients who need the procedure. We do not yet have the data to inform us of an appropriate interval that balances these considerations of access, risk, and adherence.

In addition, some physicians wonder whether waiting the recommended 10 years to repeat a colonoscopy that did not detect adenomas is too long. There have been several published reports looking at the use of noninvasive interval testing, but the data and guidelines currently do not support that approach. It is recommended, however, that if a patient develops new symptoms during the interval years, they should undergo appropriate diagnostic evaluation, which is generally a colonoscopy.

G&H How does patient comorbidity affect screening choice or utility?

DF Comorbidity should affect the decision to screen; as discussed earlier, asymptomatic people with a limited life expectancy because of advanced age or comorbidity are unlikely to live long enough to develop a cancer and die from it. Instead of benefiting from the screening, they might be harmed; there is evidence from a Medicare database that older patients and those with comorbidities are more likely to experience a complication during colonoscopy. With elderly patients who are too sick to undergo colonoscopy, there is a tendency to use noninvasive screening tests to avoid the complications of an invasive procedure. The fallacy here is that if the FOBT (or any other noninvasive test) is positive, the patient should have a colonoscopy. Even if the physician does not start with a colonoscopy, it is the common endpoint. Therefore, if a patient is too sick to undergo primary screening colonoscopy, they are too sick to undergo any screening modality. A positive screening test creates difficult decisions: should it be ignored, or should the patient be subjected to the risks of a test that the physician did not think the patient could tolerate in the first place?

Comorbidity should not affect the choice of screening modality, unless there are comorbidity-specific logistics

that would favor one test over another. For example, a patient on chronic anticoagulation therapy will need to have anticoagulation stopped for the colonoscopy. Depending upon the indication for the anticoagulation and other health conditions, the patients may require a change in therapy or even a hospital admission for heparin infusion. It might be very attractive to start with another test that does not require a change in therapy and only use colonoscopy if the initial test designates the patient as high risk.

G&H Has there been research examining the quality of colorectal cancer screening methods?

DF There have been a number of recommendations for measuring the quality of screening. The most common is the ratio of people screened over the eligible population. There is also much interest in measuring the quality of colonoscopy because, regardless of the initial modality, colonoscopy remains the follow-up procedure for any positive initial test. The difficulty of developing, validating, and implementing quality measures lies in the details: for example, how do you determine who is eligible for screening? Are there individuals in the denominator who are too sick to be screened or are actually high-risk and should not be counted in the average-risk population? How should the screening test be defined: as any test, or only as a test performed for the indication of screening? What data source should be used: chart reviews, which are expensive and time-consuming, or automated data such as administrative claims data, which may not be available for all patients or may not include sufficient clinical information to be useful or accurate?

Many suggested quality indicators do not provide the specifics for determining how to perform the measurement. In addition, elements or processes should not be measured merely because they can be measured; only factors that are truly linked to the outcome of interest should be measured. One example is withdrawal time during colonoscopy. Initially, several studies demonstrated an association between withdrawal time during colonoscopy and both polyp and adenomatous polyp detection. Withdrawal time appeared to be a reliable measure of colonoscopy quality. After the first wave of data, studies began to show that, in some circumstances, withdrawal time was not closely linked to polyp detection. The construct that should be measured is careful endoscopic technique. Withdrawal time is relatively easy to measure, but merely spending more time in the colon or waiting for a mandated period of time to pass before examining the next section of colon does not equal quality. Careful endoscopic technique is more difficult to define, measure, and document.

G&H Does the National Cancer Institute's colorectal cancer screening questionnaire have a clinical application as a screening aid?

DF This questionnaire, developed by the National Cancer Institute, was created to standardize screening questions for research. It included brief descriptions of the recommended colorectal cancer screening tests (at that time, FOBT, colonoscopy, flexible sigmoidoscopy, and double-contrast barium enema) that focused on what made each test different, followed by questions that would determine, via the patient's self-reporting, whether they had ever undergone a test, if so, the date of their most recent test, whether that test was performed for screening, and so on, so the investigator could determine whether the patient was up-to-date with their screening. This questionnaire was not perfect, but it was fairly accurate. It was most accurate with colonoscopy, with a sensitivity and specificity greater than 90%, most likely because colonoscopy is the most invasive and expensive procedure, which thus leaves the biggest impression on patients.

One limitation of this questionnaire was the use of medical records as the gold standard. In addition, procedures other than colonoscopy had low sensitivities and specificities with this questionnaire because patients were less likely to report these procedures correctly. For example, in the Veterans Affairs setting, there was a good deal of patient confusion with contrast barium enema, likely due to the frequent use of barium in other procedures, and it was clear that many patients were overreporting it.

Although this questionnaire was developed as a research tool, it would be helpful to have a clinical tool to determine whether a patient is due for screening. The United States has a decentralized medical delivery system, which makes it difficult to gain access to and find every single procedure and test in a patient's medical records. An accurate questionnaire would be helpful when a primary-care provider does not have all of a patient's records from their specialists or other primary-care encounters. However, this questionnaire is too long in its current form to be practical in a practice setting.

G&H Could you highlight any important research on colorectal cancer screening that is currently underway?

DF There is much interest in developing a blood test that would screen for colorectal cancer to eliminate many of the difficulties of other tests, particularly stool tests, as far as adherence, ease of administration, and accessibility. It would be very convenient for physicians to recommend a patient for screening and then be able to collect blood in

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their office during the same clinic visit. There have also been continuing efforts to address some of CT colonography's perceived shortcomings, including perfecting algorithms in which the patient does not need to use a bowel preparation; improving the detection of smaller polyps; and addressing the issue of extracolonic findings. There is also ongoing development of new technologies such as capsule colonoscopy to provide intraluminal views of the colon without the risk and expense of colonoscopy or requiring the limited resource of the trained endoscopist.

Suggested Reading

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