Colorectal Cancer Screening
Scientific Review

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Context Screening for colorectal cancer clearly reduces colorectal cancer mortality, yet many eligible adults remain unscreened. Several screening tests are available, and various professional organizations have differing recommendations on which screening test to use. Clinicians are challenged to ensure that eligible patients undergo colorectal cancer screening and to guide patients in choosing what tests to receive.

Objective To critically assess the evidence for use of the available colorectal cancer screening tests, including fecal occult blood tests, sigmoidoscopy, colonoscopy, double-contrast barium enema, and newer tests, such as virtual colonoscopy and stool-based molecular screening.

Data Sources All relevant English-language articles were identified using PubMed (January 1966-August 2002), published meta-analyses, reference lists of key articles, and expert consultation.

Data Extraction Studies that evaluated colorectal cancer screening in healthy individuals and assessed clinical outcomes were included. Evidence from randomized controlled trials was considered to be of highest quality, followed by observational evidence. Diagnostic accuracy studies were evaluated when randomized controlled trials and observational studies were not available or did not provide adequate evidence. Studies were excluded if they did not evaluate colorectal screening tests and if they did not evaluate average-risk individuals.

Data Synthesis Randomized controlled trials have shown that fecal occult blood testing can reduce colorectal cancer incidence and mortality. Case-control studies have shown that sigmoidoscopy is associated with a reduction in mortality, and observational studies suggest colonoscopy is effective as well. Combining fecal occult blood testing and sigmoidoscopy may decrease mortality and can increase diagnostic yield.

Conclusion The recommendation that all men and women aged 50 years or older undergo screening for colorectal cancer is supported by a large body of direct and indirect evidence. At present, the available evidence does not currently support choosing one test over another.

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EVIDENCE FOR COLORECTAL CANCER SCREENING

Death from colorectal cancer can be prevented by the detection of early-stage disease that has not metastasized. The disease itself can be prevented by the detection and removal of colorectal adenomas, from which greater than 95% of cancers arise. The majority of these adenomas are polyloid growths. But as many as 20% to 30% of adenomas are flat or depressed, which make them more difficult to detect and remove.

The optimal means to prevent colorectal cancer remain uncertain. Evidence for the efficacy of the commonly practiced colorectal cancer screening tests are reviewed.

Fecal occult blood testing had 3 RCTs and sigmoidoscopy had 1 randomized trial and 3 case-control studies that assessed mortality. No RCTs were found for colonoscopy, but 4 observational studies were identified in which asymptomatic individuals underwent colonoscopy and in which adenoma and cancer incidences were assessed. Combined FOBT and sigmoidoscopy screening had 5 trials that assessed clinical outcomes: 1 trial assessed mortality, and the other trials assessed incidence of polyps and/or cancer. Finally, for double-contrast barium enema, no RCTs or observational studies were identified that assessed clinical effectiveness and 4 diagnostic accuracy studies were identified and evaluated.

Fecal Occult Blood Testing

Evidence of Clinical Efficacy. Results from 3 large RCTs of serial FOBTs conducted in Minnesota, United Kingdom, and Denmark, involving more than 250000 subjects followed for up to 18 years, have consistently demonstrated that serial FOBT reduces colorectal cancer mortality (Table 1). Screening with FOBT reduced colorectal cancer mortality from 15% to 33%, with the absolute risk reduction for colorectal cancer death ranging from a low of 0.8 per 1000 person-years with biennial screening in the UK study to a high of 4.6 per 1000 person-years with annual screening in the Minnesota trial. Recent 18-year follow-up data from the Minnesota trial demonstrate that annual and biennial serial FOBT screening reduces colorectal cancer incidence by 17% to 20% as well.

