

Screening for Colorectal Cancer

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Colorectal cancer screening can prevent the development of colorectal cancer and reduce the risk for death. Screening recommendations include fecal occult blood testing, sigmoidoscopy, radiographic imaging of the colon, and colonoscopy. This article focuses on recommendations for average-risk individuals and discusses the potential benefits and limitations of each. High-risk individuals should be screened with colonoscopy. Cost-effectiveness analyses of colorectal cancer screening are summarized.

THE IMPORTANCE OF COLORECTAL CANCER SCREENING

Colorectal cancer (CRC) is the second leading cause of cancer death in North America and Western Europe. The biology of CRC presents a unique opportunity for cancer prevention because most cancers begin as premalignant polyps. If more patients with advanced neoplasia polyps were detected and the polyps removed, many—if not most—cancers could be prevented. Compelling evidence now exists that shows screening of average-risk asymptomatic individuals >50 years of age not only reduces mortality from CRC but also reduces CRC incidence rates. In the National Polyp Study, patients had a complete colonoscopy with removal of all polyps (1). The expected rates of CRC over the following 6 years were reduced by 76% to 90%. The Minnesota Colon Cancer Group reported that patients who were screened with a fecal occult blood test (FOBT) had lower rates of cancer incidence over time than did nonscreened controls (2). The authors attributed this benefit to the discovery and removal of premalignant adenomas. Therefore, when we consider the effectiveness of screening tests, we should hold them to a higher standard than simply early cancer detection. Screening test efficacy should be based on the

KEY POINT

Compelling evidence shows that screening of average-risk, asymptomatic individuals >50 years of age reduces both CRC mortality and incidence rates.

likelihood that the test will detect advanced neoplasia and reduce mortality from CRC.

Screening of average-risk individuals has been advocated by many organizations and experts (3–7). Colorectal cancer screening recommendations for all individuals are provided in **Table I**. **Table II** shows the risk levels for colorectal cancer.

SCREENING STRATEGIES FOR AVERAGE-RISK INDIVIDUALS

Fecal Occult Blood Testing

Three randomized, controlled trials have demonstrated a significant reduction of the CRC mortality rate (15% to 33%) among patients who were screened compared with nonscreened controls (8–10). The benefit is thought to be due to early cancer detection and incidental discovery and removal of adenomatous polyps, which may lead to

TABLE I.

COLORECTAL CANCER SCREENING RECOMMENDATIONS

Average-Risk Individuals

Beginning at age 50 years the following options are acceptable choices:

- Fecal occult blood test (FOBT) annually
- Flexible sigmoidoscopy every 5 years
- Combination of FOBT and sigmoidoscopy
- Colonoscopy every 10 years
- Barium enema with air contrast every 5 years

Individuals at Increased Risk

Colonoscopy is recommended

Includes individuals with:

- History of colorectal cancer in any first-degree relative at age 60 years or less
- Personal history of colorectal cancer or adenoma

Individuals at High Risk

Special recommendations apply

Includes individuals with:

- Familial adenomatous polyposis
- History of hereditary nonpolyposis colorectal cancer syndrome
- Inflammatory bowel disease of the colon (ulcerative colitis or Crohn’s disease)

KEY POINT

In one study, the combination of one-time sigmoidoscopy and FOBT identified 76% of cases of advanced neoplasia, but the data suggested that the combined tests are less effective with increasing age due to the increased prevalence of proximal neoplasia with age.

cancer prevention. Furthermore, the Minnesota Colon Cancer Group reported that CRC incidence was reduced by 20% in patients screened compared with nonscreened controls (2). The authors suggest this benefit was largely due to polyp detection and removal during the screening period.

Recent data from the VA Cooperative Study demonstrate important limitations of the FOBT (11). A one-time FOBT detects less than 25% of

patients with advanced neoplasia; therefore, screening effectiveness depends on compliance with repeat annual screening. In clinical practice, adherence to repeat annual testing is poor. The VA data confirm that the FOBT is not an effective adenoma detection test and so has limited effectiveness in cancer prevention. The cancer-prevention benefit depends on the rates of colonoscopy in the screening program. The reduction in cancer incidence demonstrated in the Minnesota study was due in part to high rates of colonoscopy in the cohort (2).

Flexible Sigmoidoscopy

Two case-control studies showed significant reductions in the CRC mortality rate among patients who had a sigmoidoscopy—a benefit limited to the portion of the colon examined (12,13). Two recent studies used complete screening colonoscopy to determine how many cases of advanced neoplasia in the proximal colon would not be detected with sigmoidoscopy (14,15). These analyses assumed that sigmoidoscopy reaches the splenic flexure and that all

TABLE II.

