

# Screening for Colorectal Cancer in Adults at Average Risk: A Summary of the Evidence for the U.S. Preventive Services Task Force

Michael Pignone, MD, MPH; Melissa Rich, MD; Steven M. Teutsch, MD, MPH; Alfred O. Berg, MD, MPH; and Kathleen N. Lohr, PhD

**Purpose:** To assess the effectiveness of different colorectal cancer screening tests for adults at average risk.

**Data Sources:** Recent systematic reviews; *Guide to Clinical Preventive Services*, 2nd edition; and focused searches of MEDLINE from 1966 through September 2001. The authors also conducted hand searches, reviewed bibliographies, and consulted context experts to ensure completeness.

**Study Selection:** When available, the most recent high-quality systematic review was used to identify relevant articles. This review was then supplemented with a MEDLINE search for more recent articles.

**Data Extraction:** One reviewer abstracted information from the final set of studies into evidence tables, and a second reviewer checked the tables for accuracy. Discrepancies were resolved by consensus.

**Data Synthesis:** For average-risk adults older than 50 years of age, evidence from multiple well-conducted randomized trials

supported the effectiveness of fecal occult blood testing in reducing colorectal cancer incidence and mortality rates compared with no screening. Data from well-conducted case-control studies supported the effectiveness of sigmoidoscopy and possibly colonoscopy in reducing colon cancer incidence and mortality rates. A nonrandomized, controlled trial examining colorectal cancer mortality rates and randomized trials examining diagnostic yield supported the use of fecal occult blood testing plus sigmoidoscopy. The effectiveness of barium enema is unclear. Data are insufficient to support a definitive determination of the most effective screening strategy.

**Conclusions:** Colorectal cancer screening reduces death from colorectal cancer and can decrease the incidence of disease through removal of adenomatous polyps. Several available screening options seem to be effective, but the single best screening approach cannot be determined because data are insufficient.

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The U.S. Preventive Services Task Force (USPSTF) last considered its recommendations regarding colorectal cancer screening in 1996 (1). At that time, the available evidence included one randomized, controlled trial showing that fecal occult blood testing (FOBT) reduced mortality rates (2); a case-control study showing that persons having sigmoidoscopy were less likely to die of colorectal cancer (3); and one nonrandomized, controlled trial of FOBT combined with rigid sigmoidoscopy that suggested some benefit from the two tests together (4). On the basis of this evidence, the USPSTF recommended screening for colorectal cancer with FOBT, sigmoidoscopy, or both (a grade B recommendation) but did not recommend for or against other means of screening (digital rectal examination, double-contrast barium enema, or colonoscopy) because the available evidence was insufficient. (See the companion article in this issue for a description of the USPSTF classification of recommendations.) The Task Force also recommended that FOBT be performed yearly but did not specify an interval for sigmoidoscopy.

Since 1996, important new evidence has emerged regarding the effectiveness of colorectal cancer screening. We performed an updated systematic review to help the USPSTF evaluate new evidence on the effectiveness of different colorectal cancer screening tests as it updated its previous recommendation. We examined the evidence concerning the effectiveness of screening in adults older than 50 years of age who are at average risk for colorectal cancer. The effectiveness, accuracy, and adverse effects of digital rectal examination (with or without a single office-based FOBT),

traditional three-card FOBT (hereafter referred to as FOBT), sigmoidoscopy, FOBT with sigmoidoscopy, double-contrast barium enema, and colonoscopy were examined. Other tests or combinations of tests have not been well evaluated and are not discussed here. A more detailed report of our review can be found on the Web site of the U.S. Agency for Healthcare Research and Quality ([www.ahrq.gov/clinic/uspstfix.htm](http://www.ahrq.gov/clinic/uspstfix.htm)) (5). The USPSTF's updated recommendations for colorectal cancer screening recommendations can be found in the companion article in this issue (6).

## METHODS

To identify the relevant literature, we used the *Guide to Clinical Preventive Services*, 2nd edition (1); existing systematic reviews; focused MEDLINE literature searches from 1966 through September 2001; and hand searches of key articles. When available, systematic reviews were used to identify older relevant studies. Literature searches were used to identify newer studies. Detailed descriptions of the literature searches can be found in the Appendix (available at [www.annals.org](http://www.annals.org)).

