CME CREDIT

CAROL ANN BURKE, MD
Department of Gastroenterology, Cleveland Clinic

ROSALIND VAN STOLK, MD
Director, Center for Colorectal Cancer Prevention, Northwestern University Medical School. Chicago, IL

Colorectal cancer screening: Making sense of the different guidelines

ABSTRACT

Screening for colorectal cancer, as called for by new guidelines from three different groups, should result in a lower mortality rate from this disease. This paper reviews the guidelines' similarities and differences and gives our recommendations for situations in which the data remain incomplete and controversy persists.

KEY POINTS

Beginning at age 50, persons with no identifiable risk factors for colon cancer should undergo fecal occult blood testing every year and flexible sigmoidoscopy every 5 years. Barium enema radiography with flexible sigmoidoscopy or colonoscopy are other screening options.

Persons should undergo colonoscopy if they have an abnormal finding on any of the other types of screening tests.

Patients with risk factors for colon cancer should undergo colonoscopy at regular intervals, perhaps for the rest of their lives.

COLORECTAL CANCER SCREENING is dismally underused. In one study, only 17.3% of people age 50 and older had undergone fecal occult blood testing the previous year, and only 9.4% had undergone sigmoidoscopy in the previous 3 years.[1] In another study,[2] only 28% had undergone sigmoidoscopy in the previous 5 years, and fewer than 35% had been tested for fecal occult blood.

This situation may soon change. Evidence is growing stronger that screening with fecal occult blood testing and flexible sigmoidoscopy reduces colon cancer mortality. Screening guidelines have been updated, and Medicare recently started paying for colorectal cancer screening. Together, these trends should lead to wider use of screening and to a continued decline in colorectal cancer morbidity.

In this article, we review the new guidelines for colorectal cancer screening from three different groups, giving our own recommendations in situations in which the data remain incomplete and controversy persists.

PREVALENCE

Colorectal cancer is one of the most common types of cancer. Each year in the United States, more than 130,000 people are diagnosed with colorectal cancer, and 46,000 die of it. The 5-year survival rate is over 90% in patients with early-stage disease. Unfortunately, at the time of diagnosis more than half of patients have either locally advanced disease (which carries a 5-year survival rate of 50%) or metastatic disease (with a 5-year survival rate less than 10%).

TABLE 1

American Cancer Society guidelines for colorectal cancer screening

RISK CATEGORY	RECOMMENDATIONS
Average risk	
People with none of the risk factors listed below	Starting at age 50, either: Fecal occult blood testing every year plus flexible sigmoidoscopy every 5 years, or Total colonic examination (colonoscopy every 10 years or dual-contrast barium enema radiography every 5 to 10 years)
Moderate risk	
People with small (< 1 cm) adenomatous polyps	Colonoscopy at time of initial polyp diagnosis; Total colonic examination within 3 years after polyp removal; if normal, screen per average risk recommendations (above)
People with large (≥ 1 cm) or multiple adenomatous polyps	Colonoscopy at time of initial polyp diagnosis; Total colonic examination within 3 years after polyp removal; if normal, repeat every 5 years
People who have undergone resection of colon cancer with curative intent	Total colonic examination within 1 year; if normal, repeat in 3 years; if still normal, repeat in 5 years
People with a first-degree relative younger than age 60 with colorectal cancer or adenomatous polyps; or two or more first-degree relatives of any age	Total colonic examination at age 40 or 10 years before youngest case in family (whichever is earlier); repeat every 5 years
People with other relatives with colorectal cancer not listed above	Screening according to average-risk recommendations; may consider beginning before age 50
High risk	
Family history of familial adenomatous polyposis	In puberty, begin surveillance with endoscopy; counseling to consider genetic testing; referral to a specialty center If genetic test is positive or polyposis is confirmed, consider colectomy; otherwise endoscopy every 1 to 2 years
Family history of hereditary nonpolyposis colon cancer	At age 21, colonoscopy and counseling to consider genetic testing; referral to a specialty center If genetic test is positive or if patient has not had genetic testing, colonoscopy every 2 years until age 40, then every year
Inflammatory bowel disease	Colonoscopy with biopsy for dysplasia starting 8 years after the start of pancolitis or 12 to 15 years after start of left-sided colitis; repeat every 1 to 2 years

