Colorectal Cancer Screening: Clinical Guidelines and Rationale

Evidence exists that reductions in colorectal cancer (CRC) mortality can be achieved through detection and treatment of early-stage CRCs and the identification and removal of adenomatous polyps, the precursor to these cancers. An expert, multidisciplinary panel was convened to review this evidence and to produce recommendations to guide clinicians and the public in making decisions regarding CRC screening and surveillance. As part of its review, the panel also commissioned a simulation model that estimates and compares the clinical consequences (benefits and major complications) of each screening approach. This guideline report presents the panel's recommendations with respect to screening and surveillance in people at average risk for CRC and those at increased risk because of a family history of CRC or genetic syndromes or a personal history of adenomatous polyps, inflammatory bowel disease, or curative-intent resection of CRC. The cost-effectiveness of potential screening strategies was taken into account when preparing the recommendations. A summary of the evidence on each screening test's performance, effectiveness, frequency, complications, and patient acceptance is included. Also provided are suggestions for ways to increase compliance with the recommendations, questions for which additional research is needed, and the results of the simulation model on screening consequences.

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The following organizations have endorsed the clinical practice recommendations in this report: American Cancer Society, American College of Gastroenterology, American Gastroenterological Association, American Society of Colon and Rectal Surgeons, American Society for Gastrointestinal Endoscopy, Crohn's and Colitis Foundation of America, Oncology Nursing Society, and Society of American Gastrointestinal Endoscopic Surgeons. Other endorsements are pending.

The recommendations in this report are based on the clinical literature as of September 1996. Additional evidence that appears after this date should be considered when making clinical judgments. Atypical circumstances pertaining to individual cases may justify deviation from patient care guidelines.

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Contents

I. RECOMMENDATIONS FOR COLORECTAL CANCER SCREENING AND SURVEILLANCE IN PEOPLE AT AVERAGE RISK AND AT INCREASED RISK

This report, which was prepared by a multidisciplinary expert panel, contains clinical guidelines for colorectal cancer screening and surveillance. The report consists of two main sections. The first contains specific recommendations for screening and surveillance in people at average and at high risk for colorectal cancer. The second section describes the evidence used to develop the recommendations.

The following general guidelines serve as the background against which these recommendations should be applied:

- **People with symptoms that suggest the presence of colorectal cancer or polyps should have appropriate diagnostic evaluation; they are not candidates for screening.**
- **Personal and familial risk factors need to be evaluated when considering screening.**
- **Screening for colorectal cancer and adenomatous polyps should be offered to all men and women without risk factors, beginning at age 50.**
- **Physicians should recommend a diagnostic evaluation of the colon to follow up a positive screening test.**
- **Follow-up surveillance should be considered after treatment of colorectal cancer or removal of adenomatous polyps or in the presence of underlying premalignant conditions such as inflammatory bowel disease.**
- **Health care providers who perform the tests should have appropriate proficiency, and the tests should be performed correctly.**
- **Screening should be accompanied by efforts to optimize the participation of patients and health care providers, both with screening tests and appropriate diagnostic follow-up.**
- **People who are candidates for screening should be given adequate information on the risks and benefits of the various screening procedures.**

Screening, diagnostic evaluation, and surveillance strategies are presented as options that the panel thought were acceptable, based on the evidence. The options differ in strength of evidence, size of benefit, clinical performance, effectiveness in preventing colorectal cancer, simplicity, safety, patient acceptance, cost, and cost-effectiveness. Choice of options by individual patients and physicians requires consideration of these factors.

This report contains recommendations for colorectal cancer screening and surveillance in various risk groups. These recommendations (boldface) and their respective rationale are derived from consideration of the supporting evidence and are summarized below. Clinicians are encouraged to review the text of the report for more complete information. The recommendations are presented in algorithmic form in Figure 1.

People at Average Risk (Asymptomatic, Age $\geq$50 years, No Other Risk Factors) for Colorectal Cancer

The fecal occult blood testing and flexible sigmoidoscopy screening options presented below are supported by strong evidence of effectiveness.