To identify relevant studies, one reviewer examined the abstracts of the articles identified in the initial search. A second reviewer examined the excluded articles. Disagreements about inclusion were resolved by consensus. Two reviewers examined the full text of the remaining articles to determine final eligibility. We used evidence from randomized, controlled trials or observational studies that measured patient outcomes, particularly changes in colorectal

cancer mortality rates and incidence. When such data were not available, we included indirect information on the accuracy of screening tests. Details about study inclusion are available in the Appendix (available at [www.annals.org](http://www.annals.org)). We rated the quality of the included articles by using the criteria developed by the USPSTF Methods group (7), which are described in the accompanying article in this issue (6). We used the final set of eligible articles to create evidence tables and a draft report. The draft report was extensively peer reviewed by the USPSTF, experts in the field, governmental agencies, and nongovernmental organizations.

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This evidence report was funded through a contract to the Research Triangle Institute–University of North Carolina Evidence-based Practice Center from the Agency for Healthcare Research and Quality. Staff of the funding source contributed to the study design, reviewed draft and final manuscripts, and made editing suggestions.

## RESULTS

Our general search identified 719 articles published since 1995 on colorectal cancer screening. We retained 19 of these articles in our final document. Specific searches from 1966 through 2001 for articles about the accuracy of barium enema and complications of screening yielded 621 and 839 articles, respectively. After review, we retained 13 articles about barium enema and 19 articles about complications of screening. We also included 15 articles identified from the previous USPSTF review or from hand searches of other articles. Table 1 summarizes our findings.

### Digital Rectal Examination

#### Effectiveness

A case–control study from the Kaiser Permanente Medical Care Program in northern California examined the effect of screening with digital rectal examination on death from colorectal cancer (8). The investigators identified patients 45 years of age and older who died of distal rectal cancer between 1971 and 1986 and selected matched controls from the patient membership. They examined medical records to determine whether the patients and controls had undergone screening digital rectal examination within a year of cancer diagnosis. Investigators found no difference between groups after controlling for potential confounders, although the confidence interval was wide (odds ratio, 0.96 [95% CI, 0.56 to 1.7]).

#### Accuracy

The potential sensitivity of screening digital rectal examination is low; fewer than 10% of cases of colorectal cancer are within reach of the examining finger (28). The specificity of positive results on digital rectal examination has not been examined in outpatients at average risk for colorectal cancer.

### In-Office Fecal Occult Blood Testing after Digital Rectal Examination

#### Effectiveness

No studies have examined the effect of a single in-office FOBT after digital rectal examination on colorectal cancer incidence or mortality rates.

#### Accuracy

A single in-office FOBT is likely to be less sensitive than the traditional three-card FOBT performed at home because only one sample is taken (9). In a large study from Japan, Yamamoto and Nakama (10) found that the first test card detected only 58% of cancer found after a three-card test. The single in-office FOBT may be less specific than a properly performed three-card FOBT because the in-office test does not allow degradation of the vegetable peroxidases that sometimes produce false-positive results (9). In addition, the potential trauma from the in-office examination itself may also result in lower specificity (9). Two studies of poor to fair quality that used existing data to retrospectively compare the specificity of the single in-office FOBT and the three-card home FOBT (11, 12) found little difference in specificity between the two groups. However, the validity of these studies is limited because neither could ensure that similar patient samples received each test.

### Fecal Occult Blood Testing

#### Effectiveness

In addition to an older randomized trial performed in Minnesota (2), which was available to the USPSTF in 1996, two newer randomized, controlled trials have examined the effectiveness of biennial FOBT for reducing death from colorectal cancer (13, 14). These more recent trials, from the United Kingdom (13) and Denmark (14), found 15% and 18% reductions in mortality rates, respectively, with biennial testing. Neither trial used slides that were rehydrated before development (Table 2).

The Minnesota trial compared annual and biennial testing with no screening and rehydrated most test cards (83%). Cumulative colorectal cancer mortality rates after 18 years of follow-up were 33% (CI, 17% to 49%) lower among persons randomly assigned to undergo annual FOBT than in a control group that was not offered screening (absolute rates, 9.5 deaths per 1000 participants vs. 14.1 deaths per 1000 participants; difference, 4.6 deaths per 1000 participants) (2). Biennial screening, which did not show a reduction in mortality rates at 13-year follow-up, produced a 21% (CI, 3% to 38%) reduction in mortality rate at 18 years (15). The 18-year follow-up also showed that the incidence of colorectal cancer decreased by 20% (CI, 10% to 30%) and 17% (CI, 6% to 27%) in the groups screened annually and biennially, respectively, compared with controls (16). Because of differences in hydration, test frequency, duration, and effect size, the results of these trials could not be combined in a meta-analysis.