How the Test Is Performed. The FOBT detects blood loss in the stool. It can detect blood loss caused by colorectal neoplasms, which tend to bleed more than normal colonic mucosa. A variety of FOBTs are available, but the Hemocult II is most widely used in the United States (Beckman-Coulter, Palo Alto, Calif). This test detects the pseudoperoxidase activity found in hemoglobin when it interacts with a guaiac-impregnated card in the presence of a hydrogen peroxide developer. A positive result is indicated by the immediate appearance of a blue color on addition of the hydrogen peroxide developer. The testing process requires that the patient apply 2 distinct samples of 3 different stools to 6 test card windows. Because the test detects peroxidase or pseudoperoxidase activity in stool, it is not specific for human hemoglobin. Dietary substances can result in false positive (eg, rare red meat, turnips, horseradish) or false negative (eg, vitamin C) results. However, a recent systematic review found that a restricted diet does not reduce the positivity rate but it may reduce patient compliance.

A rehydration procedure that enhances the sensitivity of the Hemocult II is sometimes employed. It can increase the number of true positive results and has been shown to double the sensitivity of the guaiac test. Such a rehydration procedure has been shown to reduce the number of false negative results because of dietary substances such as ascorbic acid, iron, and hematin, which reduce the guaiac color reaction.

Table 1. Summary of Clinical Trials for Fecal Occult Blood Testing

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Mandel et al (United States)</th>
<th>Hardcastle et al (United Kingdom)</th>
<th>Kronborg et al (Denmark)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of study participants</td>
<td>46 551</td>
<td>150 251</td>
<td>61 933</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>18</td>
<td>7.8</td>
<td>13</td>
</tr>
<tr>
<td>Relative risk mortality with annual FOBT (95% CI)</td>
<td>.67 (.51-0.83)</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Relative risk mortality with biennial FOBT (95% CI)</td>
<td>.79 (.62-0.97)</td>
<td>.85 (.74-0.98)</td>
<td>.82 (.69-0.97)</td>
</tr>
<tr>
<td>Absolute risk reduction for CRC death per 1000 subjects</td>
<td>4.6 (annual)</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>No. of subjects needed to screen to prevent CRC death</td>
<td>217 (annual)</td>
<td>1250</td>
<td>555</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FOBT, fecal occult blood testing; RR, relative risk.
cult test, at the expense of specificity, can be performed by adding a few drops of water to the stool samples before adding the hydrogen peroxide to the test windows. This procedure reduces the positive predictive values of the test by more than 50%. In the Minnesota Colon Cancer Control Society trial, of the guaiac-impregnated cards, 83% were screened using this procedure, and as a result, colonoscopy was performed on 38% of the participants in the annually screened group and 28% of the participants in the biennially screened group during the first 13 years of the study. By comparison, only 4% to 5% of subjects in the UK and Denmark studies underwent colonoscopy.

No direct comparison has been made with respect to the efficacy of the rehydrated and nonrehydrated procedures for FOBT, and any incremental benefit of rehydration with respect to mortality reduction may be small in light of the increased costs due to a much higher false positive rate. In the Minnesota Colon Cancer Control Society trial, use of the rehydration procedure reduced the 13-year cumulative mortality rate by 33% for colorectal cancer. It has been argued that some of the mortality reduction in this trial was simply a consequence of high rate of colonoscopy performed (ie, a similar benefit would have been demonstrated in the population if the number of colonoscopies performed in the study had been randomly allocated).

The degree of the reduction in the rate of colorectal cancer incidence has been demonstrated in the Minnesota trial and additional mathematical modeling. At the present time, professional organizations, such as the World Health Organization, US Preventive Services Task Force, and American College of Physicians, do not recommend the rehydration FOBT procedure because of the uncertainties regarding effectiveness and cost, compared with the nonrehydrated FOBT procedure. Guaiac-based tests other than the Hemoccult II also are available, but they are not often used. Recently, the World Health Organization endorsed the Hemoccult Sensa (Beckman Coulter, Palo Alto, Calif) as the test of choice because of its greater sensitivity than the Hemoccult II and its greater specificity than the rehydrated Hemoccult. Immunochemical FOBTs have the advantage of not requiring dietary or drug restrictions, but these tests are more expensive, and published data on effectiveness are limited. Based on evidence from large RCTs, FOBT should be repeated at least every other year to be clinically beneficial. An annual FOBT may offer greater reductions in mortality than a biennial screening, but at an increased cost.