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ADENOMA'S SLOW GROWTH

Colorectal cancer is believed to arise from a precursor lesion known as an adenoma. Several observational studies suggested that an adenoma takes about 10 years to transform into a carcinoma, during which it undergoes multiple and progressive alterations in oncogenes and tumor suppressor genes. This interval allows ample time to detect and remove the adenoma before cancer develops—if we look for it. Support for this concept comes from a landmark study of 1,418 patients who underwent colonoscopic polypectomy, resulting in an incidence of colorectal cancer that was lower than anticipated.[3]

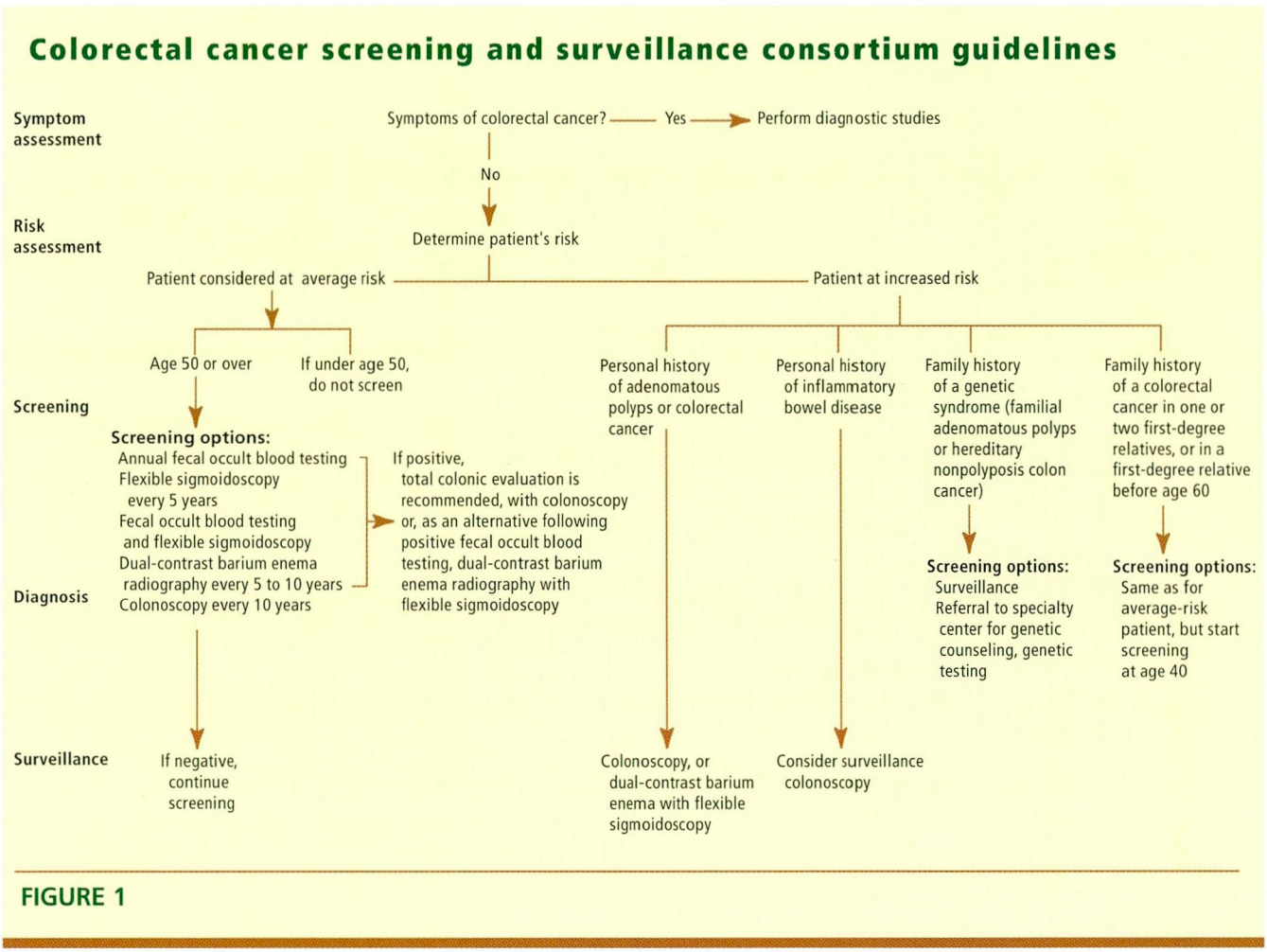

FIGURE 1

NEW SCREENING GUIDELINES

In the past few years, three groups published new guidelines for screening:

- The American Cancer Society (TABLE 1)[4]
- The United States Preventive Service Task Force[5]
- A consortium including the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, the American College of Gastroenterology, the American Society of Colon and Rectal Surgeons, and the Society of American Gastrointestinal Endoscopic Surgeons, initially supported by the Agency for Health Care Policy and Research (FIGURE 1).[6]

These guidelines are based on new studies that demonstrated that screening with fecal occult blood testing[7–9] and flexible sigmoidoscopy[10] reduce colorectal cancer mortality.