Fecal Occult Blood Testing

Recommendation: Offer fecal occult blood screening each year.

Rationale: This recommendation is based on direct evidence discussed in this report and on indirect evidence from the panel's model of the clinical consequences of screening over time. Testing of two samples from each of three consecutive stools for the presence of fecal occult blood (FOBT) followed by colonoscopy has been shown in three randomized controlled trials to reduce the risk of death from colorectal cancer. In these trials, patients with a positive FOBT had mostly colonoscopy as their diagnostic workup. Results of a nonrandomized controlled trial and a case-control study are consistent with these findings. Disadvantages of this strategy are that currently available tests for fecal occult blood fail to detect many polyps and some cancers, and many people who test positive will undergo the discomfort and risk of full bowel examination to find that they do not have adenomatous polyps or cancers. Yearly testing is chosen because the randomized trials show that yearly testing is more effective than testing every 2 years, because the frequency of testing has small effects on overall inconvenience and cost, and because yearly testing may detect lesions that were missed on earlier rounds of screening but have not yet progressed to the stage in which they are less curable. Rehydration improves the sensitivity of the test at the expense of specificity, and a special diet can decrease the rate of false positive tests. Newer generation tests may increase sensitivity with minimal loss of specificity.

Diagnostic Work-up of Positive FOBT

Recommendation: Average-risk people with an abnormal screening test result with FOBT (i.e., a positive test on any sample) should have recommended to them an accurate examination of the entire colon and rectum by colonoscopy. An alternative is double-contrast barium enema, preferably with flexible sigmoidoscopy.

Rationale: A higher level of performance (sensitivity and specificity) is expected for diagnostic tests than for screening tests. Colonoscopy can examine the entire colon with few false negative or false positive findings and can provide definitive treatment of polyps and some cancers during the same procedure. The effectiveness of diagnostic colonoscopy coupled with screening FOBT is established by three randomized and one nonrandomized controlled trials. Double-contrast barium enema (DCBE) also can examine the entire colon with relatively high sensitivity and specificity for large polyps ($>$1 cm) and

