Screening Techniques for Prevention and Early Detection of Colorectal Cancer in the Average-Risk Population

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ABSTRACT

Colorectal cancer (CRC) is associated with considerable morbidity and mortality, with more than 1,000,000 new cases and 500,000 deaths occurring annually. CRC has a natural history of transition from normal mucosa through adenoma to malignant lesion that spans, on average, 15 to 20 years, providing a window of opportunity for effective prevention and intervention through routine screening. The optimal screening strategy for the average-risk population aged ≥ 50 years remains the subject of debate, however. Endoscopic screening is undoubtedly the most effective screening method, and is also therapeutic since it permits polyp removal. The simplest and best-evaluated available screening method is the fecal occult blood test, which is relatively inexpensive and noninvasive, but less accurate than colonoscopy. This method detects cancer at an early stage but, since precancerous polyps rarely bleed, it is not suitable for disease prevention. Compliance with current screening methods is a major barrier to optimal prevention. Several new screening modalities, such as self-navigating colonoscopes, prepless virtual colonoscopy, and stool genetic testing, may improve compliance. Until these technologies are available or shown to be appropriate for routine screening, however, conventional colonoscopy remains the most efficient method for CRC screening and prevention.

Gastrointest Cancer Res 1:98–106.

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Colorectal cancer (CRC) is a leading cause of cancer-related mortality in the Western world, with an estimated lifetime risk of 6%, an incidence of over 1,000,000 new cases per year worldwide, and a long-term survival rate of about 50%.[1–3] Approximately two thirds of cases involve average-risk men and women, with a sharp increase of incidence beginning in the fifth decade of life.[3] The disease is highly preventable and can also be successfully treated in early stages. CRC has a natural history of transition from normal mucosa to a premalignant precursor lesion (ie, adenoma) and then to malignancy. The entire process may span 15 to 20 years, with the transition from adenoma to adenocarcinoma taking up to 10 years. These intervals provide a window of opportunity for screening, effective intervention, and prevention of CRC.[4–8] Indeed, a reduction of up to 90% in the occurrence of CRC has been demonstrated in individuals who underwent colonoscopy with polyp removal.[6,7]

As for early detection, survival is directly related to stage of disease at the time of diagnosis. If metastasis to distant sites has occurred, the 5-year survival rate is close to zero. However, when the cancer is found early at a localized preinvasive stage, 5-year survival rate is approximately 95%.[1–3] These characteristics of CRC make it highly suitable for routine screening programs. Several screening techniques are available and in common use. However, improvements in screening techniques could both increase preventive yield and reduce the costs associated with screening.

The optimal screening approach in individuals should be determined by risk stratification based on a detailed personal and family history. It is important to emphasize that patients with any symptoms or signs that may be related to CRC should undergo a complete diagnostic evaluation and not just routine screening tests. Asymptomatic individuals with a personal and/or family history of CRC or adenoma are classified as at moderate risk, while those with familial neoplastic syndromes or inflammatory bowel are considered at high risk for developing CRC. Persons at high risk require specific screening and surveillance programs that include frequent colonoscopies (usually once a year), beginning at a young age. For moderate-risk patients, colonoscopy is usually performed every 5 years or at shorter intervals according to endoscopic results. Screening for average-risk men and women is widely recommended beginning at 50 years of age, though a consensus on the optimal approach for average-risk screening does not exist.

Current primary screening modalities in the average-risk population include fecal

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occult blood test (FOBT), sigmoidoscopy, and colonoscopy. The value of computed tomographic (CT) colonography (virtual colonoscopy) and fecal DNA testing for primary screening is still under evaluation. Navigating colonoscopy and endomicroscopy are two new and promising modalities. This review presents the current strategies and potential future modalities for the prevention and early detection of CRC in the average-risk population.

CURRENT SCREENING TECHNIQUES

Fecal Occult Blood Test

Fecal occult blood testing is a low-cost, noninvasive periodic procedure that detects fecal hemoglobin. The test does not require cathartic bowel preparation and the findings may reflect the full length of the aerodigestive tracts. Current FOBT technology employs a guaiac or immunochemical analysis. Several factors affect the accuracy of FOBT, including stool rehydration (increases sensitivity, decreases specificity), heme degradation (reduces sensitivity), medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), and interfering dietary substances such as peroxidases and meat heme.

Proof of concept for reducing the mortality from CRC by FOBT testing was provided in the 1980s. Three large prospective randomized trials have demonstrated that an annual FOBT can decrease CRC mortality by 15% to 33% when positive results are followed by colonoscopy (for review, see Ref. 3).[9–12] A meta-analysis pooling these three studies with data from a Swedish trial estimated a 16% to 23% reduction in CRC mortality,[13] while the Minnesota trial with an 18-year follow-up found that biennial FOBT decreases CRC-related death by 21%.[10]

The estimated FOBT sensitivity for cancer ranges widely, between 30% and 90% (for review, see Ref. 3).[9–12] In a study using comparative screening with guaiac and immunochemical tests, the best results for cancer detection were achieved by a combination of the two methods with a sensitivity and specificity of 66% and 97%, respectively (for review, see Ref. 3). A Japanese trial using FOBT in a set of five different immunochemical tests reported a sensitivity of 48% and specificity of 96% for detection of large adenomas.[14] A 75% sensitivity for CRC or advanced adenoma was found for both FOBT methods in a mixed cohort that included individuals at above-average risk.[15] The specificity and positive predictive value of the immunochemical test (94% and 60%, respectively) were higher than those with the guaiac test (34% and 12%, respectively).[15]

Limitations

The limitations of FOBT include its being an indirect screening test; patients with positive results are referred for colonoscopy to confirm the presence of polyps or cancer. Thus, much of the efficacy of screening in the Minnesota trial, for example, may reflect the fact that colonoscopy was performed in a large segment of screenees (38%), including those with false-positive results. Indeed, at least 6% to 11% of the reported reduction of mortality was attributed to incidental detection of lesions by colonoscopy.[3,9–12]

Another consideration is that other sources of occult bleeding (including the upper gastrointestinal tract) or false-positive results due to medications (NSAIDs) or dietary ingredients may lead to unnecessary colonoscopies. In a study by Lieberman et al[16,17] in which 3,121 asymptomatic persons underwent colonoscopy, positive FOBT results 3 successive days before bowel preparation identified only 23.9% cases of advanced cancer; thus, FOBT alone failed to detect 76.1% cases of advanced neoplasia.

