

Melvin Schapiro, M.D., Series Editor

Screening for Colorectal Cancer: Which Test for Which Patients in 2007?



John H. Bond

Colorectal cancer is suited for a screening approach because it is common and lethal, usually has a long preclinical phase, treatment of screen-detected cancers or premalignant polyps is effective, and safe, acceptable, and cost-effective screening methods now are available. The two objectives of screening are to detect curable cancers and to prevent cancer by resecting premalignant adenomatous polyps. Current evidence-based guidelines recommend that asymptomatic, average-risk people be offered screening beginning at age 50 with one of five options. Each option has unique advantages and limitations that should be considered by both providers and their patients before choosing the method that best fits their situation, concerns, and resources. Two new, emerging methods of screening—CT-colonography and stool DNA tests—are currently under consideration by the guideline panels. Those at above average-risk because of a strong family history of the disease should be screened with colonoscopy.

INTRODUCTION

According to the International Union Against Cancer, colorectal cancer is ideally suited for a screening approach for several reasons. First the burden of disease is high in the U.S., Europe, Australia, New Zealand, and increasingly also in many other

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areas of the world. It is the second leading cause of cancer death in the U.S. with an estimated 145,500 new cases diagnosed each year and over 55,000 deaths. Although the age-adjusted incidence of colorectal cancer is higher in men than in women, both genders have almost an equal lifetime risk (about 6%) because women enjoy a longer life-expectancy. Second, the disease usually has a relatively long preclinical (asymptomatic) phase during which screening can detect easily treatable, curable neoplasia. Most (>95%) colorectal
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cancers arise in benign adenomatous polyps that usually develop and grow slowly over many years before they turn malignant (1). Third, early colorectal neoplasia can be successfully treated. Most advanced adenomas can be completely resected during colonoscopy thus preventing cancer, and the five-year survival rate after surgical resection of screen-detected cancers exceeds 85%. Lastly, we have several safe, acceptable, and cost-effective methods to screen for colorectal neoplasia.

Evidence-based screening guidelines separately developed and recently revised by the U.S. Preventive Services Task Force, and a joint expert panel of the American Cancer Society (ACS) and the U.S. Multi-society Task Force on Colorectal Cancer recommend that primary providers screen their asymptomatic, average-risk patients for colorectal neoplasia beginning at age 50 (2). The guidelines also recommend that, before screening is initiated, each patient first should be evaluated for any special risks for colorectal cancer that could indicate the need for earlier or more intense screening (Table 1). The guidelines currently recommend screening average-risk patients with one of five different options: annual fecal occult blood tests (FOBT), flexible sigmoidoscopy (FS) every five years, the combination of annual FOBT plus FS every five years, double-contrast barium enema (DCBE) every five years, or colonoscopy every 10 years (Table 2). The two primary objectives of screening are to detect early, curable cancers and to detect and resect advanced adenomatous polyps before they can turn cancerous. This review will discuss the unique advan-

Table 1
Risk stratification for colorectal cancer (2)

1. Is the patient age 50 years or older and asymptomatic?
2. Is there a past history of colorectal cancer or an adenomatous polyp?
3. Is there a history of inflammatory bowel disease that might predispose to colorectal cancer?
4. Has a family member had colorectal cancer or an adenomatous polyp? If so, how many, was it a first-degree relative (parent, sibling, or child), and at what age was it diagnosed?

Table 2
Colorectal Cancer Screening Guidelines: Acceptable Screening Options for Asymptomatic, Average-risk Men and Women \geq 50 Years of Age (2)

1. Annual screening with fecal occult blood tests (FOBT)
2. Flexible sigmoidoscopy screening every five years
3. The combination of annual FOBTs and flexible sigmoidoscopy every five years
4. Double-contrast barium enema every five years
5. Direct colonoscopy screening every 10 years

tages and limitations of each of these five screening options. This should help physicians and their patients choose a method that fits their particular situation, concerns, and resources. Two emerging new methods of screening that currently are being considered by the guideline expert panels—CT-colonography (“virtual colonoscopy”) and stool DNA tests—also briefly will be presented. Lastly, screening recommendations for patients who, because of a family history of colorectal neoplasia, are above-average risk for the disease briefly will be reviewed.