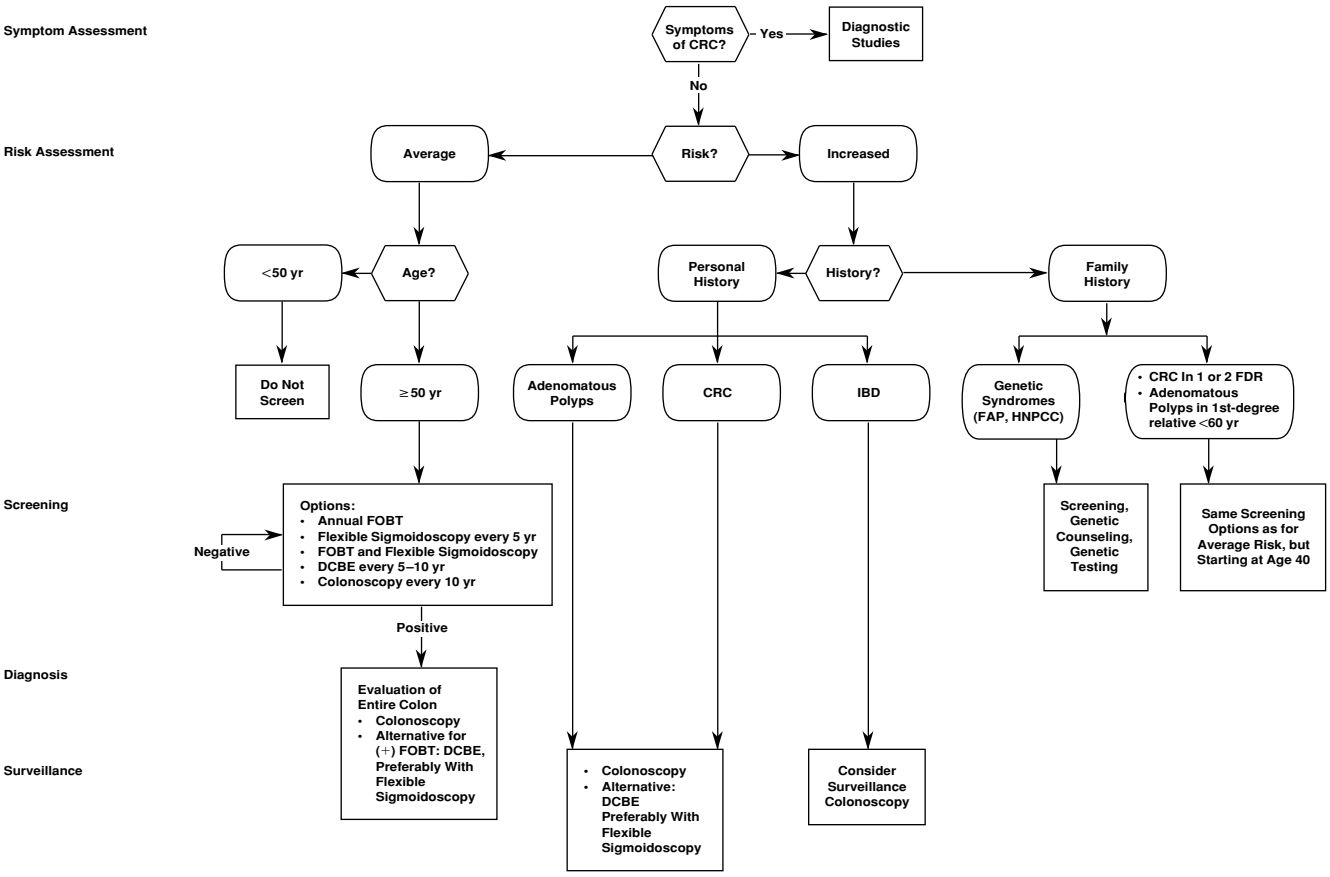

Figure 1. Algorithm for CRC screening and surveillance in average-risk and increased-risk populations. Consult the text for more complete information on the screening strategies given in each cell. Note that the strength of evidence for screening options and their overall performance varies.

cancers and is safer and less expensive than colonoscopy. However, it is not possible to biopsy or remove neoplasms during the same procedure, so that patients with abnormalities must undergo an additional examination, by colonoscopy, to establish the diagnosis and provide treatment. Adding flexible sigmoidoscopy to DCBE increases sensitivity but is also more difficult to accomplish and the magnitude and clinical importance of the additional sensitivity is uncertain. DCBE and flexible sigmoidoscopy together have been shown to have a performance comparable to colonoscopy, but there is presently no evidence concerning the effect of diagnostic DCBE, with or without flexible sigmoidoscopy, coupled with screening FOBT on colorectal cancer deaths. Both the extent to which the entire colon is visualized and accuracy in the part examined depend on the skill of the examiner; this should be taken into account when choosing a diagnostic test.

Flexible Sigmoidoscopy

Recommendation: Offer screening sigmoidoscopy with a flexible sigmoidoscope every 5 years. Polyps <1 cm should be biopsied, and if adenomatous polyps or cancers are found, the patient should be offered colonoscopy to remove polyps, biopsy cancers, and examine the rest of the bowel. If large (>1 cm) polyps are found, colonoscopy should be recommended. Patients with tubular adenomas <1 cm should decide with their physician whether to undergo colonoscopy.

Rationale: The effectiveness of screening sigmoidoscopy is supported by direct evidence from two case-control studies reporting a reduction in mortality in patients who had been screened and from a cohort study and a case-control study showing that removing adenomatous polyps reduces the risk of colorectal cancer. Disadvantages of this strategy are that sigmoidoscopy alone detects only about half of all colorectal cancers and polyps and that the procedure involves some discomfort, risk, and inconvenience for the patient. A 5-year interval is chosen because of strong (randomized trial) evidence that colonoscopy is equally effective at 1- or 1- and 3-year intervals, weaker (case control) evidence that sigmoidoscopy is effective at up to 10-year intervals, and the observation that few polyps arise and progress to advanced cancer in a 5-year period. If a small, tubular adenoma is found on sigmoidoscopy, the probability of finding a clinically important proximal neoplastic lesion is small, and such patients are apparently not at greater risk of colorectal cancer than people without such polyps. Nevertheless, some patients with