RISK STRATIFICATION FOR COLORECTAL CANCER

<i>Risk Level</i>	<i>Condition as % of all CRC*</i>	<i>Lifetime Risk of Cancer</i>	<i>Recommendations for Screening</i>
High Risk			
• Familial polyposis	1	100%	Sigmoidoscopy in teenage years; genetic screening can be considered; total colectomy if detected
• Hereditary nonpolyposis colorectal cancer	3	>80%	Colonoscopy in 3rd/4th decade at 2-year intervals; genetic screening can be considered
• Chronic ulcerative colitis/Crohn's disease	<1	Increased [†]	Colonoscopy every 2 years beginning at 8 to 10 years after onset of colitis
Moderate Risk			
• Familial risk First-degree relative	15–20	2- to 4-fold increase	Begin screening at an age 10 years younger than age of index case; consider colonoscopy screening
• Personal history of breast, uterine, ovarian cancer	<1	Uncertain	No specific recommendation
Average Risk			
• Age >50 years	70–75	6%	Begin screening at age 50 years

*For example, asymptomatic individuals represent 70% to 75% of all cancer cases, hereditary nonpolyposis colorectal cancer syndrome patients represent 3% of all cancer cases, etc. [†]Incidence of 1% to 2% per year after 20 years of disease. CRC = colorectal cancer.

patients with adenomas would undergo colonoscopy. The studies showed that overall 70% to 80% of all cases of advanced neoplasia in the colon would be detected with sigmoidoscopy, but that 50% of cases of advanced neoplasia in the proximal colon would not be detected. Therefore, sigmoidoscopy screening could be very effective for reducing cancer incidence and mortality rates for cancers arising in the distal colon. With increasing age, however, the prevalence of proximal neoplasia increases, and sigmoidoscopy would be a less effective screening test.

Combined Flexible Sigmoidoscopy and Fecal Occult Blood Testing

Few studies have evaluated combined screening (16–18). In a nonrandomized study, a group who underwent FOBT plus sigmoidoscopy had a longer average survival time after detection of CRC than did a group who underwent only sigmoidoscopy. In 2 randomized studies, rates of detection of advanced

KEY POINT

Imaging could be more effective than sigmoidoscopy in the detection of both polyps and cancer because of visualization of the entire colon. All imaging procedures have drawbacks, however, and further study is needed.

neoplasia were higher among subjects offered both tests than among subjects who were offered FOBT alone (17,18). The VA Cooperative Study determined the detection rate of advanced neoplasia by combining a distal colon examination (rectum plus sigmoid colon) and FOBT (11). The combination of one-time sigmoidoscopy and FOBT identified 76% of cases of advanced neoplasia. The data suggested,

however, that the combined tests are less effective with increasing age due to the increased prevalence of proximal neoplasia with age, an important limitation because cancer rates continue to increase with age.

Imaging Studies

No direct data are available to evaluate imaging modalities in screening populations. Imaging could be more effective than sigmoidoscopy in the detection of both polyps and cancer because of visualization of the entire colon. However, the National Polyp Study showed that barium studies fail to identify up to 50% of cases of polyps >1 cm in diameter (19).

Computed tomographic (CT) colography (also known as *virtual colonoscopy*) uses helical CT scanning to render 3-dimensional images of the colon. In recent studies, CT sensitivity for the detection of large polyps ranged from 50% to 91% (20,21). Problems with bowel preparation and colon spasm impact both sensitivity and specificity of the CT procedure. Another important issue is cost. CT colography can detect more than 50% of small polyps, and many of these are non-neoplastic hyperplastic polyps. If these tests are considered positive, colonoscopy is usually recommended; therefore, potentially large numbers of patients would undergo both CT and colonoscopy, increasing the cost of a screening program (20–22). When these data are applied to the VA study population (14), more than 50% of patients would have a positive test and require colonoscopy. If these data were applied to a low-risk population, 30% to 35% of patients would end up with colonoscopy. If many patients received both virtual CT and colonoscopy, CT colography would likely not be cost-effective unless the cost is very low. Sonnenberg et al modeled CT colography and colonoscopy and found that colonoscopy dominated CT over a broad range of assumptions (22). Magnetic resonance (MR) colography data are preliminary but show that MR colography is not likely to be superior to CT.

All of the imaging procedures involve drawbacks having to do with adequate bowel preparation, interpretation (stool versus polyp), and small polyps. Further study is needed before these tests

can be recommended to patients.