Adequate follow-up after FOBT can be erratic. A recent study in patients with positive FOBT findings during screening tests showed that approximately three quarters of these patients were referred to a gastroenterologist, and only 44% underwent a complete colon examination within 12 months.[18] The main reasons identified for failure to complete evaluations were lack of referral for further testing and patient noncompliance.

Fecal occult blood testing essentially permits detection of cancer at an earlier stage rather than allowing true prevention of CRC. Since some carcinomas and most adenomas do not bleed, FOBT will not detect them. Although FOBT is unarguably superior to no screening at all, it has relatively low sensitivity and provides only a moderate decrease in CRC mortality compared to other available screening options. Thus, annual FOBT alone is insufficient for effective CRC prevention and should at least be combined with sigmoidoscopy when used for screening.

Sigmoidoscopy

Sigmoidoscopy is a direct endoscopic examination of the distal part of the colon during which diagnostic biopsies can be obtained. Sigmoidoscopy is considered less invasive than colonoscopy and it is performed after a short bowel preparation that requires only two enemas. The procedure usually does not require sedation and it can be performed by trained nurses. If a neoplastic lesion is found during sigmoidoscopy, the entire large bowel should be evaluated by colonoscopy.

The current published data on reducing CRC mortality using screening sigmoidoscopy are drawn from nonprospective, case-control studies. These studies indicate that screening sigmoidoscopy can reduce the incidence and death rates of distal CRC by 59% to 80%[19–22] (for review, see Ref. 3) and lower overall CRC mortality by up to 40% to 50% (for review, see Ref. 3).[19–21,23,24] The recommendation for a 5-year interval between examinations is based on evidence indicating that the protective benefit of sigmoidoscopy appears to last about 6 to 10 years, and that a 5-year interval for reexamination after colonoscopy is sufficient for preventive purposes.[6,7,25,26]

Limitations

The main drawback of sigmoidoscopy is the limited extent of the colon that can be examined. The desired extent of screening sigmoidoscopy is about 60 cm, including the rectum, sigmoid colon, and descending colon up to the splenic flexure. Unfortunately, the actual range that can be achieved is often shorter. Jensen et al[27] showed that in the hands of expert endoscopists, the sigmoidoscope is advanced only to the sigmoid-descending colon junction in more than 50% of cases.

A considerable proportion of proximal advanced lesions occur in the absence of distal lesions and, therefore, will not be detected by sigmoidoscopy.

Lieberman et al[16,17] demonstrated that 52% of patients with proximal advanced lesions (ie, advanced adenoma or carcinoma) had no lesions in the distal colon; thus, more than half of the advanced neoplastic lesions would have been missed by sigmoidoscopy. The absence of distal adenomas was also reported in 65% of proximal cancer cases in a prospective study on colonoscopy in average-risk persons.[28] In our recently published study,[29] 21% to 43% of cases with neoplasia had proximal lesions beyond the reach of sigmoidoscopy. A proximal shift of neoplasia in older ages was suggested, since the prevalence of proximal findings in the absence of distal lesions was significantly higher in patients aged 65 to 75 years compared to those aged 50 to 64 years.

Combined FOBT and Sigmoidoscopy

The combined use sigmoidoscopy at 5-year intervals and an annual FOBT would appear to be a rational approach to screening, but there are limited prospective data to support the strategy thus far. One Danish FOBT trial reported a 28% reduction in proximal CRC mortality but only an 8% reduction in distal CRC, leading the authors to conclude that sigmoidoscopy should be complementary to FOBT.[30] Winawer et al[31] reported that the combined approach gained about a 20% advantage over sigmoidoscopy alone for early detection of CRC and resulted in longer survival. Lieberman and Weiss[17] estimated that the addition of FOBT to sigmoidoscopy would increase the yield of sigmoidoscopy from 70% to 76%. Altogether, it seems very likely that this combination improves the relative efficacy of each test alone, and it has been offered as an alternative option to screening colonoscopy.[32]

Colonoscopy

There is no doubt that colonoscopy is the gold standard to identify colorectal cancer.[3,33,34] It provides a direct diagnostic examination of the entire length of the large bowel combined with polyp removal and tumor sampling. The examination is performed by skilled gastroenterologists after a cathartic bowel preparation. Using back-to-back colonoscopies, Rex et al[35] found that the sensitivity of a single colonoscopy is about 90% to 95% for cancers and large adenomas, and 75% for polyps < 1 cm. In a recent systematic review, the detection rates for adenomas ≥ 10 mm, adenomas 5 mm to 10 mm, and adenomas 1 mm to 5 mm were 98%, 87%, and 74%, respectively.[36] Colonoscopy miss rates are related to the skills of the endoscopist and to the withdrawal technique.[37] Improvement of these factors may reduce the miss rate for small lesions.