Fecal occult blood testing itself is safe, but false positive results can lead to unnecessary further invasive tests, such as colonoscopy, that have a measurable complication rate.

The greater the number of test windows that are positive, the higher the positive predictive value of the test. However, even if only 1 of the 6 test windows is positive, the overall test should be considered positive, and these individuals should be referred for complete colonoscopy. This was the approach used by the Minnesota and Denmark FOBT studies.

Performance Characteristics. Fecal occult blood testing performed on a single occasion for the detection of colorectal cancer and adenomas shows poor sensitivity. However, the key to the success of FOBT lies in serial testing. In the UK and Denmark studies, FOBT screening detected 27% of the patients in the intervention group who developed cancer. In the Minnesota trial, after 13 years, 39% of patients in the biennial group and 49% of patients in the annual group who developed colorectal cancer were identified through FOBT screening.

Flexible Sigmoidoscopy

Evidence of Clinical Effectiveness. No completed large RCTs have demonstrated the effectiveness of sigmoidoscopy in the prevention of colorectal cancer death. The National Cancer Institute is funding the Prostate, Lung, Colorectal, and Ovarian screening trial, which is evaluating 60-cm flexible sigmoidoscopy, and the UK FlexiScope Trial is being conducted to study one-time screening sigmoidoscopy in subjects between ages 55 years and 64 years. These 2 large studies ultimately will enroll more than 250000 subjects, but no outcome data are yet available.

The Telemark Polyp Study, a small randomized trial, demonstrated that one-time flexible sigmoidoscopy screening could reduce colorectal cancer incidence. However, no reduction in colorectal cancer mortality was observed in the screened group.

The major evidence supporting the effectiveness of sigmoidoscopy comes from well-designed, retrospective case-control studies. The landmark study by Selby et al found that rigid sigmoidoscopy screening was associated with a 59% reduction in colorectal cancer mortality (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.25-0.69). The reduction in mortality from cancers within the reach of the sigmoidoscope was 70% (OR, 0.30; 95% CI, 0.19-0.48), while there was no significant reduction in mortality seen from cancers proximal to the reach of the sigmoidoscope (OR, 0.80; 95% CI, 0.54-1.19). These results have been confirmed by 2 other well-designed case-control studies by Newcomb et al and Muller and Sonnenberg, which have expanded the findings to include flexible sigmoidoscopy (TABLE 2). In addition, 2 case-control studies have demonstrated a reduction in incidence of colorectal cancer using flexible sigmoidoscopy.

How the Test Is Performed. Flexible sigmoidoscopy generally is performed using a 60-cm flexible endoscope. Preparation for the procedure requires that at least 1 to 2 saline enemas are administered to the patient the morning of the examination. The examination can be performed in a physician’s office or in the hospital. Special training is required to perform the procedure, but a variety of practitioners (physician’s assistants, nurses, primary care physicians, and other trained personnel) can perform the procedure.
care physicians, gastroenterologists) routinely perform the procedure. The procedure takes about 10 minutes to perform. The patient often experiences some tolerable abdominal pain. Sedation is not administered, and the patient may drive alone to the physician’s office or hospital and return to work immediately following the procedure.

The flexible sigmoidoscopy procedure is safe when performed by experts. In a retrospective review of 49,501 flexible sigmoidoscopy procedures performed during a 10-year period, only 2 perforations occurred (0.004%). Similar low complication rates have been reported from large population-based flexible sigmoidoscopy screening programs in the United States and the United Kingdom.

**How to Interpret the Test Results.** An important question is which lesions identified by sigmoidoscopy should prompt evaluation of the entire colon. Guidelines published by the 3 major U.S. organizations specializing in the gastrointestinal tract state that the finding of an adenomatous polyp 1 cm or larger in diameter, or one with advanced histologic findings (eg, villous changes or high-grade dysplasia), or multiple polyps, at sigmoidoscopy examination requires follow-up with complete colonoscopy, even if the lesions were removed at the initial examination.