ANNUAL FOBT SCREENING

FOBT is the only screening option that has been shown in randomized controlled trials to reduce both the mortality and incidence of colorectal cancer. The Minnesota FOBT Screening Trial reported in 1993 that screening asymptomatic individuals between the ages of 50 and 80 with annual rehydrated Hemoccult® tests (Beckman-Coulter, Palo Alto, CA) and performing colonoscopy for those with a positive result, reduced the mortality from CRC by 33% (3). Investigators in this trial estimated that a screening program using their methods with 100% compliance would reduce colorectal cancer mortality by about 45% compared with that of a totally unscreened control group. The Minnesota Trial later showed that annual screening was substantially more effective in reducing mortality than was biennial screening (33% vs. 21% mortality reduction)(4). In addition, a program of annual screening reduced subsequent colorectal cancer incidence by 20%, presumably from

detection and resection of advanced premalignant polyps (5). Although studies have shown that the sensitivity of a one-time FOBT test for detecting cancer is only 30%–50%, a program of repeated annual screening can detect up to 92% of all cancers, most of them at an early, curable stage (6). Other important advantages of FOBT screening are its general availability and acceptability, and its very low up-front cost.

The main disadvantages of FOBT screening are that frequent screening is required, it fails to detect many polyps (especially smaller ones) and some cancers (especially distal ones), and test specificity is relatively low—there are many “false positive” tests requiring patients without clinically significant disease to undergo colonoscopy. Some argue, however, that unlike the case with indirect screening tests for other cancers, a false-positive FOBT is not completely without benefit to the patient. At worst, it initiates a colonoscopy, a highly definitive diagnostic test that many now are vigorously recommending for direct screening anyway. With its high negative-predictivity, a negative colonoscopy provides considerable reassurance about future colorectal cancer risk, and obviates any further screening for average-risk patients for at least 10 years according to the guidelines. All of the large trials of FOBT screening used the guaiac-based Hemoccult test. The guidelines recommend that if Hemoccult tests are used for screening, two samples from each of three consecutive stools should be tested after following a diet free of red meat and peroxidase-rich fruits and vegetables. Rehydration, which increases the sensitivity of guaiac tests, is not recommended because it may interfere with the readability of the test and it increases false-positivity. Use of the more sensitive version of Hemoccult, the Hemoccult-Sensa test may be the preferred guaiac FOBT because it approximates the sensitivity for detecting blood of the rehydrated test but has better performance characteristics. FOBT screening of a single stool sample obtained by a digital-rectal examination (DRE)—a common practice in primary care clinics—now is discouraged because such screening recently was shown to be very inaccurate (7). A positive DRE-FOBT requires colonoscopy, but a negative DRE-FOBT is uninformative and further screening with 6-sample, spontaneously-passed stool should be carried out.

Newer more specific immunochemical FOBTs are being introduced into clinical practice that likely will correct some of the disadvantages of the guaiac tests. These will be discussed in detail in another article in this colorectal cancer screening series. A positive screening FOBT always should be followed by colonoscopy with no exceptions.

FLEXIBLE SIGMOIDOSCOPY EVERY FIVE YEARS

Flexible sigmoidoscopy (FS) provides a highly accurate (high sensitivity and specificity) examination of the left colon, site of most colorectal cancers and advanced adenomas. Advantages of FS for screening are that, when performed by an experienced well-trained examiner, it is a safe, effective, quick and inexpensive examination acceptable to most patients after a relatively simple bowel preparation. Cohort and case-control studies indicate that FS screening alone reduces mortality from colorectal cancers within its reach by 60%–85%, and the protective effect lasts for up to 10 years (8–10). The U.S. VA Multicenter Colonoscopy Screening Study demonstrated that endoscopy performed to the sigmoid-descending colon junction would diagnose about 70% of all advanced colonic neoplasia, provided that full colonoscopy is performed whenever neoplasia is found in the distal colon (11). The main disadvantages of FS is that, because it is performed without sedation, it is poorly tolerated by many patients, and the examination performed alone will miss over 30% of advanced neoplasia located proximal to its reach. There is some evidence that older patients and women are more likely to have proximal advanced neoplasia without synchronous distal disease, and therefore flexible sigmoidoscopy screening alone may be less effective for these people. Bowel perforations are uncommon after flexible sigmoidoscopy. A recent study from the Mayo Clinic in Arizona identified only two perforations in 49,501 sigmoidoscopy procedures (12).

THE COMBINATION OF ANNUAL FOBT AND FS EVERY FIVE YEARS

Although this option has not been directly studied, indirect evidence suggests that the combination of FOBT and FS screening is a highly effective approach.