Although there are no published prospective studies on direct reduction of CRC mortality by primary screening colonoscopy, a large body of evidence supports this effect. Much of the reduction of CRC mortality by screening in the FOBT trials was attributed to the use of colonoscopy in a large segment of the study cohort and to incidental detection of lesions by colonoscopy.[3,9-12,15] In light of the proven reduction in CRC-related death by screening sigmoidoscopy,[3,19-21] colonoscopy should be even more effective in reducing mortality since it enables an examination of the entire colon along with the opportunity to perform polypectomy. The National Polyp Study has demonstrated a 76% to 90% decrease in the incidence of CRC at 6 years after colonoscopy and polypectomy, compared to appropriately selected controls.[6,7] Two additional cohort studies have demonstrated a decrease in the incidence of CRC after colonoscopy and polypectomy compared to historic controls.[22,38] In subjects who underwent colonoscopy with polyp removal, a prospective 13-year follow-up demonstrated a relative risk of 0.2 for CRC compared to the control group.[22]

The use of colonoscopy in asymptomatic subjects between 50 and 75 years of age was assessed in several large-scale trials. In a study by Imperiale et al,[39] 17.7% of 1,994 screenees had adenoma. The prevalence of advanced neoplasia (defined as villous adenoma, adenoma with high-grade dysplasia, or carcinoma) was 3.1% in the distal colon and 2.5% in the proximal colon. Lieberman et al[16] examined 3,121 asymptomatic subjects and reported point prevalence rates of 1%, 10.5%, and 36.5% for CRC, advanced neoplasia, and overall adenomas, respectively. FOBT and sigmoidoscopy would have failed to detect 76.1% and 52% of cases of advanced neoplasia, respectively, in the same cohort.[17]

We recently reported the results of a primary screening colonoscopy program in 1,177 asymptomatic men and women aged 40 to 80 years at average risk for CRC.[29] The prevalence rates of overall colorectal neoplasia, advanced lesions, and cancer were 20.9%, 6.3%, and 1.1%, respectively. In the main age group of 50 to 75 years, overall adenoma, advanced neoplasia, and cancer prevalence rates were 21.3%, 6.7%, and 1.2%, respectively.[29] Among the neoplasia cases, 21% to 43% harbored proximal neoplasia beyond the reach of sigmoidoscopy, without distal lesions. The prevalence of proximal neoplasia without distal lesions was significantly higher (up to 60%) in the subgroup of patients aged 65 to 75 years compared to those 50 to 64 years of age (43%). These findings suggest a possible proximal shift of neoplasia in older ages and support the use of colonoscopy rather than sigmoidoscopy for screening in this age group. Our report was the first on screening colonoscopy in healthy persons aged 76 to 80 years at average risk for CRC. Neoplasia was detected in a high percentage (28.6%) of this age group. The

COLORECTAL CANCER SCREENING TECHNIQUES

Current Techniques

- Fecal occult blood test (FOBT)
- Sigmoidoscopy
- FOBT + sigmoidoscopy
- Colonoscopy

Emerging Modalities

- Fecal DNA test
- Magnification and high-resolution endoscopy
- Chromoendoscopy
- Computed tomographic colonography (virtual colonoscopy)

Technologies on the Horizon

- Assisted colonoscopy (eg, ColonoSight®)
- Self-propelling, self-navigating colonoscope (eg, Aer-O-Scope™)
- Videocapsule endoscopy

prevalence rates of advanced neoplasia and CRC (14.3% and 2.6%, respectively) were more than twice as high as the rates in the 50- to 75-year-old age group. Since life expectancy at 70 years of age for a person with no functional limitations is about 14.3 years,[40] these high rates should encourage the inclusion of healthy elderly patients in future studies on screening programs.

Limitations

The bowel preparation required prior to colonoscopy entails some inconvenience, though it has become easier with the application of monobasic and dibasic sodium phosphate instead of polyethylene glycol as the cleansing agent. Perceptions that colonoscopy is a painful procedure may be largely unwarranted, since the examination is performed under conscious sedation and discomfort is rarely reported. Indeed, patients who underwent both procedures reported that nonsedated sigmoidoscopy was associated with a significantly higher level of discomfort than conscious-sedated colonoscopy.[41] Colonoscopy is, nevertheless, considered a relatively invasive procedure. Compared with older series that estimated the overall risks of colonoscopy, including in-hospital and emergency procedures, recent studies in the setting of ambulatory screening examinations have shown considerably lower risk, with morbidity rates of 0.1% to 0.3% and absence of perforations or procedure-related deaths.[29,42] In a study that assessed 116,000 colonoscopies in the community, perforations were rare (0.03%) and no procedure-related mortality occurred.[43]

Colonoscopy costs more than FOBT or sigmoidoscopy. However, a fuller appreciatioon of true cost comes from cost-effectiveness analyses that define costs and benefits in terms of life-years saved by screening with the different techniques. A detailed comparison of the cost-effectiveness of screening modalities is presented in the summary section below.

EMERGING DIAGNOSTIC MODALITIES

Although several newly developed screening tests for CRC show substantial promise, none is sufficiently developed yet to be offered as a screening modality.

Fecal DNA Test

The fecal DNA test is a stool-based molecular analysis of DNA markers in exfoliated colonocytes that are regularly shed into the stool. This test has several important advantages over other currently available CRC screening modalities: (1) it is noninvasive; (2) it requires no unpleasant cathartic bowel preparation; (3) there is no need for a formal health care visit; (4) there is no loss of time away from routine activities; and (5) testing can be performed on mailed-in specimens, so geographic access to stool screening is essentially unimpeded. The rationale for this technique is that normal colonocytes are sparse and apoptotic (eg, contain short DNA fragments), while neoplastic colonocytes are abundant and harbor high molecular weight DNA (long DNA).

The first report of using stool for the detection of CRC came from Sidransky and colleagues,[44] who detected CRC based on analysis of *ras* mutations in stool samples. Subsequently, panels of genetic markers have been applied in clinical studies to assess sensitivity and specificity of stool DNA testing, with these panels differing in type and number of point mutations used. Ahlquist et al[45] reported a sensitivity of 91% and 82% for CRC and large adenomas, respectively, with their panel. Several other studies found sensitivity rates of 52% to 63.5% for CRC and 41% to 57% for advanced adenomas.[45–48] The overall specificity of the test for any neoplastic lesion has ben reported at 93% to 96%.[45,46,48] DNA amplification was the most frequent neoplastic marker in the stool. The most prevalent genetic alternations were mutations in *K-ras* and *p53* genes, followed by microsatellite instability and adenomatous polyposis coli gene mutations.[47]

Limitations

Fecal DNA testing is a promising technology that appears to have higher sensitivity and specificity rates than FOBT, but it has not yet been assessed as a screening strategy in large-scale prospective trials. At present, the high cost of the test is another drawback, particularly since its effectiveness in screening has not been established. Song et al[49] used the Markov model for a decision analysis that compared stool DNA testing with conventional CRC screening strategies. Relative to no screening, fecal DNA testing at intervals of 5 years was estimated to reduce the incidence and mortality of CRC by 35% and 54%, respectively. The test was found to gain fewer life-years and to cost more than conventional screening methods. Altogether, the cost-effectiveness of fecal DNA was inferior to other tests, such as FOBT and colonoscopy.