However, controversy remains regarding the appropriate follow-up for the finding of 1 or 2 small tubular adenomas. Some experts recommend complete colonoscopy if any adenoma is found at sigmoidoscopy examination, while others feel that no additional procedure is required if only 1 or 2 small adenomas are detected and removed at sigmoidoscopy examination. These recommendations are based on a large number of studies that correlate the findings in the distal region of the colon and rectum, with the likelihood of finding a cancer or an advanced polyp in the proximal region of the colon at complete colonoscopy examination (Table 3).

After a negative sigmoidoscopy result in which no adenoma is found, the standard recommendation is to repeat the screening examination in 5 years. This recommendation is based on case-control studies that have demonstrated that the protective effects of sigmoidoscopy appear to last at least 6 years and a prospective follow-up sigmoidoscopy study in which the likelihood of finding an advanced adenoma or cancer was 0 in the 3 to 4 years following a negative sigmoidoscopy result. However, preliminary data from the large-scale Prostate, Lung, Colorectal, and Ovarian (PLCO) sigmoidoscopy screening trial indicated that the risk of advanced adenoma in the distal region of the colon 3 years after an initial negative sigmoidoscopy result was 0.8%, although the incidence of cancer in this region of the colon was less than 0.1%. Longer term follow-up of this study will further clarify the importance of this finding.

**Performance Characteristics.** Flexible sigmoidoscopy only examines a portion of the colon, and therefore important colonic lesions will be missed even if the finding of any adenoma on sigmoidoscopy examination indicates a complete colonoscopy. Only 20% to 30% of colorectal cancers in the proximal region are associated with an adenoma in the distal region that might be detected at flexible sigmoidoscopy examination. Furthermore, recent observational studies on colonoscopy screening suggest that one half of all advanced adenomas and cancers in the proximal region would be missed on sigmoidoscopy examination. However, sigmoidoscopy screening followed by complete colonoscopy appears to last at least 6 years and the importance of this finding.

### Table 2. Case-Control Studies of Mortality Reduction Associated With Sigmoidoscopy Screening

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Selby et al&lt;sup&gt;38&lt;/sup&gt;</th>
<th>Newcomb et al&lt;sup&gt;39&lt;/sup&gt;</th>
<th>Muller and Sonnenberg&lt;sup&gt;40,41&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases of colorectal cancer</td>
<td>261</td>
<td>66</td>
<td>441</td>
</tr>
<tr>
<td>Type of sigmoidoscopy</td>
<td>Rigid</td>
<td>Rigid and flexible</td>
<td>Rigid and flexible</td>
</tr>
<tr>
<td>Odds ratio (95% CI) for colorectal cancer death</td>
<td>0.41 (0.25-0.69)</td>
<td>0.21 (0.08-0.52)</td>
<td>0.41 (0.33-0.5)</td>
</tr>
<tr>
<td>Interval of apparent protective effect, y</td>
<td>9-10</td>
<td>Not specified</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