ASSESSING COLORECTAL CANCER RISK

The guidelines distinguish between persons at average risk for colon cancer and those with risk factors, ie:

- Personal or family history of colonic adenomas or colorectal cancer
- Constitutional genetic mutations
- Chronic inflammatory diseases of the colon such as ulcerative colitis or Crohn colitis.

TABLE 2 shows a simple scheme for stratifying risk. Bear in mind, however, that only 30% of patients with colorectal cancer have any of these risk factors.

SCREENING IN PERSONS AT AVERAGE RISK

For persons at average risk (ie, without any identifiable risk factors for colorectal cancer),

TABLE 2

Risk factors for colorectal cancer

Moderate risk

Personal history of adenomatous polyps or colorectal cancer
Family history of colorectal cancer (one or more first-degree relatives)
Family history of adenomas before age 60

Highest risk

Familial adenomatous polyposis
Hereditary nonpolyposis colorectal cancer and family cancer syndromes
Inflammatory bowel disease (ulcerative colitis or Crohn disease)

screening should begin at age 50. Four methods are available: fecal occult blood testing, flexible sigmoidoscopy, barium enema radiographic examination with flexible sigmoidoscopy, and colonoscopy. TABLE 3 compares the cost, sensitivity, and specificity of these methods.

Fecal occult blood testing

All three sets of guidelines recommend fecal occult blood testing every year.[4–6]

In three randomized controlled trials, fecal occult blood testing reduced mortality from colorectal cancer by 15% to 33%.[7–9] Under study conditions, the test has a specificity of up to 99%. Unfortunately, its sensitivity is only 45% to 65%, and patient compliance with correct test procedures tends to be low.

At least 40% of polyps and cancers are beyond the reach of the flexible sigmoidoscope

The test is outpatient-based: patients are sent home with test cards and written instructions, which aim to reproduce the methods used in the clinical studies mentioned above. The instructions include a list of foods and drugs to avoid because they can cause false-positive or false-negative results (TABLE 4).[11]

The accuracy of fecal occult blood testing done at the time of a digital rectal examination or while the patient is not on the specified diet is unknown. Because the test has a low sensitivity, it should not be used in patients with an above-average risk of colonic neoplasia, conditions that may result in misleading results (inflammatory bowel disease, active hemorrhoidal bleeding, peptic ulcer disease), or symptoms that suggest colorectal cancer.

A positive test result is defined as at least one positive slide window and warrants a complete colonoscopic evaluation. Repeating the test for confirmation is *not* considered appropriate.

Flexible sigmoidoscopy

The American Cancer Society[4] and the consortium[6] recommend performing flexible sigmoidoscopy every 5 years in persons at average risk. The United States Preventive Service also recommends flexible sigmoidoscopy, but does not specify how often.[5]

Flexible sigmoidoscopy offers the advantage of visualizing the colonic mucosa directly. It is highly accurate in detecting polyps and cancers in the segment of the bowel within its examining range. Unfortunately, at least 40% of polyps and cancers are beyond the limits of detection of the longest (60-cm) flexible sigmoidoscope.

A number of case-control studies suggested that sigmoidoscopy (predominantly with rigid scopes) could reduce the risk of death from colorectal cancer by 59% to 80%. In the best-known of these studies,[10] 8.8% of patients who died of colorectal cancer had undergone sigmoidoscopic screening in the previous 10 years, compared with 24.2% of controls matched for age and sex.

Many studies tried to determine if adenomas found in the rectosigmoid colon are "sentinels" for, or markers of, neoplastic polyps in proximal colonic segments. A British study of rigid sigmoidoscopy[12] (with colonoscopy performed later) suggested that patients with a single tubular adenoma smaller than 1 cm are at low risk of subsequent colorectal cancer. Another study[13] found that one third of patients with distal adenomas smaller than 0.5 cm harbored adenomas in more proximal segments of the colon, and that 6% had advanced lesions.