Magnification and High-Resolution Endoscopy

Since the development of the first flexible fiber endoscope in 1961, ongoing development has taken place in the arena of endoscopy design. The new electronic videoendoscopes are equipped with charged couple device chips of 100K to 300K pixels. The recent generation of videoendoscopes were introduced with 850K-pixel density and referred to as high-resolution endoscopes. In addition, some endoscopes, including high-resolution endoscopes, are equipped with an optical zoom facility that can provide a magnified image. The combination of both high resolution and magnification may become an important additive tool in CRC screening. High resolution can increase the detection rate of small and flat lesions while magnification can enhance details in the suspected lesions, thereby making endoscopic diagnosis more accurate.

Chromoendoscopy

Chromoendoscopy consists of staining the mucosal surface of the gastrointestinal tract in order to enhance the diagnostic yield of endoscopy. The main purpose is to screen for neoplastic or preneoplastic lesions (in particular flat or depressed lesions) and to direct endoscopic biopsies. Indigo carmine is a contrast vital stain that accumulates in pits and valleys between cells, highlighting the mucosal architecture that becomes even more apparent with the use of magnification and/or high-resolution endoscopy.[50] The technique requires only a special spraying catheter; therefore, using this modality while performing regular colonoscopy is inexpensive and rather simple. The only disadvantage of the technique is that it prolongs the overall procedural time. Currently, chromoen-

doscopy is reserved for high-risk patients (ie, persons with a history of neoplasia, inflammatory bowel disease, or familial neoplastic syndromes). Two recent large-scale studies evaluating the use of chromoendoscopy in average-risk patients undergoing colonoscopy showed that the technique improved the detection rate of flat and depressed neoplasia.[51,52]

Computed Tomographic Colonography (Virtual Colonoscopy)

Virtual colonoscopy uses a spiral CT scan for the generation of two-dimensional (2D) or three-dimensional (3D) images of the entire colon. Similar to colonoscopy, the examination requires cathartic bowel preparation and air insufflations for intestinal distention. It is considered a minimally invasive procedure and patients are not sedated. In cases of suspected CR lesions, the examination should be followed by a conventional colonoscopy. Virtual colonoscopy offers the additional advantages of an abdominal CT scan, including information on the extent of tumor invasion, lymph node involvement, metastasis, and other abdominal findings (including incidental ones).

Several studies have assessed the accuracy of this procedure for the detection of colorectal neoplasia relative to optical colonoscopy, with the lowest reported detection rates ranging from 32% to 78% for lesions ≥ 1 cm.[53–58] Use of different techniques (ie, CT protocols and the use of 2D vs. 3D), interoperator variation, and the learning curve with this new modality may have contributed to the decreased accuracy in these reports. The sensitivity for findings ≥ 10 mm was higher in later studies, ranging from 81% to 94%.[59-65] The detection rate of polyps ≥ 6 mm was 39% to 94%.[54,58,59,61,65] In a meta-analysis of 14 trials, the sensitivity for lesions 6 mm to 9 mm and for lesions ≤ 5 mm was 62% to 84% and 43% to 65%, respectively.[64] Specificity rates for detection of polyps ≥ 10 mm and polyps 6 mm to 9 mm were 94% to 98% and 79% to 92%, respectively.[54,58,59,61,65]

The performance of virtual colonoscopy without bowel preparation (using fecal tags to distinguish stool from true lesions) is under evaluation. This option seems appealing, especially in terms of patient compliance, but further information on the sensitivity and specificity of the procedure is needed before any conclusions can be drawn about its value. It should be noted that the promising results noted above were obtained in the context of clinical studies in referral centers. Such results are not likely to be obtainable in a community setting. Currently, the use of virtual colonoscopies is most widely accepted following an incomplete colonoscopy.

Virtual colonoscopy has been under development for more than a decade, but only in recent years, following several technologic advances, has it become practical to consider its use for CRC screening in the community. The technologic improvements include the advent of multislice CT scan, and in particular, the use of thin-slice CT scan, which has improved the efficacy of detecting small lesions (< 3 mm). In addition, advances in computer software have reduced the time required for the reconstruction of 3D images and the time required for radiologist interpretation. Moreover, data suggest that the addition of oral contrast for tagging residual colonic fluid and stool may further increase the sensitivity and specificity of CT colonography. In this case, it may become the ideal screening modality, as the need for colonic preparation is recognized as a major drawback of colonoscopy. The prototype of this "prepless" virtual colonoscopy technology is already being evaluated in clinical trials.[66,67]

Limitations

There are no published data on the prevention or reduction of the incidence and mortality of CRC by virtual colonoscopy. The accuracy of the test for lesions > 10 mm is acceptable but its sensitivity for smaller polyps is relatively low, while data on the detection of flat and depressed adenomas are not available. The risk of missing adenomas < 10 mm and, in particular, adenomas 6 mm to 9 mm is of concern, raising the general issue of the importance of establishing the limits of what should be considered clinically significant lesions. Another major drawback is the possibility of high miss rates for flat and depressed adenomas, which have been reported to account for 22% to 30% of all adenomas.[68,69]

Distention of the bowel by air insufflations may cause discomfort to the patients as well as pose risk of perforation.[70] The morbidity rate of virtual colonoscopy should be further assessed in large-scale studies. Up to 40% of the screenees will also be referred for conventional colonoscopy on the basis of false- and true-positive findings. The inconvenience of repeating the bowel preparation and performing both procedures may be reduced by the option of performing back-to-back virtual and endoscopic colonoscopy in multidisciplinary centers. The cost-effectiveness of the examination has not been well established, and any cost analysis should include the price of unnecessary optical colonoscopies that follow false-positive tests. Two studies accounting for such factors have estimated that virtual colonoscopy is less cost-effective than standard colonoscopy.[71,72]

In summary, prior to implementing virtual colonoscopy as a routine screening test, several questions would need to be answered regarding risks (including perforation and the potential hazardous effects of radiation exposure), cost-effectiveness, and the optimal interval between examinations. Until then, virtual colonoscopy may be reserved for patients who pose technical or other difficulties (including psychologic) in performing a conventional colonoscopy.