small, tubular adenomas and their clinicians prefer to follow up such lesions with colonoscopy because it offers greater certainty that proximal adenomas have been identified and excised. In addition to the foregoing direct evidence, additional support for sigmoidoscopy screening derives from the panel's model on the clinical consequences of colorectal cancer screening over time.

The individual components of the following strategy are supported by strong evidence but the added value of combining the two, while theoretically present, is not well established by research evidence.

Combined Fecal Occult Blood Testing and Flexible Sigmoidoscopy

Recommendation: Offer screening that includes both FOBT and sigmoidoscopy (as described above) together.

Rationale: The combination of both screening methods may correct some of the limitations of each method used alone. Evidence that these two modalities together are more effective than either one alone comes from a nonrandomized controlled trial of FOBT in patients who had had screening sigmoidoscopy. Indirect evidence supporting this recommendation is that FOBT alone is a weak strategy for detecting polyps anywhere in the bowel and may be least effective in finding polyps or cancers in the distal colon and that the sigmoidoscope cannot visualize the entire colon. Additional indirect support derives from the panel's model on the clinical consequences of colorectal cancer screening over time. The main disadvantage of this screening strategy is that people incur the costs and complications of both tests with an uncertain gain in effectiveness.

The following strategies are not *supported by direct evidence (from randomized trial, nonrandomized trial, or case-control studies) that they reduce mortality from colorectal cancer.*

Double-Contrast Barium Enema

Recommendation: Offer double-contrast barium enema every 5–10 years.

Rationale: There are no studies evaluating whether screening DCBE alone reduces the incidence or mortality from colorectal cancer in people at average risk of the disease. This strategy is based on evidence that screening DCBEs can image the entire colon and detect cancers and large polyps almost as well as colonoscopy and better than FOBT or sigmoidoscopy. The panel's decision analysis on the clinical consequences of colorectal cancer screening also supports DCBE screening. The procedure probably is safer than sigmoidoscopy or colonoscopy. This method can, however, miss small polyps, does not permit removal of polyps or biopsy of cancers, and it is more likely than colonoscopy to identify artifacts and other findings (such as stool) as polyps so that patients with an abnormal barium enema may need a subsequent colonoscopy. The procedure involves some discomfort and inconvenience for the patient. Adding flexible sigmoidoscopy to DCBE increases sensitivity but is also more difficult to accomplish and the magnitude and clinical importance of the additional sensitivity are uncertain.

Colonoscopy

Recommendation: Offer colonoscopy every 10 years.

Rationale: There are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from colorectal cancer in people at average risk of the disease. However, colonoscopy was an integral part of randomized and nonrandomized controlled trials of FOBT that showed a reduced mortality in screened patients. Also, colonoscopy, which can visualize the entire colon, is analogous in performance and effectiveness to sigmoidoscopy, and there is direct evidence that screening sigmoidoscopy reduces colorectal cancer mortality. In addition, colonoscopy has been shown to reduce the incidence of colorectal cancer in a cohort of people with adenomatous polyps. Because colonoscopy permits visualization of the entire colon directly, detection and removal of polyps, and biopsy of cancers throughout the colon, it can be considered for screening average-risk individuals. Colonoscopy involves greater risk and inconvenience to the patient than sigmoidoscopy, and not all examinations visualize the entire colon. An interval of 10 years was chosen for asymptomatic, average-risk people because of strong direct evidence that few clinically important lesions are missed by this examination. In addition, a controlled trial has shown a very low incidence of advanced adenomas during surveillance follow-up colonoscopy after an initial negative examination. Weaker support of this interval includes a case-control study of screening proctosigmoidoscopy that suggested a protective effect from death due to distal cancer lasting up to 10 years. Indirect evidence from the National Polyp Study as well as estimates by pathologists indicate that few polyps will arise and progress to advanced cancer in less time in patients with no special risk factors. The panel's model on the clinical consequences of colorectal cancer screening over time also supports this recommendation.