Colonoscopy

In 2 recent studies, colonoscopy was performed in more than 5000 asymptomatic individuals (14,15). The colonoscopy screening studies revealed the high prevalence of advanced neoplasia in asymptomatic subjects. The prevalence of advanced pathology defined as cancer, adenoma with high-grade dysplasia, adenoma with villous histology, or tubular adenoma >9 mm in diameter was 10.6% in the VA

KEY POINT

Colonoscopy is the most effective test for the detection of adenomas and likely has a greater impact on cancer incidence rates than any other form of screening.

study and 7.0% in the Indiana study (14,15). Many of these cases would not have been detected with sigmoidoscopy. These studies were not designed to measure mortality rate reduction or incidence reduction. The VA study reported severe complications in 0.3% of patients. In most cases, adverse events occurred in patients who underwent polypectomy.

Considerable indirect evidence shows that colonoscopy screening could be an effective test for cancer prevention. As stated in the National Polyp Study, patients underwent colonoscopy with removal of all adenomas, and during 6 years of follow-up, cancer incidence was reduced by 76% to 90% compared with expected rates in control populations (1). The recent report of incidence reduction in the Minnesota FOBT trial strongly supports the hypothesis that detection and removal of adenomas may prevent cancers (2). There is little doubt that colonoscopy is the most effective test for the detection of adenomas and likely has a greater impact on cancer incidence rates than any other form of screening.

Risks of colonoscopy are higher than those of other types of screening. It may be argued that the greatest risk is assumed by patients with

TABLE III.

SCREENING TEST EFFICACY FOR COLORECTAL CANCER

<i>One-Time Testing</i>	<i>Detection Rate of Advanced Neoplasia (%)</i>
FOBT alone	24
Sigmoidoscopy alone	70
Combined FOBT and sigmoidoscopy	76
Barium enema	48
Virtual colonoscopy	50–90
Colonoscopy	95

FOBT = fecal occult blood test.

polyps who are also most likely to benefit. In any case, the long-term risk-benefit ratio in practice settings is not known. Most current data suggest that colonoscopy should be performed only by well-trained experts. Implementation of widespread screening would require careful consideration of resource management.

Screening Test Efficacy

Each of the recommended screening tests has potential benefits and limitations (Table III). The screening colonoscopy studies provide information that physicians did not have for average-risk, asymptomatic populations (11,14,15). Patients choosing FOBT screening should understand that one-time testing fails to detect more than 75% of cases of advanced neoplasia. Repeat annual testing would no doubt be more effective and should be strongly recommended if this type of screening is preferred. Patients and physicians should not be reassured by negative results. Patients choosing sigmoidoscopy should understand that as they age important lesions in the proximal colon may go undetected. The combination of one-time FOBT and sigmoidoscopy misses almost 25% of cases of advanced neoplasia. Patients choosing radiographic imaging should recognize that these modalities have never been evaluated in a screening population and that their effectiveness is uncertain. Finally, patients choosing colonoscopy should understand that the effectiveness of colonoscopy depends on obtaining a complete examination by a well-trained endoscopist.

KEY POINT

Screening for CRC with any of the recommended tests is more clinically effective, leading to mortality reduction, and more cost-effective than other medical interventions and treatments.

Cost and Compliance of Colon Screening

During the past few years, there has been considerable discussion about which screening program is most effective. Although this question is far from resolved, several sophisticated cost-effectiveness models are available, all of which show the same thing—screening for CRC with any of the recommended tests is more clinically effective, leading to mortality reduction, and more cost-effective than other medical interventions and treatments (23–29). Although more work is needed to clarify the clinical effectiveness of each screening program, it is obvious that no program is effective if compliance is poor; therefore, physicians need to focus more attention on obstacles to compliance.

Despite compelling evidence that screening average-risk individuals >50 years of age can save lives, in the United States compliance with recommended screening tests is only ~30% to 40%. These rates are much lower than rates achieved for cervical cancer and breast cancer screening. There are many obstacles to compliance (Table IV), but

TABLE IV.

OBSTACLES TO SCREENING COMPLIANCE

<i>Problem</i>	<i>Status</i>
● Public awareness	Improving (Katie Couric effect)
● Physician awareness of screening	Improving
● Public acceptance of screening tests	Poor
● Payer coverage Medicare	Fecal occult blood test, sigmoidoscopy, and colonoscopy are covered as of July 2001
Private	Mandated coverage in Virginia, Missouri; otherwise varies from no coverage to specific test coverage
Uninsured	No progress

perhaps the most important is the failure of health care providers to discuss screening with patients. A 1998 Gallup poll found that 88% of nonscreened patients said their health care providers had not discussed screening. Obviously, further study is needed to better understand and overcome the barriers

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Dialogue Box

ADVISORY BOARD

What do you think of the FOBT as a colon cancer screening method?