Table 1. Characteristics of Screening Tests for Colorectal Cancer\*

Screening Strategy for CRC	Effectiveness in Reducing Incidence of and Death from CRC	Evidence Graded†	Ability To Detect Cancer	Evidence Graded†
Digital rectal examination	Case-control study found no difference in mortality rates; OR, 0.96 [0.56–1.7] (8)	Level II—poor	Pathologic data suggest <10% of CRC is within reach of examining finger	
Office FOBT (one card)	Unknown		Only 58% of cancer cases are detected on the first of three cards, suggesting lower sensitivity than three-card testing (10)	Level III—fair
Home FOBT (three cards), unrehydrated	Biennial testing: 2 trials found mortality reductions of 15% [1%–26%] (13) and 18% [1%–32%] (14)	Level I—good	One-time sensitivity 30%–40% Unrehydrated FOBT finds about 25% of cancer cases (9)	
Home FOBT (three cards), rehydrated	Annual testing: 33% [13–50] reduction in mortality (2); 20% [10%–30%] reduction in cancer incidence (16) Biennial testing: 21% [3%–38%] reduction in mortality (15); 17% [6%–27%] reduction in cancer incidence (16)	Level I—good	Single-test accuracy 50% [30%–70%] for cancer, 24% [19%–29%] for advanced neoplasms (17) Over 13 years, rehydrated FOBT finds 50% of cancer cases (2)	Level III—good
Sigmoidoscopy	Small RCT found decreased CRC mortality rates with screening; RR, 0.50 [0.10–2.72] (18)	Level I—fair	One-time screening detects 68%–78% of advanced neoplasia (17, 20)	Level III—good
	Case-control studies suggest a 59% [31%–75%] reduction in mortality rate within reach of scope (3)	Level II—good		
Combined FOBT and sigmoidoscopy	Nonrandomized trial found a 43% reduction in mortality rate when FOBT was added to rigid sigmoidoscopy; RR, 0.57 [0.56–1.19] (4)	Level I—fair to poor	One-time screening detects 76% of advanced neoplasia (17) Increased yield when sigmoidoscopy is added to FOBT (21–23)	Level III—good
Double-contrast barium enema	Unknown		Sensitivity of one-time test for cancer or large polyps 48% [24%–67%] (24)	Level III—fair
Colonoscopy	Case-control study found an OR of 0.43 [0.30–0.63] for death from CRC; CRC incidence decreased by 40%–60% (26)	Level II—fair	Sensitivity for large adenomas >90%; sensitivity for cancer probably higher (27)	Level III—good

\* CRC = colorectal cancer; FOBT = fecal occult blood test; NA = not applicable (see text); OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk. Numbers in square brackets are 95% CIs; numbers in parentheses are reference numbers.

† Level I = evidence from one or more controlled trials; level II = evidence from cohort or case-control studies; level III = evidence from diagnostic accuracy studies or case series. For each level, the investigators have assigned a quality score based on methods described in reference 7.

**Accuracy**

A systematic review from 1997 found that the sensitivity of a single unrehydrated FOBT for cancer was approximately 40%; its specificity seems to range from 96% to 98%. Rehydration was found to increase sensitivity to between 50% and 60% but decreased specificity to 90% (9, 29). In a recent study, Lieberman and colleagues (17) found that the sensitivity of rehydrated FOBT for cancer was 50% (CI, 30% to 70%). For advanced neoplasia (cancer and polyps that are large, villous, or dysplastic), sensitivity was 24% (CI, 19% to 29%) and specificity was 94% (CI, 93% to 95%).

In the annual screening arm of the 13-year Minnesota trial, which primarily used rehydrated test cards and had a high initial rate of participation (approximately 90%), 49% of patients who developed colorectal cancer were identified through screening. Thirty-eight percent of all patients had had at least one colonoscopy (2). Biennial screening detected 39% of patients with cancer in the intervention group, and 28% of patients required colonoscopy. Compared with the Minnesota trial, the two European trials were population-based, lasted 8 to 10 years, used only biennial testing, and had lower participation rates (60% to 70% of patients completed the first screen-

ing). Screening detected 27% of patients in the intervention group who developed colorectal cancer, and only 5% of patients had colonoscopy (13, 14).

**Adverse Effects**

Fecal occult blood testing itself has few adverse effects, but false-positive results lead to further tests, such as colonoscopy, during which adverse effects may occur. The specific adverse effects of colonoscopy are described later in this review. Theoretically, a previously negative result on FOBT could falsely reassure patients and lead to delayed response to the development of colorectal symptoms if cancer were to develop, but this concern has not been evaluated empirically.