TECHNOLOGIES ON THE HORIZON

As noted, conventional colonoscopy is associated with a number of drawbacks, including requiring the services of a skilled gastroenterologist for each procedure and being associated with suboptimal patient compliance. Technologies are being developed to address some of these drawbacks, including skill-independent, anesthesia-free, self-propelling, and self-navigating miniaturized endoscopic devices.[73]

Assisted Colonoscopy

The ColonoSight® device (Sightline Technologies Ltd., Haifa, Israel), recently approved by the US Food and Drug Administration (FDA), is ergonomically similar to existing colonoscopes. The major differences between the ColonoSight® and existing colonoscopes are as follows: (1) The device is covered by a disposable sleeve, allowing the physician's hands to

remain clean. (2) All channels within the device (insufflation, irrigation, suction/working) are completely disposable. (3) No fiber-optics are necessary due to an incorporated LED light source. (4) Air used for sleeve deployment adds a small amount of additional forward force just below the scope tip, which enhances device navigation and forward motion. Pilot studies in Israel, Italy, and the United States were reported during the annual meeting of the American Gastroenterology Association in 2004.[74] In these studies, 63 procedures were performed in a hospital, and 9 in an office setting. Mean examination time was 12.4 ± 10.8 minutes with an insertion length of 117 ± 26 cm.

Self-Propelling, Self-Navigating, Skill-Independent Colonoscope

Attempts to develop a self-propelling, self-navigating miniaturized colonoscopic device have been ongoing for more than 2 decades. One such device is the Aer-O-Scope™ (G.I. View Ltd., Ramat Gan, Israel) — a skill-independent, anesthesia-free, self-propelling, self-navigating miniaturized endoscopic device that moves along the entire length of the colon transmitting video pictures of the colonic mucosa via digital camera. The disposable device is supplied with electricity, air, water, and suction via a thin supply cable, which is pulled behind the device. The optical system consists of a conic lens and a mirror allowing for simultaneous 20º forward, 360º circumferential, and 30º retro vision without the need for retroflexion.

Proof of concept was reported in 2006; the cecum was reached by the device in 10 of 12 subjects (83%), with the hepatic flexure being reached in 2.[75] The time to complete advancement to the cecum averaged 14.0 ± 7 minutes and the driving pressures averaged 34 ± 2.3 mbar. Two subjects requested analgesics during the procedures (in both cases the cecum was reached); four subjects experienced sweating and a bloating sensation that resolved spontaneously. All subjects received follow-up for up to 48 hours and then for 30 days postprocedure, and no complications were observed. Thus far, studies in humans have included more than 50 subjects, with no complications being observed. The procedure has been performed without sedation in the majority of cases, and the device has passed the hepatic flexure in the last 40 patients studied.

There are numerous advantages to such a device, including freeing the gastroenterologist from performing colonoscopy in all patients. The device could be operated by nurse technicians, with the gastroenterologist reading the recorded results and performing a biopsy in those patients in whom it is necessary (eg, in the estimated 1 in 4 low-risk patients in whom biopsy is required on the basis of colonoscopy screening). Such a scenario may allow more individuals to be screened and actively treated, which would constitute a considerable public health benefit.

Videocapsule Endoscopy

Videocapsule endoscopy (VCE) was approved for clinical use several years ago.[76] This technology provided a major breakthrough in the diagnosis of diseases involving primarily the small intestine mucosa, but it has the potential of examining other parts of the gastrointestinal tract. VCE contains a miniature video camera, a light source, batteries, and a radio transmitter. Video images are transmitted by means of radio telemetry to the sensor array attached to the body, allowing images to be captured from the entire gastrointestinal tract. Images from a recording time of up to 8 hours are stored in a portable recorder.

The American Cancer Society position statement on CRC screening modalities[77] indicates that there is no evidence to support the use of VCE for detecting colorectal polyps or cancers. The colon is poorly visualized with VCE in its conventional form for a number of reasons: (1) Stool obscures visualization of the colonic mucosa. (2) The slower transit time in the colon and its larger diameter, compared to the small bowel, make visualization of the entire colonic mucosa practically impossible. (3) Colonic peristalsis is antegrade as well as retrograde; thus, it is possible for the camera to miss areas of the colon simply because the camera is pointed in the wrong direction. (4) The current batteries for the capsule last only 6 to 8 hours, while it takes the capsule up to 72 hours to be excreted.

Attempts to modify VCE for potential use as a CRC screening modality are under way. A colonic capsule has been developed that has longer battery life with delayed onset, and it contains two lenses on both sides of the capsule — features that might be able to overcome the above-mentioned obstacles. An international multicenter study investigating VCE with the new capsule and standard colonoscopy, performed back-to-back, in more than 100 patients was recently completed, and reporting of results is awaited.

DISCUSSION

Determining the optimal screening strategy for CRC in the average-risk population should take into account efficacy and safety of the tests, cost-effectiveness, and likelihood of patient compliance.