People at Increased Risk for Colorectal Cancer

People With Close Relatives Who Have Had Colorectal Cancer or an Adenomatous Polyp

Recommendation: People with a close relative (sibling, parent, or child) who has had colorectal cancer or an adenomatous polyp should be offered the same options as average-risk people but beginning at age 40 years. If the close relative was diagnosed with colorectal cancer before the age of 55 years or with an adenomatous polyp before age 60, special efforts should be made to assure that screening takes place.

Rationale: There is evidence from cohort and case-control studies that people with close relatives with colorectal cancer have an increased risk of colorectal cancer and develop the disease at a younger age than people without a family history

of colorectal cancer. In people with a single first-degree relative, the incidence of colorectal cancer at age 40 years is comparable to that in people without a family history of colorectal cancer at age 50 years. Within each age group, the risk is greatest in those whose relatives developed cancer at a younger age. There is evidence that first-degree relatives of patients with adenomatous polyps also are at increased risk for colorectal cancer when the polyp has been diagnosed below the age of 60 years. People whose first-degree relative has developed colorectal cancer or adenoma at a relatively early age may prefer periodic complete evaluation of the colon, although there are no studies that have addressed the effectiveness of this approach directly.

People With a Family History of Familial Adenomatous Polyposis

Recommendation: People with a family history of familial adenomatous polyposis (FAP) should receive genetic counseling and consider genetic testing to see if they are gene carriers. A negative genetic test result rules out FAP only if an affected family member has an identified mutation. Gene carriers or indeterminate cases should be offered flexible sigmoidoscopy every 12 months beginning at puberty to see if they are expressing the gene. If polyposis is present, they should begin to consider when they should have colectomy.

Rationale: People with a family history of FAP have a high probability of carrying the disease because it is inherited as an autosomal dominant. Genetic testing within kindreds is available and can distinguish whether the patient is a carrier. However, it should not be offered before puberty. People with FAP have nearly a 100% chance of developing colorectal cancer. Genetic counseling is needed to deal with the high risk and the prospects of the only preventive strategy, colectomy. Because adenomatous polyps occur throughout the bowel, and precede cancer, sigmoidoscopic surveillance in a gene carrier is sufficient to discover if the patient is expressing the syndrome. Yearly examinations will alert the physician to any gene expression long before the cancer would develop. In patients with known FAP, colonoscopic surveillance is not helpful in identifying polyps with advanced pathology and in detecting early cancers because there are so many polyps. Colectomy is the only feasible way to prevent the development of cancer and should be accomplished as soon after the presence of the syndrome is confirmed and the procedure is acceptable to the patient.

People With a Family History of Hereditary Nonpolyposis Colorectal Cancer

Recommendation: People with a family history of colorectal cancer in multiple close relatives and across generations, especially if cancers occur at a young age, should receive genetic counseling and consider genetic testing for hereditary nonpolyposis colorectal cancer (HNPCC). They should be offered an examination of the entire colon every 1–2 years starting between the ages 20 and 30 years and every year after age 40 years.

Rationale: The Amsterdam criteria for identifying HNPCC families are: three or more relatives with colorectal cancer; one patient a first-degree relative of another (sibling, parent, child); two generations with cancer; and one cancer diagnosed below age 50. The cancers are preceded by adenomatous polyps, and both are predominately proximal to the splenic flexure. Risk of colorectal cancer is increased by age 21 and very high by age 40. Individuals are identified by family history, and genetic tests are positive in only 80% of these families. Because the Amsterdam criteria are relatively strict and may be falsely negative in some families, clinicians may want to counsel and test some people whose families do not meet all of the criteria. Genetic counseling is needed to help the patient deal with the high lifetime risk of colorectal cancer and other cancers and the need for aggressive screening. Because of the proximal anatomic distribution of cancers, the entire colon must be examined; sigmoidoscopy is insufficient, and FOBT has too low a sensitivity for the polyps that precede the cancer. Colonoscopy is the preferred examination because of the proximal distribution of polyps and cancer; the high risk of cancer; the high frequency of finding polyps that need to be resected, and the presence of adenomatous polyps that are flat and small and that rapidly progress to advanced pathology even when small. An alternative examination is double contrast barium enema, preferably with sigmoidoscopy. The interval between screening examinations should be shorter than for average-risk people because of evidence that polyps may form and progress from a small size to cancer rapidly in people with HNPCC and because the probability of cancer and adenomatous polyps being present at each examination is so high that the risk of missing a clinically important lesion is substantial. There is no direct evidence on which to base a precise screening interval.

