

## Screening for Colorectal Cancer in 2006—Advantages and Limitations of the Different Screening Options

a report by

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Evidence-based colorectal cancer (CRC) screening guidelines separately developed and recently revised by the American Cancer Society and the US Multisociety Taskforce on Colorectal Cancer recommend that all asymptomatic, average-risk women and men be offered screening for CRC beginning at age 50 using one of five screening options:

- annual fecal occult blood tests (FOBT);
- flexible sigmoidoscopy (FS) every five years;
- the combination of FOBT and FS;
- double-contrast barium enema every five years; or
- colonoscopy every 10 years.

The two primary objectives of screening are to detect early, curable cancers and to detect and resect advanced adenomatous polyps before they turn cancerous. Relative to these two objectives, each of the screening options has advantages and limitations that clinicians and their patients need to consider when selecting a screening approach.

### 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%. Investigators in this trial estimated that a screening program using their methods with 100% compliance would reduce CRC 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. In addition, a program of annual screening reduced subsequent

colorectal cancer incidence by 20%, presumably from detection and resection of advanced premalignant polyps. Although studies have shown that the sensitivity of a single 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. Other 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 significant disease to undergo colonoscopy.

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. Newer guaiac-based and immunochemical FOBTs now are available that have greater sensitivity than standard Hemoccult tests, but also have acceptable specificity. The immunochemical tests, which now are being widely used in Japan and Australia, are still undergoing field testing in the US. These FOBTs are especially promising because they are specific for human globin and therefore are not affected by diet or medications. FOBT screening of a single stool sample obtained by digital-rectal examination—a common practice in primary care clinics—is now discouraged because such screening recently has been shown to be highly inaccurate. A positive screening FOBT should be followed by colonoscopy, no exceptions.

### Flexible Sigmoidoscopy Every Five Years

Flexible sigmoidoscopy (FS) using modern 60cm endoscopes provides a highly accurate (few false-



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positives or false-negatives) examination of the left colon, site of most CRCs 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 reduces mortality from CRCs within its reach by 60–85%, and the protective effect lasts for five to 10 years. The Veterans Affairs (VA) Multicenter Colonoscopy Screening Study demonstrated that endoscopy to the sigmoid colon–descending colon junction would diagnose about 70% of all advanced colonic neoplasia, provided that, if an adenoma is found in the distal colon, full colonoscopy then is performed. The main disadvantage of FS is that, because it is performed without sedation, it is poorly tolerated by many patients, and the examination performed alone will miss about 30% of advanced neoplasia located proximal to its reach.

#### **The Combination of Annual FOBT and FS Every Five Years**

Although this option has not been directly studied, indirect evidence suggests it is a highly effective screening 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-risk left colon. FS when done alone, however, misses about 30% of neoplasia located in the right colon beyond its reach. Such lesions, as they advance, will likely be detected by a program of annual FOBTs before they become incurable. Although this approach is complicated and frequent screening is required, it largely corrects the limitations of performing either FOBT or FS screening alone.

#### **Double-contrast Barium Enema Every Five Years**

Barium enema is not used much for population-based CRC screening in the US, 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 US National Polyp Study performed a single-blinded comparison of double-contrast barium enema and colonoscopy performed back-to-back in the same 580 patients that showed that the sensitivity of the barium enema for detecting polyps >1cm was only 48%. A large retrospective study of patients with CRC in Indiana indicated that the sensitivity of barium enema for detecting CRCs was only 83% (versus 95% for colonoscopy).

#### **Direct Colonoscopy Screening Every 10 Years**

Most gastroenterologists and many patients now prefer the option of direct screening with colonoscopy because it is clearly the most accurate way to accomplish with a single test both of the major objectives of screening. Unfortunately, there are no randomized, controlled trials of direct screening colonoscopy proving efficacy. All of the scientific evidence that supports this option, although compelling, are indirect. The National Polyp Study showed that colonoscopy reduced the incidence of metachronous CRC in adenoma-bearing patients by 76–90%. Case-control studies suggest that screening colonoscopy or FS reduces mortality from cancers located in the examined colon by 50–85%. Lastly, CRC mortality and incidence reductions in the large FOBT trials was largely due to colonoscopy performed in subjects with a positive screening test.