A few studies looked at the incidence of proximal neoplasia based on the histology of polyps detected with flexible sigmoidoscopy. In two such studies, proximal neoplasia were detected in 33% to 42% in patients with distal adenomas, in 29% to 39% of patients with hyperplastic polyps, and in 15% of patients with normal flexible sigmoidoscopic examinations.[14,15]

The risk of advanced adenomas and colorectal cancer in patients found to have a sin-

TABLE 3

Cost, sensitivity, and specificity of colorectal cancer screening tests

TEST	COST PER TEST	SENSITIVITY	SPECIFICITY
Fecal occult blood testing	$10–$20	26%–92%	90%–98%
Flexible sigmoidoscopy	$150–$500	90%	98%
Dual-contrast barium enema radiography	$300–$500	50%–80%	98%
Colonoscopy	$1,000–$1,500	75%–95%	100%

gle, small adenoma or hyperplastic polyp detected on flexible sigmoidoscopy is presumed to be low. However, on the basis of studies that found proximal adenomas in approximately 30% of patients with distal hyperplastic polyps and small adenomas, we strongly favor a position that all patients with distal polyps detected by flexible sigmoidoscopy undergo colonoscopy to search for proximal neoplasia.

Combining fecal occult blood testing with flexible sigmoidoscopy

Combining fecal occult blood testing with sigmoidoscopy improves the sensitivity of either test alone. One controlled trial[16] reported that patients who had both tests had reduced colorectal cancer mortality, more early-stage cancers detected, and longer survival than did those who had sigmoidoscopy alone.

Barium enema radiography

Compared with fecal occult blood testing and flexible sigmoidoscopy, barium enema radiography has the advantage of imaging the entire colon. Barium enema radiography can be performed with barium alone ("single-contrast") or with air instilled after most of the barium has been evacuated ("dual-contrast"). The dual-contrast method allows the best imaging of the colonic mucosa and is the radiographic test of choice for detecting colorectal polyps and cancer.

The risk of serious complications such as perforation of the bowel is only 0.02%. Unfortunately, the sensitivity is only 50% to 75% for detecting cancer, and lower for polyps.[17–21]

In the only study to date to address the use of barium enema radiography in screening for colorectal cancer,[22] adenomatous polyps were detected in 4% of 738 asymptomatic, average-risk persons using the single-contrast method. No carcinomas were found. This is a very low yield compared with screening colonoscopy, which reveals adenomatous polyps in 26% to 41% of patients without risk factors and cancer in about 1%.[6,23–26] In a study in clinical practice, the sensitivity of barium enema radiography was 83% for detecting colorectal cancer, compared with 95% for colonoscopy.[27]

We do not recommend barium enema radiography for colorectal cancer screening. If it is used, then flexible sigmoidoscopy also should be done, because the rectosigmoid colon is often not adequately visualized in barium enema radiography, owing to overlapping bowel loops.

Colonoscopy

Colonoscopy, the "gold standard" for detecting colonic neoplasms, should be performed if abnormalities are found on any of the other screening examinations. It is also listed as a first-line screening option by the American Cancer Society[4] and the consortium guidelines,[6] to be considered on a case-by-case basis.

If colonoscopy could be performed in everyone on a regular basis, we would probably reduce the mortality rate from colorectal cancer, as suggested by a case-control study.[28] However, for screening colonoscopy to become a practical option, the cost would have to be reduced and more specialists would have to be trained.

Colonoscopy can be completed in over

The decision to screen with colonoscopy is done case by case

TABLE 4

Recommendations for fecal occult blood testing: What to tell patients

In the 48 to 72 hours before and during testing, avoid:

Foods and medications that can produce false-positive results:
- Red meat (beef, lamb), liver
- Uncooked turnips, horseradish, broccoli, radishes
- Aspirin in doses > 325 mg/day
- Nonsteroidal anti-inflammatory drugs

Foods and medications than can produce false-negative results:
- Cantaloupe and other melons (watermelon is permitted)
- Vitamin C supplements

Take two smears from two sites of three bowel movements (6 windows)

Develop within 7 days without rehydration

95% of examinations. The risk of serious complications (eg, perforation) is 0.2%.

If a patient at average risk undergoes colonoscopy with negative results, the time to restart alternative screening strategies such as fecal occult blood testing and sigmoidoscopy is unknown. The biology of the adenoma-carcinoma sequence would suggest a delay of at least 5 years is appropriate.

We recommend colonoscopy 3 years after surgery, and every 5 years thereafter

SCREENING IN PEOPLE AT MODERATE RISK

Most people at moderate risk of colorectal cancer need to undergo colonoscopy at regular intervals for the rest of their lives.