**Sigmoidoscopy**

**Effectiveness**

Thiis-Evensen and coworkers (18) performed a small randomized trial of sigmoidoscopy screening in Norway. In 1983, 799 men and women who were 50 to 59 years of age and were drawn from a population registry were randomly assigned to receive screening flexible sigmoidoscopy (400 patients) or no screening (399 patients). Eighty-one percent of those offered flexible sigmoidoscopy accepted.

Table 1—Continued

Chance of False-Positive Results	Evidence Graded	Adverse Effects	Evidence Graded
Unknown		No direct adverse effects known	
Little difference compared with three-card testing (11, 12)	Level III—poor	No direct adverse effects known	
Single-test specificity 96%–98% 5%–10% of patients will require colonoscopy over 10 years of biennial testing (9)	Level III—good	No direct adverse effects known	
Single-test specificity 90% Over 10 to 13 years, 38% of patients tested annually and 28% tested biennially with rehydrated FOBT required colonoscopy (2)	Level III—good	Inconvenience, adverse events resulting from follow-up tests after positive results	
NA		Perforation rate for diagnostic examinations <1 in 10 000; bleeding in 2.5% of patients after diagnostic studies, 5.5% after procedures with polypectomy (19)	Level III—good
NA		Sum of adverse effects from each test alone	
One-time specificity, 85% [82%–88%] (24)	Level III—fair	Perforation rate 1 in 25 000 in a study with screening and symptomatic patients (25)	Level III—poor
NA		Diagnostic procedures: perforation rate 1 in 2000 Polypectomy: perforation rate 1 in 500–1000; bleeding rate 1 in 100–500; mortality rate 1 in 20 000 (5)	Level III—fair to good

All patients found to have polyps on sigmoidoscopy underwent immediate diagnostic colonoscopy and had surveillance examinations 2 and 6 years later. Over the 13 years of the trial, two cases of colorectal cancer were diagnosed in the intervention group and 10 were diagnosed in the control group (relative risk for colorectal cancer, 0.2 [CI, 0.03 to 0.95]). One person who was assigned to the intervention group but never had sigmoidoscopy died of colorectal cancer, as did three controls (relative risk, 0.50 [CI, 0.10 to 2.72]). Overall mortality rate was higher in the intervention group than in the control group (14% vs. 9%; relative risk, 1.57 [CI, 1.03 to 2.40]), mostly because of an excess of cardiovascular deaths. No clear relationship emerged between excess deaths and any procedure-related complications.

Two ongoing randomized trials using flexible sigmoidoscopy will report their initial results within 5 years. One trial in the United Kingdom is examining the effect of screening with sigmoidoscopy once per lifetime (19), and a second trial in the United States is examining sigmoidoscopy screening every 5 years in patients who are assumed to be receiving FOBT as part of usual care (30).

Two older, well-designed case-control studies that provide other important information on the effectiveness of sigmoidoscopy screening were available to the USPSTF in 1996. Using data from the Kaiser Permanente Medical

Care Program in northern California, Selby and associates (3) found that rigid sigmoidoscopy had been performed in 9% of persons who died of colorectal cancer occurring within 20 cm of the anus and in 24% of persons who did not die of cancer occurring within 20 cm of the anus. The adjusted odds ratio of 0.41 (CI, 0.25 to 0.69) suggested that sigmoidoscopy screening reduced the risk for death by 59% for cancer within reach of the rigid sigmoidoscope.

The investigators noted that the adjusted odds ratio was 0.96 for proximal colon cancer that was beyond the reach of the sigmoidoscope (3). This finding added support to the hypothesis that the reduced risk for death from cancer within reach of the rigid sigmoidoscope could be attributed to screening rather than to confounding factors. The risk reduction associated with sigmoidoscopy screening did not diminish during the first 9 to 10 years after the test was performed. The study by Selby and associates mostly used rigid sigmoidoscopes. However, in another case-control study supporting the effectiveness of sigmoidoscopy, 75% of the examinations were performed with a flexible instrument (31).

**Accuracy**

Two recent studies have examined the sensitivity of screening sigmoidoscopy for cancer or advanced adenomas

Table 2. Trials of Fecal Occult Blood Testing

Trial Characteristics	Trial (Reference)		
	Minnesota (2)	United Kingdom (13)	Denmark (14)
Frequency of testing	Annual and biennial	Biennial	Biennial
Participants, <i>n</i>	>45 000 men and women	>150 000 men and women	>60 000 men and women
Age, <i>y</i>	50–80	45–74	45–74
Duration of follow-up, <i>y</i>	18 (annual and biennial)	8	10
Hydration of slides	Yes (83%)	No	No
Participation rate, %*	90 (annual and biennial)	60	67
Patients requiring colonoscopy, %	38 (annual); 28 (biennial)	5	5
Positive predictive value, %	1.9 (annual); 2.7 (biennial)†	10–12	8–18
Relative risk reduction for death from colorectal cancer [95% CI], %	33 [17–49] (annual); 21 [3–38] (biennial)	15 [1–26]	18 [1–32]
Absolute risk reduction for death from colorectal cancer per 1000 participants	4.6 (annual); 2.9 (biennial)	0.8	1.4