FOBT screening is insensitive for detecting small polyps and distal cancers, while FS is highly accurate for diagnosing all neoplasia located in the high-incidence left colon. As discussed previously, however, FS when done alone misses about 30% of advanced neoplasia located in the right colon beyond its reach. These lesions if they advance likely will be detected by a program of annual FOBTs before they become incurable. Although this approach is complicated (frequent screening is required), it largely corrects the limitations of performing either FOBT or FS screening alone. If both a FOBT and a flexible sigmoidoscopy are recommended at a given time, the FOBT always should be done first. A positive FOBT is an indication for colonoscopy and obviates the need for the screening flexible sigmoidoscopy.

DOUBLE-CONTRAST BARIUM ENEMA EVERY FIVE YEARS

Barium enema is not used much for population-based colorectal cancer screening in the U.S. and there are no direct studies demonstrating efficacy. In addition, barium enema examinations are substantially less sensitive and specific than colonoscopy for detecting neoplasia. The U.S. National Polyp Study performed a single-blinded comparison of DCBE and colonoscopy performed back-to-back in the same 580 patients that showed that the sensitivity of the barium enema for detecting polyps >1 cm was only 48% (13). A more recent study by Rockey, et al showed that the sensitivity for DCBE for detecting large polyps and cancer was 39% and 89%, respectively (14). A large retrospective study of patients with colorectal cancer in Indiana indicated that the sensitivity of barium enema for detecting colorectal cancers was only 83% (vs. 95% for colonoscopy) (15). Because of its lower sensitivity for cancer and polyps, when DCBE is used for screening, the guidelines currently recommend a screening interval of five years. Few complications have been reported in patients undergoing DCBE. In a study from Sweden in which DCBE was performed in 1,987 patients as part of their screening workup, no perforations or other serious complications occurred (16). In a survey from the U.K. of all barium enema examinations over a three-year period performed for

any reason, perforation occurred in only 1/25,000 examinations (17).

DIRECT SCREENING WITH COLONOSCOPY EVERY TEN YEARS

In the U.S. most gastroenterologists and many primary care providers and their average-risk patients now prefer the option of direct screening with colonoscopy because it clearly is the most accurate way to accomplish with a single test both of the major objectives of screening. Almost unheard of 10 years ago, this option is somewhat of a perturbation of the classic World Health Organization's definition of a screening test. Instead of performing a simple, acceptable, inexpensive and indirect test to identify those in the average-risk population who might benefit from a further definitive evaluation, we instead have moved up-front to the direct performance of a complex, expensive and somewhat invasive, diagnostic and therapeutic examination. Screening colonoscopy now is championed by many physician and patient groups because it accurately detects almost all cancers and advanced adenomas, and it allows removal of almost all polyps during a single sitting with a single bowel cleansing preparation. There are no randomized, controlled trials of direct screening colonoscopy proving and quantifying efficacy; the scientific evidence that supports this screening option, although compelling, therefore is indirect. For example, the National Polyp Study showed that colonoscopy and polypectomy reduced the incidence of metachronous colorectal cancer by 76%-90% in a large group of polyp-bearing patients compared with that of three reference populations (18). In addition, cohort and case-control studies suggest that screening colonoscopy or FS reduces mortality from cancers located in the examined colon by 50%-85% (19). Lastly, the colorectal cancer mortality and incidence reductions reported in the large FOBT trials was largely due to colonoscopy performed in those found to have a positive screening test for occult stool blood.

Direct colonoscopy screening of average-risk patients has been included as an option in U.S. screening guidelines since 1997. It was proposed as the pre-

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ferred method of screening by the American College of Gastroenterology in 2000. Reimbursement for direct colonoscopy screening for Medicare patients was established by Congress in 2001, and many other managed care organizations and third-party payers now are also paying for colonoscopy screening for people beginning at age 50. Advantages of screening colonoscopy, in addition to its accuracy and efficacy, are that infrequent screening is recommended, and the examination is both diagnostic and therapeutic at a single sitting with a single bowel-cleansing preparation. When performed by experienced, well-trained endoscopists, screening colonoscopy is feasible, well-tolerated, and has an acceptable safety record. The large VA Multicenter Colonoscopy Screening Study performed screening colonoscopy in 3,196 asymptomatic volunteers (20). Colonoscopy was complete to the cecum in 97.7% of cases and the incidence of major complications (mainly bleeding after polypectomy) was only 0.3%. There were no perforations. In patients who did not have polyps (diagnostic-only studies), there was only one major complication (a cardiovascular event) in 1,492 cases. The complication rate for community-based screening colonoscopy is not known, but likely is higher. Reports of complications for colonoscopy performed for all indications found a range of 0.07% - 0.72% for colonic perforations in therapeutic (polypectomy) cases, and post-polypectomy bleeding in 0.2%–2.67% (21). The VA study, performed mainly in men, showed that 52% of patients with advanced adenomas located in the proximal colon had no distal synchronous adenoma that would have been detected by screening flexible sigmoidoscopy. Another screening colonoscopy study by Schoenfeld, et al (the "CONCeRN" trial) performed totally in women also showed that a high percentage of those with proximal adenomas had no distal adenoma that would have been detected by screening flexible sigmoidoscopy (22). Because of colonoscopy's high negative predictive value and the long natural history of the adenoma-carcinoma sequence, infrequent screening every 10 years is currently recommended by the guidelines.