Colonoscopy is the undisputed gold standard in terms of efficacy, having the highest sensitivity and specificity and offering the capacity to carry out therapeutic intervention during the procedure (ie, polypectomy). Reduction of CRC mortality with FOBT alone was 15% to 33% when positive FOBT results resulted in colonoscopy (for review, see Ref. 3).[9,11,12] A screening sigmoidoscopy can reduce the incidence and death rates of distal CRC by 59% to 80%[19-22] (for review, see Ref. 3) and overall CRC mortality by up to 40% to 50% (for review, see Ref. 3).[19–21,23,24]

In the National Polyp Study, colonoscopy with polypectomy reduced the incidence of CRC by 76% to 90% at 6 years, compared with appropriately selected controls.[6,7] Two additional cohort studies demonstrated a decrease in the incidence of CRC after colonoscopy with polypectomy compared to historic controls.[22,38] A prospective 13-year follow-up demonstrated a relative risk of 0.2 for CRC for these patients compared with a control group.[22]

Colonoscopy is the most invasive of currently available screening modalities. In the ambulatory setting, the procedure-related morbidity rate of colonoscopy is 0.1% to 0.3%,[29,42] with a 0.03% perforation rate and no mortality.[43] Sigmoidoscopy is considered less invasive, and has been associated with lower rates of serious adverse events (bleeding and perforation). In one population-based study, the perforation rate was about 0.09% in 35,300 sigmoidoscopies, compared with a rate of 0.2% with colonoscopy.[78]

Screening the entire population aged ≥ 50 years is an expensive proposition. However, the costs of missing a curable malignancy or failing to prevent cancer by resecting a premalignant lesion (polyp) may be significantly greater.[79] Calculations of costs per life-year saved vary around the world, mostly depending on the cost of colonoscopy.[3] Several studies reported an average cost of $7,100 to $7,800 per one case of CRC detected by FOBT.[80,81] Using data from the Minnesota FOBT trial, health economists from the National Cancer Institute and the US Office of Technology Assessment estimated that the cost of FOBT screening was less than $15,000 per quality-adjusted life-year gained.[82] On the other hand, the relatively low specificity and low predictive value of FOBT carries with it the burden of further endoscopies. According to this calculation, a cost of $25,000 per life-year saved is accepted in the developed world.[3]

Several studies have shown that sigmoidoscopy is also a cost-effective screening modality for CRC, with the cost of sigmoidoscopy per life-year saved being comparable to that with colonoscopy and considerably lower than that with FOBT.[83–85] Lieberman et al[8] assessed the cost-effectiveness of several CRC screening programs. In a realistic model of a < 50% compliance rate, the estimated cost per death prevented was similar for FOBT and endoscopic screening modalities. If colonoscopy costs were below $750, a single colonoscopy performed once in a lifetime was found to be more cost-effective than any other screening modality at every level of compliance. Calculations using the Markov model showed reasonable costs per life-year saved of $10,983 and $2,981 with colonoscopy performed once in 10 years or once in a lifetime, respectively.[85] The cost-effectiveness of virtual colonoscopy remains to be established, and the cost analysis should include the price of unnecessary conventional colonoscopies that follow false-positive tests. Two studies suggest that virtual colonoscopy is less cost-effective than conventional colonoscopy.[71,72]

In a comparison of fecal DNA testing with conventional CRC screening strategies,[49] testing stool DNA at intervals of 5 years was estimated to reduce the incidence and mortalilty of CRC by 35% and 54%, respectively, compared with no screening. However, the test was found to gain fewer life-years and to cost more than conventional screening methods, with cost-effectiveness inferior to that with FOBT and colonoscopy.

Compliance rates are largely related to the perception of the nature of the test by the general population. There are no published data on the compliance rate for colonoscopy, but it is estimated that the long interval between colonoscopic examinations should enhance compliance relative to that for other tests that need to be performed with greater frequency. The easier bowel preparation and the use of sedation should also markedly improve compliance. As noted, one study showed that patients graded sigmoidoscopy as more painful than sedated colonoscopy.[41]

The low compliance rate associated with FOBT (15%–40%) further declines with time, and not all persons screened receive or respond to referrals for further diagnostic work-up (for review, see Ref. 3). Poor rates of appropriate evaluation of patients with positive FOBT are of concern and constitute a factor that should be taken into consideration when evaluating and comparing screening modalities.

In spite of the proven ability to prevent CRC cases and the acceptable cost-effectiveness of screening, many Western countries do not have routine population-based programs for appropriate CRC screening or do not actively promote such programs. CRC screening makes economic sense and reduces suffering. Today, the options include a 10-year colonoscopy or an annual FOBT combined with a 5-year sigmoidoscopy. In the near future, such emerging techniques as fecal DNA testing, prepless virtual colonoscopy, or self-navigating colonoscopy may become preferred diagnostic screening tests, and conventional colonoscopy may be reserved mainly for therapeutic procedures. The suitability of these promising new modalities for routine CRC screening awaits demonstration in further studies.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al: Cancer Statistics 2004. *CA Cancer J Clin* 54:8–29, 2004
2. Peeters M, Haller DG: Therapy for early stage colorectal cancer. *Oncology* 13:307–315, 1999
3. Burt RW: Colon cancer screening. *Gastroenterology* 119:837–853, 2000
4. Morson B: President's address. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 67:451–457, 1974
5. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. *Cell* 61:759–767, 1990
6. Winawer SJ, Zauber AG, O'Brien MJ: Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N Engl J Med* 328:901–906, 1993
7. Winawer SJ, Zauber AG, Ho MN, et al: The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med* 329:1977–1983, 1993
8. Lieberman DA: Cost-effectiveness model for colon cancer screening. *Gastroenterology* 109:1781–1790, 1995
9. Mandel JS, Bond JH, Church TR, et al: Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Eng J Med* 328:1365–1371, 1993
10. Mandel JS, Church TR, Ederer F, et al: Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst* 91:434–437, 1999
11. Hardcastle JD, Chamberlain JO, Robinson MHE, et al: Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 348:1472–1477, 1996
12. Kronborg O, Fenger C, Olsen J, et al: Randomized study as of screening for colorectal cancer with faecal occult blood test. *Lancet* 348:1467–1471, 1996
13. Towler B, Irwig L, Glasziou P, et al: A systemic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. *BMJ* 317:559–565, 1998
14. Nakama H, Fattah A, Zhang B, et al: A comparative study of immunochemical fecal tests for detection of colorectal adenomatous polyps. *Hepatogastroenterology* 47:386–389, 2000
15. Levi Z, Hazazi R, Rozen P, et al: A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. *Aliment Pharmacol Ther* 23:1359–1364, 2006
16. Lieberman DA, Weiss DG, Bond JH, et al: Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Group 380. *N Engl J Med* 343:162–168, 2000
17. Lieberman DA, Weiss DG: One-time screening for colorectal cancer with combined fecal occult blood testing and examination of the distal colon. Veterans Affairs Cooperative Group 380. *N Engl J Med* 345:555–560, 2001
18. Fisher DA, Jeffreys A, Coffman CJ, et al: Barrier to full evaluation for a positive fecal occult blood test. *Cancer Epidemiol Biomarkers Prev* 15:1232–1235, 2006
19. Selby JV, Friedman GD, Quesenberry CP Jr, et al: A case-control study of screening sigmoidoscopy and mortality from CRC. *N Engl J Med* 326:653-657, 1992