LIEBERMAN

The FOBT is a cost-effective method that has been shown in 3 randomized trials to reduce mortality from colorectal cancer. However, it does have a number of limitations. First of all, it works reasonably well as a cancer detection test but not as a cancer prevention test. Although evidence suggests that it detects cancers at an early stage, a significant number of patients with a positive test will have advanced cancers at the time of detection. My own view of colorectal cancer screening is that the bar needs to be raised from the detection of early, curable cancer to its actual prevention by the detection of high-risk premalignant lesions. Only endoscopic screening tests, colonoscopy, and flexible sigmoidoscopy are capable of doing this. Second, the FOBT should be done on an annual basis, but for various reasons, including aesthetic ones, patient compliance is not often achieved. Third, the FOBT may not be as cost-effective as it seems when one factors in false-positive rates as well as the indirect costs of main-

taining an effective office operation designed to ensure annual testing—costs not factored into the cost analyses that have been published. Finally, let's not overlook that a one-time FOBT fails to detect 76% of advanced neoplasia in the colon, which can lead to a false sense of reassurance on the part of the patient.

ADVISORY BOARD

How do you define advanced neoplasia?

LIEBERMAN

In our study and in most other studies it's defined as follows: (1) cancer; (2) an adenoma with high-grade dysplasia, termed by some pathologists as carcinoma-in-situ, which signifies there are malignant cells limited to the mucosa that have not crossed beyond this barrier; (3) a villous adenoma; and (4) the most controversial lesion, adenomatous polyps >1 cm. Statistically speaking, as you get above 1 cm in size, the risk of cancer increases significantly. The rationale is that a 1-cm polyp is a lesion you can identify in a screening test and then remove because some of those patients will go on to develop cancer.



Dialogue Box

ADVISORY BOARD

The Minnesota Colon Cancer Group used the FOBT and ended up with lower rates of cancer incidence over time than nonscreened controls. Was that because they picked up cancerous lesions or were the polyps bleeding?

LIEBERMAN

In that group's published analysis, the investigators believed it was due to the detection and removal of premalignant adenomatous polyps. In that study they used a rehydrated FOBT, which resulted in fairly high rates of colonoscopy (38%) in the screened group during the 15 years of the study, and it's likely that the benefit seen was attributable to that fact. If you believe in the adenoma-cancer hypothesis that most, if not all, cancers evolve from adenomas, this study provides proof of the principle that if you can detect and remove high-risk adenomas, you can prevent cancer.

ADVISORY BOARD

Doesn't the Minnesota Colon Cancer Group study also support the notion that the FOBT identifies those patients who will benefit from colonoscopy with polyp removal?

LIEBERMAN

It clearly does that. Moreover, in a study recently published by our group in *The New England Journal of Medicine*, although the sensitivity of the FOBT was relatively low, it was found that a patient who had a positive test had a 3½-fold increase in risk for having advanced neoplasia in the colon.

ADVISORY BOARD

A limitation of virtual colonoscopy is its inability to detect small non-neoplastic hyperplastic polyps. Are there any data on how long you

can safely observe small polyps not pathologically defined?

LIEBERMAN

Few data are available because there are ethical issues involved in identifying patients who have potentially premalignant lesions and are not doing anything about them. In a barium enema study that was conducted by the Mayo Clinic in the pre-colonoscopy era, patients found to have 1-cm polyps were followed and the rates of cancer development documented. There was a fairly predictable progression rate of cancer in those individuals. To my knowledge there haven't been any other studies done for average-risk individuals. Based on epidemiologic studies, we do know that about 30% to 50% of us will develop adenomas in our lifetime but only 5% to 6% of us will develop cancers. Therefore, most adenomas do not appear to become cancers recognized during life.

ADVISORY BOARD

Independent of histologic type, does the size of a polyp also determine cancer risk?

LIEBERMAN

I think the best we can say is that patients with polyps >1 cm, using size as the sole criterion, have a higher risk of developing colon cancer than those with adenomas <1 cm. Although this could be due to the cancer emerging from that particular polyp, the polyp could also be simply a "marker" of a malignancy milieu—that is, the polyp may be indicative of an individual who genetically and/or environmentally is predisposed to developing colon cancer at a later time. We also know that larger polyps are more likely to harbor cancer within them at the time of detection; thus, a 2- or 3-cm polyp has a much higher chance of being a malignant polyp as opposed to a benign one.



Dialogue Box

ADVISORY BOARD

Give us your recommendations for the management of specific types of polyps that are detected on flexible sigmoidoscopy and biopsied. What do you recommend for hyperplastic polyps?