### Table 3. Rate of Advanced Proximal Neoplasm<sup>*</sup> According to Colorectal Findings in the Distal Colon

<table>
<thead>
<tr>
<th>Findings in Distal Colon, % (No./Total)</th>
<th>Source</th>
<th>Normal</th>
<th>Hyperplastic Polyp</th>
<th>Tubular Adenoma &lt;1 cm</th>
<th>Multiple Tubular Adenomas &lt;1 cm†</th>
<th>Advanced Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td>2.7 (48/1765)</td>
<td>2.8 (13/464)</td>
<td>6.4 (35/543)</td>
<td>9.1 (4/44)</td>
<td>11.7 (32/274)</td>
</tr>
<tr>
<td>Zarchy and Ershoff&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Not reported</td>
<td></td>
<td>Not reported</td>
<td>0.8 (1/124)</td>
<td>Not reported</td>
<td>11.8 (12/102)</td>
</tr>
<tr>
<td>Read et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Not reported</td>
<td>6.9 (13/189)‡</td>
<td>Not reported</td>
<td>28.6 (4/14)</td>
</tr>
<tr>
<td>Schoen et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Not reported</td>
<td></td>
<td>Not reported</td>
<td>2.9 (15/521)</td>
<td>2.4 (2/85)</td>
<td>5.9 (27/460)</td>
</tr>
<tr>
<td>Wallace et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Not reported</td>
<td></td>
<td>Not reported</td>
<td>1.6 (3/190)</td>
<td>10.4 (5/48)</td>
<td>7.4 (5/63)</td>
</tr>
<tr>
<td>Levin et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>5.3 (29/544)</td>
<td></td>
<td>Not reported</td>
<td>5.0 (22/444)</td>
<td>6.3 (20/319)</td>
<td>8.8 (147/1665)</td>
</tr>
<tr>
<td>Imperiale et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>1.5 (23/1564)</td>
<td>4.0 (8/201)</td>
<td>7.1 (12/168)</td>
<td>Not reported</td>
<td>11.5 (7/61)‡</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup>Defined as invasive cancer or adenoma 1 cm or larger in diameter or with villous features or high-grade dysplasia.
†Defined as 3 or more adenomas.
‡Includes adenomas with villous features.
§Does not include adenomas 1 cm or larger.

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be interpreted with some caution. In the US National Polyp Study, only 5 colorectal cancers were detected in the study population for an incidence of 0.6 cancers per 1000 years of subject follow-up, and all the patients were asymptomatic and the cancers were in early stages (4 in stage I and 1 in stage II). This low incidence of metachronous cancer represented a 76% to 90% reduction in cancer incidence compared with 3 reference populations, the Mayo Clinic cohort, the St Mark’s cohort, and the US Surveillance, Epidemiology, and End Results Program cohort (Figure). Third, recent cross-sectional colonoscopy screening studies indicate that colonoscopy is more sensitive than flexible sigmoidoscopy or sigmoidoscopy plus FOBT for the detection of large adenomas and cancers. It has not been shown but it can be assumed that increased sensitivity would translate into increased effectiveness.

How the Test Is Performed. Colonoscopy generally is performed by a gastroenterologist or a surgeon using a 160-cm flexible endoscope. Extensive training is required to perform the procedure safely and effectively. The day prior to the procedure the patient must only have consumed clear liquids and then consume some form of purgative (low-volume sodium phosphate purge or high-volume polyethylene glycol purge). Sedation is administered and patients cannot drive so they must be accompanied by another individual to escort them home. The patient should not experience pain during the examination and often the patient cannot recall the procedure. In a recent large study of colonoscopy screening, a complete examination was possible in 98% of patients, with a mean procedure time of 30 minutes. Recovery time for the patient is approximately 2 to 3 hours.

Flexible sigmoidoscopy has been shown to be a safer procedure than colonoscopy, but colonoscopy is considered safer. For instance, in a large study on colonoscopy screening, no deaths were directly attributable to colonoscopy and no colonic perforations occurred. Major morbidity did occur in 0.3% of subjects, including gastrointestinal tract bleeding, myocardial infarction, and stroke, and 3 subjects died within 1 month of the screening examination.

How to Interpret the Test Results. Colonoscopy is considered the criterion standard for detecting colorectal cancers and adenomas. If an adenoma is detected, a repeat surveillance examination is generally recommended in 3 or 5 years, depending on the number, size, and histologic findings of the adenomas removed. The recommendations for the appropriate surveillance interval after a positive finding at colonoscopy examination are based on data from the US National Polyp Study. If no adenomas are detected, the test result is negative. The recommendation for the 10-year repeat screening interval is based on indirect evidence. Case-control studies of sigmoidoscopy screening suggest that the protective effect of endoscopy screening lasts about 10 years. In addition, in the US National Polyp Study, low rates of metachronous adenomas or cancer were seen after colonoscopic polypectomy during extended follow-up. Finally, 2 small prospective studies have found that the incidence of cancer is less than 1% within 5 years after a negative colonoscopy screening result.