People with adenomas

If a person has undergone colonoscopy to have adenomas removed, he or she can wait 3 years to undergo colonoscopy again—a large, randomized study found no benefit in doing it sooner.[29] If the 3-year examination is negative, the standard interval is increased to 5 years.[30]

Recent data suggest that people with either multiple adenomas or polyps with advanced pathology found on baseline colonoscopy are the group of patients with a greater likelihood of having adenomas with advanced pathology (large, villous, or dysplastic) and cancer on subsequent surveillance colonoscopy.[29,31,32] Therefore, the American Cancer Society[4] and the consortium[6] recommend postpolypectomy surveillance intervals based on the size and the number of polyps detected on the baseline colonoscopy.

For patients with a single, small, tubular adenoma, the American Cancer Society[4] recommends resuming average-risk screening if the 3-year postpolypectomy examination was negative.

For patients with multiple (more than two) or large (1-cm or larger) adenomas at baseline colonoscopy, both the American Cancer Society[4] and the consortium[6] recommend the first postpolypectomy surveillance examination at 3 years and, if negative, the subsequent surveillance in 5 years. The consortium extends the surveillance interval to every 5 years even if the first postpolypectomy examination reveals a single small tubular adenoma.

Need for further studies. The new guidelines should be lauded for their attempt to stratify patients with adenomas into higher and lower risk classes based on baseline adenoma characteristics. We must be mindful that the overall rate for failing to identify adenomas during colonoscopy may be as high as 24%, although most of these missed lesions are small.[33] Until more data confirm the lack of risk of subsequent cancer in patients with a single small tubular adenoma, we recommend colonoscopic screening if patients return to the average-risk screening category.

People with previous colorectal cancer

In patients undergoing colonic resection in the hopes of curing colon cancer, it is imperative to first perform a high-quality preoperative or intraoperative colonoscopic examination to detect synchronous lesions.

If a complete perioperative examination is not performed, it should be performed at 1 year. Postoperative surveillance intervals vary in clinical practice. Some patients undergo colonoscopy every 6 to 12 months for several years, but no data support the benefit of this practice. A recent randomized study[34] found no survival benefit from early or intensive colonoscopic surveillance in patients who had undergone curative resection for colorectal cancer.

These data suggest that a 3-year interval is

safe before performing colonoscopy to look for new or recurrent lesions in patients who had an adequate perioperative examination. We recommend colonoscopy 3 years after the surgery, and every 5 years thereafter.

People with a family history of colorectal cancer

From 15% to 50% percent of colorectal cancers are familial. First-degree relatives of patients with colorectal cancer have a twofold to threefold increased risk of colorectal cancer and adenomatous polyps.[35,36] The more relatives with cancer, the higher the risk. Recent studies also showed that first-degree relatives of patients with adenomatous polyps are also at increased risk of colorectal cancer, particularly when the adenoma is diagnosed before age 60.[37,38] Evidence suggests the risk of cancer in a patient at age 40 with a first-degree relative with adenomas or colorectal cancer is the same as the risk in a 50-year-old without a family history.[39]

Recommendations. If the first-degree relative with colorectal cancer or adenoma was younger than age 60, or if two or more first-degree relatives had colorectal cancer, the American Cancer Society[4] suggests a total colonic evaluation (either colonoscopy or dual-contrast barium radiography) every 5 years beginning either at age 40, or 10 years before the youngest case in the family, whichever is earlier. The consortium[6] recommends that people with a first-degree relative who has had colorectal cancer or adenomatous polyps be offered average-risk screening, but beginning at age 40.

We recommend colonoscopy every 5 years for patients with two or more first-degree relatives with colorectal cancer, or a first-degree relative with colorectal cancer or adenomatous polyp detected before age 60. Surveillance should be started at age 40 or 10 years before the youngest case in the family, whichever is earlier.

Patients with more than one relative with colorectal cancer should be referred for genetic testing for an inherited colon cancer syndrome. Patients with one first-degree relative with colon cancer detected after age 60 should undergo colonoscopic examination every 10 years beginning at age 50.

SCREENING IN PEOPLE AT HIGH RISK

People with genetic syndromes

The risk of colorectal cancer is highest in patients with autosomal-dominant genetic syndromes—ie, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC). The gene for FAP (APC) has been identified on the long arm of chromosome 5. Patients with FAP develop hundreds to thousands of colonic adenomas in the second decade of life, and 100% will develop colon cancer by age 40 if prophylactic colectomy is not performed.