LIEBERMAN

My interpretation is that on the basis of that finding, the patient does not appear to have a high risk of proximal neoplasia and should continue in the flexible sigmoidoscopy screening program. The patient would not require colonoscopy on the basis of that finding.

ADVISORY BOARD

What would you recommend for an 8-mm or a 1.3-cm adenomatous polyp?

LIEBERMAN

Based on current data, we believe the presence of an adenoma of any size in the distal colon identifies a patient who has a high risk of advanced neoplasia in the proximal colon; thus, I would recommend a full colonoscopy. If an 8-mm polyp was the only thing found, then the patient should be enrolled in a surveillance program and have a follow-up colonoscopy at about 5 years. If a 1.3-cm adenomatous polyp was the only finding following evaluation via colonoscopy, I'd recommend a follow-up study at 3 years. This recommendation is based on the National Polyp Study data published in the mid-1990s, which suggested that patients with large polyps had a slightly higher risk of advanced neoplasia at 3 years of follow-up.

ADVISORY BOARD

Should those patients have surveillance colonoscopies performed every 3 years for life?

LIEBERMAN

No, I think you need to recertify patients each time so that if at the 3-year examination you find nothing or just small polyps, then the interval should be extended. If they continue to have large lesions, then I think you should bring them back again in 3 years.

ADVISORY BOARD

Please expand on what is known about hereditary nonpolyposis colorectal cancer syndrome.

LIEBERMAN

The hereditary nonpolyposis colorectal cancer syndrome is responsible for about 5% of all colorectal cancers. Unlike familial polyposis where patients have hundreds of polyps, patients with this syndrome form polyps early in life, while in their 30s and 40s. These polyps seem to arise on a genetic basis as a result of a mismatch repair gene mutation. The genes affected are responsible for correcting genetic mistakes, which commonly occur in all of us during the process of making new cells. Mutation in these genes results in the mistakes not being corrected, which, in turn, allows malignant cells to develop. As a result, these patients tend to develop polyps at an early age, and these polyps can become malignant fairly quickly. These patients are also at risk for developing other types of cancer, including ovarian, uterine, and breast cancers.

ADVISORY BOARD

How do you clinically differentiate these high-risk patients from those at moderate familial risk by virtue of having a first-degree relative with colon cancer?

LIEBERMAN

Two forms of criteria have been proposed. One is



Dialogue Box

the very rigid Amsterdam Criteria, which require you to have a couple of affected relatives <50 years of age in more than one generation. The more simplified Bethesda Classification suggests you think about this entity if you have a patient <50 years of age with colorectal polyps or cancer who also has a relative <50 years of age with colonic polyps or cancer.

ADVISORY BOARD

If the patient <50 years of age has cancer, isn't it irrelevant from the standpoint of screening?

LIEBERMAN

It's relevant with regard to that patient's family. Patients with hereditary nonpolyposis have a 50% to 80% chance of developing colorectal cancer over the course of a lifetime compared with the 2- to 4-fold increased risk seen in the familial moderate-risk group. In addition, identification of this syndrome also raises the question of genetic testing.

ADVISORY BOARD

What genetic tests are available?

LIEBERMAN

There are at least 4 to 5 mismatch repair gene mutations that have been identified. The 2 available primary tests detect the 2 most common mismatch repair genes that are responsible for about 50% to 60% of the patients who have this syndrome. Patients who are identified with these mutations have an extremely high risk of developing cancer.

ADVISORY BOARD

What are the tests called?

LIEBERMAN

The tests are called MSH1 and MLH2 and are quite costly. You have to consider that these tests constitute genetic screening and should take into account the tests' potential psychologic and socioeconomic impact, including the possible effect on the patient's insurability. If you are going to order these tests, make sure the patient has ready access to genetic counseling as well.

ADVISORY BOARD

What is the evidence that colonic neoplasia appears to be migrating proximally in the colon with advancing age?

LIEBERMAN

The VA Cooperative Study as well as others have demonstrated that polyps in patients who develop them later in life are more likely to be located in the proximal portion of the colon than those that develop in patients who are younger. We're not certain why. One possible theory is that genetic soil and environmental factors that accumulate over a lifetime have a greater impact on the right colon than the left. The VA study required patients with no structural examinations of the colon for 10 years prior to having the full colonoscopy done.

ADVISORY BOARD

Should the stool obtained during an annual rectal examination be checked for occult blood?

LIEBERMAN

I recommend testing the stool and if the test is positive, the patient should have a colonoscopy. However, allow me to underscore that if negative, this does not constitute adequate screening and the patient, at a minimum, still needs to be given 3 cards for a formal FOBT.