Performance Characteristics. Colonoscopy screening can detect advanced polyps and cancers that would otherwise be missed by sigmoidoscopy and/or FOBT. Although considered highly sensitive and specific for the detection of colonic neoplasia, colonoscopy is not a perfect test, and lesions can be missed. In one study in which tandem colonoscopies were performed by 2 expert examiners, the miss rates were 6% for adenomas 1 cm and larger in diameter, 13% for adenomas 6 to 9 mm in diameter, and 27% for adenomas 5 mm and smaller in diameter.

Combined FOBT and Sigmoidoscopy Screening

Evidence of Clinical Effectiveness. The limitations of using FOBT and sigmoidoscopy separately may be overcome...
by performing the 2 tests in concert. These are widely practiced procedures and little evidence in the published literature supports combination testing. In the study most commonly cited to support combination testing, the investigators nonrandomly allocated 12,479 individuals either to annual screening with FOBT combined with rigid sigmoidoscopy or to rigid sigmoidoscopy alone.\textsuperscript{71} Patient adherence to the protocol in both groups was poor. Colorectal cancer mortality was lower in the combined testing group after 5 to 11 years of follow-up (0.36 deaths per 1000 per year vs 0.63 deaths per 1000 per year), showing only a borderline statistical significance ($P = .053$).\textsuperscript{73} Given that the results are marginal, the use of yearly rigid sigmoidoscopy in the protocol and the poor compliance rates, generalizability of this study is tenuous.

**How the Test Is Performed.** The standard recommendation for patients who are undergoing colorectal cancer screening is to have an FOBT performed every year and to have sigmoidoscopy performed every 5 years. In a year in which both tests are to be performed, the FOBT should be completed first because a positive FOBT result would then require a complete colonoscopy to be performed and therefore eliminate the need for sigmoidoscopy.

**How to Interpret the Test Results.** If either the FOBT or the sigmoidoscopy procedure has an abnormal result, then complete colonoscopy is indicated.

**Performance Characteristics.** Two large RCTs have demonstrated that combination testing will detect 4 to 5 times more large polyps and cancers than FOBT alone.\textsuperscript{74,75} However, in another large randomized study, more polyps and cancers were not detected among patients undergoing FOBT and sigmoidoscopy compared with patients who underwent sigmoidoscopy alone.\textsuperscript{76} These studies involved a single application of FOBT and not serial testing, so the applicability of these findings to clinical practice is unclear. In a study recently completed in a large population from a health maintenance organization, the addition of an immunochemical FOBT did detect advanced adenomas and cancers in the proximal region of the colon that otherwise would have been missed by screening with flexible sigmoidoscopy alone. However, more than 600 individuals would need to be screened by the immunochemical FOBT to detect 1 additional advanced adenoma or cancer that otherwise would have been missed.\textsuperscript{77} Finally, in the Veterans Affairs Cooperative Study of colonoscopy screening, the addition of FOBT to sigmoidoscopy would have increased the percentage of patients identified with advanced neoplasia from 70.3% to 75.8%.\textsuperscript{31}

**Double-Contrast Barium Enema**

**Evidence of Effectiveness.** Double-contrast (air-contrast) barium enema has been advocated as a screening method for colorectal cancer, but to date no published evidence from controlled studies is available examining the effectiveness of this method.

**How the Test Is Performed.** Patient preparation for double-contrast barium enema is similar to that for colonoscopy. Sedation is not required, although patients often complain of pain and embarrassment.\textsuperscript{78} A trained radiologist must be present to perform the procedure. Barium, followed by air, is instilled into the colon under gentle pressure. The patient is then moved to different positions on an examination table while radiographs are obtained. The procedure takes 30 to 60 minutes to complete. This procedure has been shown to be safe; perforation of the colon is extremely rare, and serious complications of any type occurring have been reported in approximately 1 in 10,000 examinations.\textsuperscript{79,80}

**How to Interpret the Test Results.** Polypoid lesions and masses detected at double-contrast barium enema examination would indicate follow-up complete colonoscopy to verify the presence of the lesions, to obtain a biopsy sample, and to remove the lesions if possible. The standard recommendation is to perform screening by double-contrast barium enema every 5 to 10 years.