At least four genes on chromosomes 2, 3, and 7 have been identified in the germline of 30% of patients with HNPCC. These colon cancers occur at a young age, in the fourth to fifth decade, and often occur in the right colon. The most widely used and strictest definition of an HNPCC kindred is the Amsterdam criteria and includes[40]:

- Three or more relatives affected, one a first-degree relative of the other two
- One cancer diagnosed before age 50
- At least two successive generations affected.

Risk in Ashkenazi Jews. Most recently, a mutation in the APC gene (I1307K) was found in a young Jewish patient with colonic adenomas and a family history of colorectal cancer.[41] This gene mutation has been found in 6.1% of the general Ashkenazi Jewish population, and in 28% of Ashkenazi Jews with colorectal cancer and a family history of colorectal neoplasia. The risk of colorectal cancer is presumed to be higher in people with this genetic mutation; however, no published literature exists as to the exact risk or appropriate surveillance strategy in this population.

15% to 50% of colorectal cancers are familial

Recommendation. Several laboratories now offer genetic testing. However, studies have shown that physicians frequently misinterpret the test results, and that patients receive inadequate counseling.[42] We recommend that patients with FAP or HNPCC and Ashkenazi Jews with a personal or family history of colonic neoplasia be referred to a comprehensive medical genetics program for risk assessment, a discussion of the appropriate surveillance recommendations, genetic counseling, and, if appropriate, gene testing.

People with inflammatory bowel disease

The risk of colorectal cancer is markedly increased in patients with inflammatory bowel disease, ulcerative colitis, or Crohn colitis. This risk of cancer begins to rise 7 to 10 years after the diagnosis and has been reported to increase as much as 10% per decade.[43] Patients with pancolitis and left-sided disease are at highest risk, while patients with proctitis and proctosigmoiditis have no increased risk.

For another perspective on screening patients with ulcerative colitisis, see page 273

Recommendation. In patients with pancolitis, we recommend colonoscopic surveillance every 1 to 2 years with biopsy to detect dysplasia, beginning 8 years after the onset of disease. We recommend a similar regimen in patients with left-sided disease, to begin 12 to 15 years after onset. Patients with dysplasia should undergo colectomy.

WHOM NOT TO SCREEN

Screening is pointless for some patients. For example, if a patient has symptoms suggesting colorectal neoplasia, we would forgo fecal occult blood screening and sigmoidoscopy and proceed directly to a diagnostic colonoscopy. Other patients who should forego all testing are those who are nearing the end of life, or are not able to tolerate colonoscopy, its potential complications, or the treatment of cancer.

In 1997, Medicare approved coverage for colorectal cancer screening

ECONOMIC CONSIDERATIONS

Calculations of cost-effectiveness are fraught with uncertainty and unsupported assumptions, but we believe that screening is cost-effective if one considers the costs of treating advanced disease and the years of life lost if people are not screened. Surprisingly, screening with an inexpensive test such as fecal occult blood testing may not be much more cost-effective than using a more-expensive but more-accurate test such as colonoscopy.

Several investigators have estimated the cost-effectiveness of different screening strategies.[44,45] Lieberman[45] estimated that if we screened everyone for the 10 years between the ages of 55 and 65 years, the cost per death prevented would be:

- $225,000 for annual fecal occult blood testing
- $258,000 for flexible sigmoidoscopy every 5 years
- $260,000 for fecal occult blood testing with flexible sigmoidoscopy
- $274,000 for one-time colonoscopy
- $280,000 for a barium enema radiography every 5 years.

However, these calculations assume that all patients would be 100% compliant—which they are not. Moreover, colonoscopy would be the most cost-effective option if it could be performed for less than $750.

In 1997, Medicare approved coverage for colorectal cancer screening. Medicare patients over age 50 who are at average risk are eligible for fecal occult blood testing annually, and for flexible sigmoidoscopy or barium enema radiography every 4 years. Medicare will also pay for colonoscopy or barium enema radiography every 2 years for patients who have inherited forms of colon polyps or cancer; a personal history of colorectal cancer, polyps, or inflammatory bowel disease; or a first-degree relative with colon cancer or adenomas.

The Medicare change is important, since Medicare is the benchmark for other insurers, who usually follow suit in short order.

WHEN TO STOP SCREENING

Screening and surveillance for colorectal adenomas and cancer should be continued as long as the patient is expected to benefit from it. The decision to stop screening and surveillance should be made by the physician and patient.

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ADDRESS: *Carol Ann Burke, MD, Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail burkecl@ccf.org.*