Advantages of screening colonoscopy, in addition to its accuracy and efficacy, are that infrequent (every 10 years) 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 and has an acceptable safety record. The large VA Multicenter Colonoscopy Screening Study performed screening colonoscopy in 3,196 asymptomatic volunteers. 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%. In patients who did not have polyps, there was only one major complication (a cardiovascular event) in 1,492 cases.

Disadvantages of direct colonoscopy screening that still need attention include questions of patient acceptance and colonoscopy capacity. Many healthy people are reluctant to endure the direct and indirect costs of colonoscopy. While the risk is small, complications (especially perforation) may be very serious for a test that detects an advanced neoplasm in only 6–10% of patients. The bowel preparation, sedation, procedure, and recovery time require up to two days lost from normal activity. Lastly, capacity to perform screening colonoscopy on all average-risk people over the age of 50 likely is insufficient, 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 have not yet been screened may be severely lacking. If half the currently available US colonoscopy capacity were

dedicated completely just to screening, it would take 10 years to complete the task and reach a steady state.

### New Emerging CRC Screening Tests

#### Virtual Colonoscopy (CT Colonography)

Virtual colonoscopy (VC) is a relatively new imaging technique that combines rapid helical CT scanning of the abdomen with sophisticated computer software capable of rendering two- and three-dimensional (3-D) images of the large bowel. These images can be rotated for different views, and can even be combined for a complete 3-D view of the colon and rectum that then can be rapidly ‘flown through’, thus simulating conventional optical colonoscopy. VC has several obvious advantages over conventional colonoscopy. Examination time is much shorter and there is no need for intravenous conscious sedation with its attendant cost, inconvenience, and complications. Patients may return to their usual activity soon after their scan. The procedure has very little immediate risk, allows scrutiny of both sides of the bowel wall and of bowel folds, and precisely localizes abnormalities. It can examine the proximal colon when colonoscopy is incomplete, such as when a distal obstructing cancer is present. Disadvantages of VC still include the need for a very thorough bowel cleansing preparation, a somewhat disagreeable gas distention of the colon in order to view segments that otherwise are collapsed or spastic, and some radiation exposure. In addition, these scans currently require appreciable expensive radiologist time to set up and interpret. Lastly, VC is diagnostic only; whenever a clinically important filling defect is found, the patient must undergo a subsequent colonoscopy to biopsy or resect the lesion.

Published studies comparing the accuracy of VC with optical colonoscopy have had mixed results. One recent study by Pickhardt and colleagues, however, may show a promising future of this evolving methodology. In a multi-hospital study involving 1,233 asymptomatic, mostly average-risk adults, six experienced radiologists used multidetector CT scanners and a commercially available CT colonographic 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 corresponding 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 VC in this study for detecting polyps >6mm in diameter was as good as that of conventional colonoscopy. If there is widespread adoption of the advanced methods used in this study, VC

will undoubtedly soon be added to the colorectal cancer guidelines’ menu of acceptable screening options. VC will likely then help provide needed screening capacity in the US, and will improve compliance.

#### DNA-based Stool Tests

Acquired genetic alterations occur in increasing number as adenomatous polyps develop, grow, dedifferentiate, and turn to cancer. Cells containing these DNA changes are sloughed from the polyps and cancers into stools where the DNA can be isolated, amplified, and analyzed. Such DNA analysis has the potential to serve as a very specific stool screening test for the presence of advanced colorectal neoplasia. Not all advanced neoplasia contain the same genetic changes; therefore, an effective screening test must analyze for a panel of multiple DNA markers. Such a screening test, the PreGen-Plus test (Exact Sciences, Marlborough, MA) has now been developed, tested, and marketed. Unfortunately, in two large randomized trials reported to date, the sensitivity of the PreGen-Plus test for detecting CRC was only 31–52%. In addition, the initially marketed tests were relatively expensive. The manufacturer is optimistic, however, that by adding additional DNA markers to the test panel and by improving the analysis methodology, a more sensitive and less costly screening test soon will be available. Potential uses of an improved test include average-risk screening, screening of high-risk patients, or combining DNA stool testing with other forms of screening to decrease the chance of missing a clinically important colorectal neoplasm. Combined screening might be beneficial even if the sensitivity of the DNA test remains relatively low, because this form of testing is highly specific (few false-positives).

### Summary and Conclusions

A number of acceptable CRC screening options now are 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 should be considered when designing a screening strategy. At present, the 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. It has often been stated that “the best screening test is the one the patient actually will do” and “the only unacceptable option is not to screen.” ■

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