**Performance Characteristics.** The double-contrast barium enema examination is not as sensitive as the endoscopy examination in the detection of polyps. It does appear that double-contrast barium enema will detect a majority of advanced adenomas and cancers.\textsuperscript{81-84} In the US National Polyp Study, 862 paired double-contrast barium enema and colonoscopy examinations were compared in a surveillance population.\textsuperscript{85} In a large percentage of cases, the results of the double-contrast barium enema examination were false negatives, especially when the largest polyp found at colonoscopy was small. Even for polyps larger than 1 cm in diameter, the sensitivity of double-contrast barium enema was approximately 50%.\textsuperscript{85} However, many of the small polyps missed by double-contrast barium enema examination may be not clinically important, and therefore, a decreased sensitivity for detecting adenomas, especially those of small or medium size, does not necessarily mean that double-contrast barium enema is not an effective screening test.

**FUTURE DIRECTIONS OF COLORECTAL CANCER SCREENING**

Two new promising screening technologies are CT-assisted colonography, also termed virtual colonoscopy, and stool-based molecular testing. Before any new screening methods are routinely adopted, they should be assessed in clinical studies among average-risk patients that compare sensitivity and specificity for the detection of advanced polyps and cancers, cost, safety, and acceptability to patients with currently recommended screening tests. Ideally, clinical trials that assess the impact of these new screening tests on colorectal cancer incidence and mortality should be undertaken, but this may be impractical.

**Computed Tomography Colonography Screening**

Virtual colonoscopy is a technique that uses data generated from CT or mag-
Colorectal cancer screening if it costs approximately 50% less than conventional colonoscopy, or was associated with an initial compliance rate 15% to 20% better than colonoscopy.99

**Stool-Based Molecular Screening**

Genomic alterations drive the adenoma to carcinoma DNA sequence, and alterations in the neoplasmspecific DNA in colorectal adenomas and carcinomas have been well-characterized.100 Colorectal epithelial DNA can be extracted from stool samples and amplified, allowing for the detection of mutations indicative of colorectal neoplasia.101 Such stool-based testing is appealing because it is non-invasive, requires no special colonoscopic preparation, and has the capability of detecting neoplasia throughout the entire length of the colon. A recent study reported that mutations in the adenomatous polyposis coli (APC) gene could be detected in fecal DNA using a novel method, digital protein truncation, among 26 (57%) of 46 patients with known colonic cancers or large polyps (95% CI, 41%-71%), but in none of 28 control patients without colonic neoplasms (95% CI, 0%-12%).102 However, because the DNA alterations in colorectal cancer are heterogeneous, future assays will need to detect mutations in a number of genes typically mutated in colorectal cancer in addition to APC, such as Kirsten-ras (K-ras) and p53.103-105 A small pilot study of a proprietary assay that looks for mutations in a number of genes was more than 80% sensitive for the detection of large adenomas or cancer and was 93% specific.103 Large-scale prospective studies comparing the sensitivity and specificity of this assay with FOBT and colonoscopy in a colorectal cancer screening population are under way (David Ahlquist, MD, and Michael Ross, MD, oral communication, September 2002).

**COMMENT**

Colorectal cancer mortality can be reduced by screening all men and women aged 50 years or older for colorectal cancer. Several tests are available for colon cancer screening, including FOBT, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy. Direct and indirect evidence indicates that all the tests are effective, but they differ in their sensitivity, specificity, cost, and safety. The available evidence does not currently support choosing one test over another. In addition, other colorectal cancer tests, such as virtual colonoscopy or stool-based molecular testing, have the potential to become important screening tests in the future.

**REFERENCES**

A teacher affects eternity; he can never tell where his influence stops.
—Henry Adams (1838-1918)