Disadvantages of direct colonoscopy screening that still need attention include questions of patient acceptance, cost, and colonoscopy capacity. Many healthy people are reluctant to endure the direct and

indirect costs of colonoscopy, and the disruption of their lives caused by the examination. Conscious sedation with its attendant risk, cost, and inconvenience usually is required for screening colonoscopy. There appears also to be a considerable indirect cost. A single screening examination requires the better part of two days to complete the bowel purging preparation, the examination itself, and subsequent recovery. When time lost from work for the patient and his or her accompanying "responsible adult," plus transportation costs and other attendant expenses are considered, the indirect cost of a screening colonoscopy is substantial. While the risk is small, complications (especially perforation) may be relatively serious for a test that detects an advanced neoplasm in only about 6%-7% of patients. Lastly, capacity to perform screening colonoscopy on all average-risk people over the age of 50 likely is insufficient in the U.S., and many endoscopy clinics are experiencing long waiting times for patients to undergo recommended screening. A study by the Centers for Disease Control and Prevention (CDC) reported that the capacity to conduct direct colonoscopy screening of the 41 million eligible Americans who had not yet been screened in 2004 may be severely lacking (23). They calculated that if half the currently available colonoscopy capacity were dedicated completely just to screening, it would take 10 years to complete the task and reach a steady state.

EMERGING NEW SCREENING METHODS

CT-Colonography (CT-C)

CT-C ("virtual colonoscopy") is a relatively new imaging technique that combines rapid helical CT scanning of the abdomen with computer software capable of rendering two- and three-dimensional (2-D and 3-D) images of the large bowel. These images can be combined for a complete 3-D view of the colon and rectum that then can be rapidly "flown through," thus simulating optical colonoscopy. CT-C has several obvious advantages over conventional colonoscopy. Examination time is shorter and there is no need for IV conscious sedation. Patients may return to their normal activity right after their scans. The procedure has little

immediate risk, allows examination of both sides of bowel folds, and precisely localizes lesions. It can examine the proximal colon when colonoscopy is incomplete or when a distal obstructing cancer is present. Disadvantages of CT-C include the need for a thorough bowel cleansing preparation, a somewhat disagreeable gas distention of the colon, and some radiation exposure. Also, at present these scans require appreciable expensive radiologist time to set up and interpret. Lastly, CT-C is diagnostic only; whenever a clinically important filling defect is found, the patient must undergo a subsequent equally-expensive colonoscopy to biopsy or resect the lesion.

Published studies comparing the accuracy of CT-C with optical colonoscopy have had mixed results (24). A study published in 2003 by Pickhardt, et al, however, indicates a promising future of this evolving methodology (25). In a multihospital study involving 1,233 asymptomatic, mostly average-risk adults, six experienced radiologists used multidetector CT scanners and a commercially available CT-C computer system (Viatronix, Stony Brook, NY) that creates a 3-D endoluminal display for the initial detection of polyps, followed by rapid confirmation of findings with 2-D images. Patients underwent a standard colonic preparation and also consumed both a barium and a water soluble contrast solution that allowed the computer to differentiate between retained stool and polypoid defects and to perform electronic "fluid cleansing." Remarkably, the sensitivity of CT-C in this study for detecting polyps >6 mm in diameter was as good as that of conventional colonoscopy. The American College of Radiology Imaging Network (ACRIN) currently is carrying out a multi-center national CT-C trial comparing CT-C with optical colonoscopy for the detection of colorectal neoplasia using modern techniques and rigid quality control (26). Results of this trial, that will involve 2,607 asymptomatic subjects over the age of 50 who are already scheduled for screening colonoscopy, are expected in June 2007. If the results of this important trial are favorable, CT-C undoubtedly soon will be added to the colorectal cancer guidelines' menu of acceptable screening options. CT-C likely then will help provide needed screening capacity in the US and will improve compliance.