\* Participation was defined as completion of at least one test.  
 † Mostly rehydrated slides (83%).

in healthy patients, using colonoscopy as the criterion standard. They found that sigmoidoscopy would identify 70% to 80% of patients with advanced adenomas or cancer (17, 20). Sigmoidoscopy can produce false-positive results by detecting hyperplastic polyps that do not have malignant potential or adenomatous polyps that are unlikely to become malignant during the patient's lifetime. Because studies of diagnostic accuracy cannot measure whether small or large adenomas that are identified and removed would have become cancer, it is not possible to classify such findings in terms of accuracy in detecting cancer. In practice, most investigators consider all adenomas to be "true positives" regardless of whether they would ever progress to cancer. Comparison of the specificity of sigmoidoscopy with that of nonendoscopic screening methods, such as FOBT and barium enema, is therefore difficult.

**Adverse Effects**

Estimates of bowel perforations from sigmoidoscopy have generally been in the range of 1 to 2 or fewer per 10 000 examinations, particularly since the introduction of the flexible sigmoidoscope (32). Atkin and colleagues (19) recently reported initial results from a trial of sigmoidoscopy screening in which experienced endoscopists performed sigmoidoscopy in 1235 asymptomatic adults 55 to 64 years of age. Two hundred eighty-eight patients had polyps removed during the examination. Adverse effects, including pain, anxiety, or any degree of bleeding, were assessed by a written questionnaire immediately after the test and by a mailed questionnaire 3 months later. Of all patients, 3.2% (40 of 1235) reported bleeding, 16 of 288 (5.5%) after polypectomy and 24 of 947 (2.5%) after diagnostic studies. One patient required hospital admission, and no patients required a transfusion. Fourteen percent of patients reported moderate pain, and 0.4% reported severe pain. More than 25% of patients reported gas or flatus. No

perforations were reported, but one patient died of peritonitis after a complicated open surgical procedure to remove a severely dysplastic adenoma. A recent study of endoscopic complications from the Mayo Clinic in Arizona identified two perforations in 49 501 sigmoidoscopy procedures (33).

**Fecal Occult Blood Test and Sigmoidoscopy Effectiveness**

Currently, no randomized trials that examine death from colorectal cancer as an end point have compared FOBT alone or sigmoidoscopy alone with a strategy of performing both tests. In 1992, Winawer and coworkers (4) conducted a nonrandomized trial of more than 12 000 first-time attendees at a preventive health clinic in New York. This trial was available to the USPSTF in 1996. The control group received rigid sigmoidoscopy at the first visit, and all study participants were invited to return for annual reexamination with rigid sigmoidoscopy. Patients in the intervention group received rigid sigmoidoscopy and were also asked to complete Hemoccult (Beckman Coulter, Fullerton, California) FOBT cards. Patients who had adenomas larger than 3 mm on sigmoidoscopy or who had positive results on FOBT underwent full colonic examination with barium enema and colonoscopy. The control group received rigid sigmoidoscopy at the first visit, and participants were invited to return for annual reexamination. Few patients continued to participate after the first examination (20% had FOBT at year 2, 15% at year 3). Incidence of colorectal cancer and death were assessed over a 9-year period, and follow-up data were available for 97% of patients.

Demographic and clinical data suggest that the groups were comparable, despite the absence of randomization. More cases of colorectal cancer were detected on initial examination in intervention patients than in control patients (4.5 per 1000 participants vs. 2.5 per 1000 partici-

pants). Incidence rates (cancer detected after the initial examination) were similar between groups (0.9 per 1000 person-years in each group). Incidence of death from colorectal cancer was 0.36 per 1000 patient-years in the intervention group and 0.63 per 1000 patient-years among controls (relative risk, 0.56 [CI, 0.25 to 1.19]).

Fecal occult blood testing combined with rigid sigmoidoscopy seems to increase the yield of initial screening and may reduce mortality rates. Because rigid sigmoidoscopy is no longer used for screening, the generalizability of these results to the use of FOBT plus flexible sigmoidoscopy is unclear. Whether the incremental yield of combined screening will change after additional rounds of testing also remains uncertain.