20. Newcomb PA, Norfleet RG, Storer BE, et al: Screening sigmoidoscopy and CRC mortality. *J Natl Cancer Inst* 84:1572–1575, 1992
21. Muller AD, Sonnenberg A: Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. *Ann Intern Med* 123:904–910, 1995
22. Thiis-Evensen E, Hoff GS, Sauer J, et al: Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study. *Scand J Gastroenterol* 34:414–420, 1999
23. Muller AD, Sonnenberg A: Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. *Arch Intern Med* 155:1741–1748, 1995
24. Kavanagh AM, Giovannucci EL, Fuchs CS, et al: Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control* 9:455–462, 1998
25. Doria-Rose VP, Levin TR, Selby JV, et al: The incidence of colorectal cancer following a negative screening sigmoidoscopy: implications for screening interval. *Gastroenterology* 127:714–722, 2004
26. Rex DK, Cummings OW, Helper DJ, et al: Five-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons. *Gastroenterology* 111:1178–1181, 1996
27. Jensen J, Kewenter J, Swedenborg J: The anatomic range of examination by fiberoptic rectosigmoidoscopy. *Scand J Gastroenterol* 27:842–844, 1992
28. Rex DK, Chak A, Vasudeva R, et al: Prospective determination of distal colon findings in average-risk patients with proximal colon cancer. *Gastrointest Endosc* 49:727–730, 1999
29. Strul H, Kariv R, Leshno M, et al: The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40–80 years. *Am J Gastroenterol* 101:255–262, 2006
30. Jorgensen OD, Kronborg O, Fenger C: A randomized study of screening for CRC using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 50:29–32, 2002
31. Winawer SH, Flehinger BJ, Schottenfeld D, et al: Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J Natl Cancer Inst* 85:1311–1318, 1993
32. Rex DK, Johnson DA, Lieberman DA, et al: CRC prevention 2000: screening recommendations of the American College of Gastroenterology. American College of Gastroenterology. *Am J Gastroenterol* 95:868–877, 2000
33. Hixson LJ, Fennerty MB, Sampliner RE, et al: Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. *Gastrointest Endosc* 37:125–127, 1999
34. Macafee DA, Scholefield JH: Antagonist: population based endoscopic screening for colorectal cancer. *Gut* 52:323–326, 2003
35. Rex DK, Cutler CS, Lemmel GT, et al: Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 112:24–28, 1997
36. Van Rijn JC, Reitsma JB, Stoker J, et al: Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol* 101:343–50, 2006
37. Rex DK: Colonoscopic withdrawal technique is associated with adenoma miss-rates. *Gastrointest Endosc* 51:33–36, 2000
38. Jorgensen OD, Kronborg O, Fenger C: The Funen Adenoma Follow-up Study. Incidence and death from colorectal carcinoma in an adenoma surveillance program. *Scand J Gastroenterol* 28:869–874, 1993
39. Imperiale TF, Wagner DR, Lin CY, et al: Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 343:169–174, 2000
40. Lubitz J, Cai L, Kramarow W, et al: Health, life expectancy and health care spending among the elderly. *N Engl J Med* 349:1048–1055, 2003
41. Ringel Y, Dalton CB, Brandt LJ, et al: Flexible sigmoidoscopy: the patient's perception. *Gastrointest Endosc* 55:315–320, 2002
42. Nelson DB, McQuaid KR, Bond JH, et al: Procedural success and complications of large-scale screening colonoscopy. *Gastrointest Endosc* 55:307–314, 2002
43. Korman LY, Overholt BF, Box T, et al: Perforation during colonoscopy in endoscopic ambulatory surgical centers. *Gastrointest Endosc* 58:554–557, 2003
44. Sidransky D, Tokino T, Hamilton SR: Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. *Science* 256:102–105, 1992
45. Ahlquist DA, Skoletsky JE, Boynton KA, et al: CRC screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology* 119:1219–1227, 2000
46. Tagore KS, Lawson MJ, Yucaitis JA: Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. *Clin CRC* 3:47–53, 2003
47. Calistri D, Rengucci C, Bocchini R, et al: Fecal multiple molecular tests to detect CRC in stool. *Clin Gastroenterol Hepatol* 1:377–383, 2003
48. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al: Colorectal Cancer Study Group. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med* 351:2704–2714, 2004
49. Song K, Fendrick AM, Ladarbaum U: Fecal DNA testing compared with conventional colorectal cancer screening methids: a decision analysis. *Gastroenterology* 126:1270–1279, 2004
50. Axelrad AM, Fleischer DE, Geller AJ, et al: High-resolution chromoendoscopy for the diagnosis of diminutive colon polyps: implications for colon cancer screening. *Gastroenterology* 110:1253–1258, 1996
51. Bianco MA, Rotondano G, Marmo R, et al: Predictive value of magnification chromoendoscopy for diagnosing invasive neoplasia in nonpolypoid colorectal lesions and stratifying patients for endoscopic resection or surgery. *Endoscopy* 38:470–476, 2006
52. Trecca A, Gaj F, Di Lorenzo GP, et al: Improved detection of colorectal neoplasms with selective use of chromoendoscopy in 2005 consecutive patients. *Tech Coloproctol* 10:339–344, 2006
53. Fletcher JG, Johnson CD, Welch TJ, et al: Optimization of CT colonography technique: prospective trial in 180 patients. *Radiology* 216:704–711, 2000
54. Pineau BC, Paskett ED, Chen GJ, et al: Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology* 125:304–310, 2003
55. Mendelson RM, Foster NM, Edwards JT, et al: Virtual colonoscopy compared with conventional colonoscopy: a developing technology. *Med J Aust* 173:472–475, 2000
56. Spinzi G, Belloni G, Martegani A, et al: Computed tomographic colonography and conventional colonoscopy for colon diseases: a prospective, blinded study. *Am J Gastroenterol* 96:394–400, 2001
57. Johnson CD, Harmsen WS, Wilson LA, et al: Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterology* 125:311–319, 2003
58. Cotton PB, Durkalski VL, Pineau BC, et al: Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA* 291:1713–1719, 2004
59. Pickhardt PJ, Choi JR, Hwang I, et al: Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 349:2191–2200, 2003
60. Macari M, Bini EJ, Xue X, et al: Colorectal neoplasms: prospective comparison of thin-section low-dose multi-detector row CT colonography and conventional colonoscopy for detection. *Radiology* 224:383–392, 2002
61. Fenlon HM, Nunes DP, Schroy PC 3rd, et al: A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N Engl J Med* 341:1496–1503, 1999
62. Yee J, Akerkar GA, Hung RK, et al: Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology* 219:685–692, 2001
63. Laghi A, Iannaccone R, Carbone I, et al: Detection of colorectal lesions with virtual computed tomographic colonography. *Am J Surg* 183:124–131, 2002
64. Sosna J, Morrin MM, Kruskal JB, et al: CT colonography of colorectal polyps: a metaanalysis. *Am J Roentgenol* 181:1593–1598, 2003
65. Macari M, Bini EJ, Jacobs SL: Colorectal polyps and cancers in asymptomatic average-risk patient: evaluation with CT colonography. *Radiology* 230:629–636, 2004
66. Pickhardt PJ, Choi JR, Hwang I, et al: Stool tagging applied in thin-slice multidetector computed tomography colonography. *J Comput Assist Tomogr* 27:132–139, 2003
67. van Dam J, Cotton P, Johnson CD, et al : AGA future trends report: CT colonography. *Gastroenterology* 127:970–984, 2004
68. Rembacken BJ, Fujii T, Cairns A, et al: Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 355:1211–1214, 2000
69. Saitoh Y, Waxman I, West AB, et al: Prevalence of distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology* 120:1657–1665, 2001
70. Young BM, Fletcher JG, Earnest F, et al: Colonic perforation at CT colonography in a patient without known colonic disease. *Am J Rentgenol* 186:119–121, 2006