DNA-based Stool Tests

Acquired genetic mutations and deletions occur in increasing number as colorectal neoplasia develop, grow, and advance to cancer. Cells containing these abnormalities are sloughed from the polyps and cancers into stool from which the DNA can be isolated, amplified, and analyzed. Such stool DNA analysis has the potential to serve as a specific screening test for the presence of advanced colorectal polyps and cancers. Because not all advanced neoplasia contain the same genetic changes, an effective screening test must analyze for a panel of multiple, carefully selected DNA markers. Such a screening test, the PreGen-Plus Test (Exact Sciences, Marlborough, MA) now has been developed, tested, and marketed. Unfortunately, in two large controlled trials reported to date, the sensitivity of the initial PreGen-Plus test ("version 1.0") for detecting colorectal cancer was only 31%–52% (27). In addition, the initially marketed tests were relatively expensive. Subsequent investigation revealed that the suboptimal sensitivity of "version 1.0" resulted from DNA degradation during transit of specimens to the processing laboratory. Adding DNA-stabilizing buffer to the stool immediately upon defecation prevented DNA degradation for several days. In addition, Exact Sciences has altered their method for extraction of DNA from stool. An improved PreGen-Plus test incorporating these modifications now is the one being marketed ("version 1.1"), and one study using this current method reported a sensitivity for detecting colorectal cancer of 70% (27). In addition, Exact Sciences is testing a new prototype of the test that includes analysis for methylation of the gene Vimentin ("version 2.0"). A study by Itzkowitz, et al of this new version indicated a sensitivity for detecting cancer of 87.5% (28). This new method appears to be easier to perform and likely will be less costly. The major benefit of the DNA stool test is that it is noninvasive, and patient and provider acceptance appears to be excellent. Disadvantages of the test are the lack of data to indicate how often a negative test should be repeated, and what the sensitivity and specificity of a program of repetitive testing might be. Some worry that psychological trauma could occur in those with a positive genetic test when the cause cannot be immediately identified at colonoscopy, but this issue has not been studied or

Table 3
Colorectal cancer screening for people with familial risk (2)

<i>Familial risk</i>	<i>Screening Recommendations</i>
1 ⁰ relative with colorectal cancer or an adenomatous polyp diagnosed < age 60 or Two or more 1 ⁰ relatives with colorectal cancer	Colonoscopy every five years beginning at age 40, or 10 years before earliest diagnosis
1 ⁰ relative with colorectal cancer or an adenomatous polyp diagnosed ≥ age 60 or Two 2 ⁰ relatives with colorectal cancer	Screen as average-risk but starting at age 40

quantified. All of these data and issues currently are being weighed by the ACS-GI Guideline Panel, and a recommendation regarding whether the PreGen-Plus test might be included soon as a screening option is pending.

PEOPLE WITH A FAMILY HISTORY OF COLORECTAL NEOPLASIA

Relatives of patients with colorectal cancer or adenomatous polyps may be at above-average risk for colorectal cancer because of inherited factors that have not yet been well-defined. If the risk is estimated to be high enough, then direct screening colonoscopy is the method recommended by the guidelines for these people (Table 3) (2). People with one first-degree relative (parent, sibling, or child) with colorectal cancer or an adenomatous polyp diagnosed before age 60, or two first-degree relatives with colorectal cancer diagnosed at any age should be advised to undergo colonoscopy screening beginning at age 40 or 10 years younger than the earliest diagnosis in their family, whichever comes first. If screening is negative, it should be repeated every five years. People with a first-degree relative with colorectal cancer or adenomatous polyps diagnosed after age 60 years, or two secondary-degree relatives with colorectal cancer should be advised to be screened as average-risk persons, but beginning at age 40 years.

SUMMARY AND CONCLUSIONS

A number of acceptable colorectal cancer screening options are now available and are endorsed by current evidence-based screening guidelines. The objectives of screening are detection of early, curable cancers and the detection and removal of premalignant polyps. Each screening option has unique advantages and limitations that need to be considered when designing a screening strategy. At present, this review’s author’s screening preference, if resources allow, is to do direct colonoscopy screening. If colonoscopy screening is not feasible or acceptable to the patient, the combination of FOBT and FS is a very good alternative. Screening with FOBT alone followed by colonoscopy for all with a positive result is an acceptable option for patients reluctant to have endoscopy or if resources are substantially limited. Screening with barium enema or FS alone are the least effective of the five options. It has, however, often been stated that “the best colorectal screening test is the one the patient actually will do” and “the only unacceptable option is not to screen.” ■

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