### Accuracy

Recent randomized trials from Europe examined the additional diagnostic yield of performing sigmoidoscopy plus FOBT at one point in time for patients who were not already part of an ongoing screening program (21–23). In each study, adding sigmoidoscopy to FOBT increased the identification of significant adenomas or cancer by a factor of two or more. Adding FOBT to sigmoidoscopy did not seem to identify any additional significant lesions. Winawer and coworkers (4), however, found an increased yield from adding FOBT to rigid sigmoidoscopy. In each study, data were limited to a single round of testing. The additional yield of this strategy may be lower after the first round of testing, but the impact of this strategy on mortality rates has not been fully evaluated.

### Adverse Effects

The adverse effects of FOBT plus sigmoidoscopy are equal to the adverse effects of each test alone.

### Double-Contrast Barium Enema

#### Effectiveness

We identified no published studies that examined the effectiveness of double-contrast barium enema in reducing incidence of or death from colorectal cancer. Several studies have examined the accuracy of double-contrast barium enema for diagnosing colorectal cancer or adenomatous polyps (24, 34–43). Most are of methodologically poor quality, however, because they examined patients with symptoms or did not prospectively collect blinded data.

The National Polyp Study is a randomized trial of different intervals of surveillance after polypectomy (examinations at 1 and 3 years vs. at 3 years only). In a substudy of this trial, Winawer and colleagues (24) compared the accuracy of double-contrast barium enema with that of colonoscopy. The sensitivity of double-contrast barium enema was 32% (CI, 25% to 39%) for polyps smaller than 0.5 cm; 53% (CI, 40% to 66%) for polyps 0.6 to 1 cm; and 48% (CI, 24% to 67%) for polyps larger than 1 cm, including two cases of cancerous polyps. Results of double-contrast barium enema were positive in 83 of 470 patients

in whom colonoscopy detected no polyps (specificity, 85% [CI, 82% to 88%]).

Winawer and colleagues (24) examined patients who previously had colonoscopy and removal of all polyps. Their results, therefore, may have limited generalizability for screening because screening largely involves persons who have not had recent colonoscopic examination and polypectomy and therefore may be more likely to have large polyps or tumors. However, the low sensitivity for large polyps and tumors reported by Winawer and colleagues is cause for concern and may limit the potential effectiveness of screening with double-contrast barium enema.

### Adverse Effects

The estimated risk for perforation during barium enema is low. Kewenter and Brevinge (44) found that no perforations or other complications occurred among 1987 screening patients undergoing barium enema as part of a screening work-up. Blakeborough and associates (25) surveyed radiologists in the United Kingdom about complications of barium enema during a 3-year period (1992 through 1994). All examinations were included, regardless of the indication for the procedure. Important complications of any type occurred in 1 in 10 000 examinations. Perforation occurred in 1 of 25 000 examinations, and death occurred in 1 in 55 000 examinations, although it is not clear whether all deaths were procedure related.

### Colonoscopy

#### Effectiveness

The ability of colonoscopy to prevent colorectal cancer or death has not been measured in a screening trial. The National Polyp Study estimated that 76% to 90% of cancer could be prevented by regular colonoscopic surveillance examinations, based on comparison with historic controls (45). However, these results should be interpreted with caution. The comparison groups were not from the same underlying population, which could introduce bias. In addition, all trial participants had polyps detected and removed, limiting generalizability of the results to the average screening population.

Müller and Sonnenberg (26), in a case-control study at Veterans Affairs hospitals, found that patients with a diagnosis of colorectal cancer were less likely to have had previous colonoscopy. The odds ratios for disease incidence were 0.47 (CI, 0.37 to 0.58) for colon cancer and 0.61 (CI, 0.48 to 0.77) for rectal cancer. For death from colorectal cancer, the odds ratio was also lower for patients with previous colonoscopy (odds ratio, 0.43 [CI, 0.30 to 0.63]).

### Accuracy

Because colonoscopy is commonly used as the criterion standard examination, it is difficult to calculate its sensitivity. Using tandem colonoscopic examinations, Rex

and colleagues (27) found single-test sensitivity to be 90% for large adenomas and 75% for small adenomas (<1 cm); sensitivity for cancer probably exceeds 90%.

Recent identification of flat lesions that can be missed on regular colonoscopy suggests that some histologic variants do not progress through the typical adenoma–carcinoma development sequence and thus may not be easily detectable in the precancerous phase (46). If flat lesions account for 10% of all adenomas, sensitivity of all endoscopic screening methods may be lower than previously thought.