71. Sonnenberg A, Delco F, Bauerfeind P: Is virtual colonoscopy a cost-effective option to screen for colorectal cancer? *Am J Gastroenterol* 94:2268–2274, 1999
72. Ladabaum U, Song K, Fendrick AM: Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? *Clin Gastroenterol Hapatol* 2:554–563, 2004
73. Chen YK: Self-propelling endoscopes. *Gastrointest Endosc Clin N Am* 14:697–708, 2004
74. Shike M, Repici A, Cohen LB, et al: Major advances in colonoscopic technology: the ColonoSight® a pull-powered assisted disposable, non fiber-optic colonoscope. *Gastrointest Endosc* 59:2004 (abstr AB113)
75. Vucelic B, Rex D, Pulanic R, et al: The Aer-O-Scope: proof of concept of a pneumatic, skill independent, self propelling, self navigating colonoscope. *Gastroenterology* 130:672–677, 2006
76. Eliakim R: Wireless capsule video endoscopy: three years of experience. *World J Gastroenterol* 10:1238–1239, 2004
77. Levin B, Brooks D, Smith RA, et al: Emerging technologies in screening for CRC: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. *CA Cancer J Clin* 53:44–55, 2003
78. Gatto NM, Frucht H, Sundararajan V, et al: Risk of perforation after coolonoscopy and sigmoidoscopy: a population-based study. *J Natl Cancer Inst* 95:830–831, 2003
79. Bond JH: Improving the effectiveness of fecal occult blood screening for colorectal cancer. *J Natl Cancer Inst* 91:1602–1603, 1999
80. Bini EJ, Rajapaksa RC, Weinshel EH: The findings and impact of nonrehydrated guaiac examination of the rectum (FINGER) study: A comparison of two methods of screening for colorectal cancer in asymptomatic average risk patients. *Arch Intern Med* 159:2022–2026, 1999
81. Yamamoto M, Nakama H: Cost-effectiveness analysis of immunochemical occult blood screening for colorectal cancer among three fecal sampling methods. *Hepatogastroenterology* 47:396–399, 2000
82. Wagner JL, Tunis S, Brown M, et al: Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young G, Levin B, Rozen A (eds): *Prevention and Early Detection of Colorectal Cancer.* London (UK): Saunders, pp 321–356, 1996
83. O'Leary BA, Olynyk JK, Neville AM, et al: Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. *J Gastroenterol Hepatol* 19:38–47, 2004
84. UK Flexible Sigmoidoscopy Screening Trial Investigators: Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 359:1291–1300, 2002
85. Sonnenberg A, Delco F: Cost-effectiveness of a single colonoscopy in screening for colorectal cancer. *Arch Intern Med* 162:163–168, 2002

Disclosures of Potential Conflicts of Interest

Dr. Arber is on the scientific advisory board of GI View and Dr. Strul has no potential conflicts of interest to disclose.