The specificity of colonoscopy with biopsy is generally reported to be 99% or 100%, but this assumes that all detected adenomas represent true-positive results. As with sigmoidoscopy, most detected adenomas, especially small adenomas, will never develop into cancer. If detection of an adenoma that will not become cancer is considered a false-positive result that subjects a patient to risk without benefit, then the actual specificity of colonoscopy would be much lower.

#### Adverse Effects

Colonoscopy, which uses sedation and requires skilled support personnel, is more expensive and has a higher risk for procedural complications than other screening tests, particularly when polypectomy is performed. Use of conscious sedation adds the risk for complications attributable to the sedative agent. In our systematic review of studies examining the principal complications of colonoscopy (5), we focused on hemorrhage and perforation but noted the less frequent complications of death, infections, sedation-related events, and chemical colitis. Two recent studies examined the incidence of complications from colonoscopy performed in screening populations. Lieberman and associates (17), in a study in patients in Veterans Affairs medical centers, found that 10 of 3121 patients (0.3%) had major complications during or immediately after the procedures. Of these 10 patients, 6 had bleeding that required hospitalization and 1 each had a stroke, myocardial infarction, Fournier gangrene, and thrombophlebitis. Three other patients died within 1 month, probably of causes unrelated to the procedure. In a study of employees of a large corporation, Imperiale and coworkers (20) found that among 1994 persons 50 years of age and older who underwent colonoscopy, 1 (0.05%) had a perforation that did not require surgery and 3 (0.15%) had bleeding that required emergency department visits but not admission or surgery.

Apart from these two screening studies, most of the studies examining colonoscopy complications are retrospective reviews of endoscopy records from U.S. university hospitals that recorded only immediate complications and included a mixture of screening and diagnostic procedures (17, 20, 33, 47–61). A prospective study that also included a patient questionnaire administered 10 days after the pro-

cedure identified several additional important complications that occurred outside the hospital, suggesting that hospital record review alone may underestimate actual complication rates (47).

Despite these limitations, these studies provide a useful approximation of the complication rates that can be expected from colonoscopy. For diagnostic procedures, perforation rates were low (0.029% to 0.61%). Bleeding was not reported in enough studies to generate an estimate of its frequency. For therapeutic procedures, complication rates were higher (perforations, 0.07% to 0.72%; bleeding, 0.2% to 2.67%). Deaths occurred infrequently; reported rates ranged from 1 in 30 000 persons to 1 in 3000 persons. Mortality rates were higher in studies that included older patients and more symptomatic patients. The rate of screening-related death may be on the lower end of this range; one cost-effectiveness analysis estimated it to be 1 per 20 000 patients (29). Other clinically relevant complications were reported too infrequently and measured too inconsistently to allow accurate estimation of their true incidence.

#### DISCUSSION

Our systematic review supports the effectiveness of screening as a means of reducing death from colorectal cancer. For biennial FOBT, three high-quality randomized, controlled trials have shown disease-specific reductions in mortality rate of 15% to 21% over 8 to 13 years. Annual FOBT with rehydrated slides seems to be more effective in reducing mortality rates (33% in one trial). Case–control studies have shown that sigmoidoscopy and possibly colonoscopy are also associated with decreased death from colorectal cancer. The combined strategy of FOBT and sigmoidoscopy was supported by one nonrandomized trial that showed a borderline statistically significant reduction in mortality rates (43%) when FOBT was added to rigid sigmoidoscopy (4). This strategy was also supported by indirect evidence showing increased yield with both tests compared with FOBT alone. Double-contrast barium enema has not been studied as extensively as other screening methods; further data are required in screening populations.

Although strong direct and indirect evidence supports colorectal cancer screening, no trials have directly compared different screening strategies by using colorectal cancer incidence or mortality rates as the end point of interest. Some groups believe that recent evidence showing the superior single-test accuracy of colonoscopy proves its broader superiority and have recommended it as the procedure of choice for screening. However, these analyses have not always considered differences in yield over time, complications, and real-world performance, which may not always favor colonoscopy (62, 63). One solution to these problems would be to perform a trial of colonoscopy, but such a trial would be expensive, particularly if colonoscopy

were compared with other screening methods rather than with no screening, and would require many years of follow-up. In the face of good general evidence supporting screening but uncertainty about the most effective screening method, providers and patients may benefit from discussing pros and cons and from incorporating patients' preferences into decisions about how to screen (64).

Several areas of colorectal cancer screening and prevention warrant additional research. There is a critical need to learn more about adherence to screening among informed patients. Furthermore, we need better data on the real-world complication rates of colonoscopic screening and polypectomy, including whether complications become more or less likely as procedure volume increases. Double-contrast barium enema should be studied in a screening population. The accuracy of novel screening techniques, including virtual colonoscopy and genetic stool tests (or other novel noninvasive tests), should be evaluated in screening populations.

Additional means of prevention, including chemopreventive agents (such as nonsteroidal anti-inflammatory drugs, calcium, or estrogen), also warrant further study. Behavioral factors, including physical activity, dietary fat intake, dietary fiber intake, and fruit and vegetable consumption, seem to be related to colorectal cancer incidence. Further research would clarify whether these relationships are causal or the result of uncontrolled confounding.

Despite its apparent effectiveness, colorectal cancer screening is currently underused by age-eligible adults because of patient-, provider-, and system-specific barriers (65). Effective colon cancer screening requires ongoing efforts to ensure test ordering and adherence. Screening with FOBT, for example, may require offering annual testing to 500 to 1000 people for 10 years to prevent one death from colorectal cancer (2). Although this level of effort may seem inefficient or low in yield, the potential benefit is large and the costs per person are small. To achieve high rates of screening in real-world settings rather than in trials, which focused strictly on one aspect of preventive care, colorectal cancer screening must be integrated with other care needs, including other preventive services.

Several strategies have been shown to be effective in raising screening rates in primary care settings over the short term, including reminder systems, patient decision aids, and special screening clinics (66). Further research is needed to determine whether such systems can maintain their effect over time and to identify novel means of reaching persons at risk who currently are not served or are underserved by the existing health care system.

## APPENDIX: SEARCH STRATEGIES

To update the evidence on screening for colorectal cancer, we performed three separate literature searches using MEDLINE: one general update from January 1995 to December 2001 and two focused searches for evidence related to barium enema and

complications of screening that used search dates from 1966 through December 2001. All searches were limited to "human" subjects.

For the general search, we combined the MeSH headings "colorectal neoplasms" or "occult blood" or "sigmoidoscopy" or "colonoscopy" with the term *mass screening*. This search produced 719 results, 19 of which we retained in the final document. To identify articles on the use of barium enema, we combined the exploded MeSH terms "colorectal neoplasms" and "barium sulfate" and "enema," which yielded 621 results. We retained 13 articles in our final data set. For studies about the complications of screening, we combined the exploded MeSH terms "colonoscopy/ae [adverse effects] and sigmoidoscopy/ae [adverse effects]," "intestinal perforation," "intraoperative complications," "postoperative complications," or "gastrointestinal hemorrhage," with a search combining the test names and the keyword "complications." Our search yielded 839 articles, 16 of which we retained. In addition to these searches, we used peer review and hand searching of the bibliographies of included articles and other systematic reviews, as well as articles from the 1996 document. This yielded an additional 15 references for our final document.

Appendix Table. Eligibility Criteria\*

Test	Type of Studies Included
Digital rectal examination	Diagnostic accuracy studies, observational studies
FOBT	RCTs
Sigmoidoscopy	RCTs, observational studies
FOBT plus sigmoidoscopy	Controlled trials, observational studies, diagnostic accuracy studies
Barium enema	Diagnostic accuracy studies
Colonoscopy	Observational studies, diagnostic accuracy studies
Adverse effects (any test)	Case series, observational studies, RCTs

\* FOBT = fecal occult blood test; RCT = randomized, controlled trial.

We developed eligibility criteria to guide decisions about inclusion of articles. In general, we sought to identify and include the highest quality evidence available. The Appendix Table shows the criteria for each specific topic.

From University of North Carolina, Chapel Hill, and Research Triangle Institute, Research Triangle Park, North Carolina; Merck & Co., Inc., West Point, Pennsylvania; and University of Washington, Seattle, Washington.

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Current author addresses are available at [www.annals.org](http://www.annals.org).

**Current Author Addresses:** Dr. Pignone: University of North Carolina at Chapel Hill, Department of Medicine and Cecil Sheps Center for Health Services Research, 5039 Old Clinic Building, CB #7110, Chapel Hill, NC 27599.

Dr. Teutsch: Merck & Co., Inc., 770 Sumneytown Pike, West Point, PA WP399-169.

Dr. Rich: University of North Carolina at Chapel Hill, 724 Burnett Womack, CB 7080, Chapel Hill, NC 27599.

Dr. Berg: University of Washington, Department of Family Medicine, C-408 Health Sciences, Box 356390, Seattle, WA 98195.

Dr. Lohr: Research Triangle Institute, 3040 Cornwallis Road, Research Triangle Park, NC 27709-2194.

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