People With a History of Adenomatous Polyps

Recommendation: Patients in whom large (>1-cm diameter) or multiple adenomatous polyps are found and removed at colonoscopy should have an examination of the colon 3 years after the initial examination. The interval for subsequent examinations depends on the type of polyps that were detected. If the first follow-up is normal or only a single, small, tubular adenoma is found, the next examination can be in 5 years. In special circumstances (e.g., polyps with invasive cancer, large sessile adenomas, or numerous adenomas), a shorter interval may be necessary, according to the judgment of the clinician and the wishes of the patient.

Rationale: Colonoscopic polypectomy and surveillance has been shown to reduce subsequent colorectal cancer incidence. There is strong evidence, from a randomized controlled trial, that the rate of developing adenomas with advanced pathology after adenomas are found and removed is low after several years

of follow-up and that there is no gain from examining patients at both 1 and 3 years compared with only every 3 years. The evidence base for the interval for subsequent follow-up is not as strong. The follow-up examination is to detect and remove adenomas missed on the initial examination and to establish whether the patient has a tendency to form new adenomas with advanced pathology. The recommendation of a 5-year follow-up after a negative colonoscopy is based on the same reasoning as for after a negative sigmoidoscopy, as summarized previously. Because the effectiveness (incidence reduction) of polypectomy and surveillance in these patients has been shown with colonoscopy, this is the recommended follow-up procedure. Double-contrast barium enema is an alternative. Adding flexible sigmoidoscopy to double-contrast barium enema increases its sensitivity but is also more difficult to accomplish and the magnitude and clinical importance of the additional sensitivity is uncertain.

People With a History of Colorectal Cancer

Recommendation: Patients with a colorectal cancer that has been resected with curative intent (but who did not undergo complete adequate colonoscopic examination preoperatively) should have a complete examination of the colon within 1 year after resection. If this or a complete preoperative examination is normal, subsequent examination should be offered after 3 years and then, if normal, every 5 years.

Rationale: There is good evidence that the incidence of colorectal cancer is increased after the first occurrence, apart from recurrence of the original cancer. As with the original cancers, these subsequent cancers are preceded by adenomatous polyps that occur with increased frequency. There is no evidence to suggest that these polyps progress to cancer at a different rate from average-risk people who have not had a previous cancer. The decision whether to follow these high-risk patients with colonoscopy or double-contrast barium enema should be based on the different diagnostic and therapeutic characteristics of the two tests as described in this report. Adding flexible sigmoidoscopy to double contrast barium enema increases its sensitivity but is also more difficult to accomplish and the magnitude and clinical importance of the additional sensitivity is uncertain. Sigmoidoscopy also permits visualization of the anastamosis after distal resections.

People With Inflammatory Bowel Disease

Recommendation: In patients with long-standing, extensive inflammatory bowel disease, surveillance colonoscopy, looking for dysplasia as a marker of colorectal cancer risk, should be considered along with the extent and duration of the disease as a guide to when or if colectomy should be considered.

Rationale: There is good evidence for the increased rate at which colorectal cancer develops in patients with inflammatory bowel disease relative to the duration and extent of disease, and it is self-evident that colectomy eliminates the risk of colorectal cancer. It is common practice to perform surveillance colonoscopy every 1–2 years beginning after 8 years of disease in patients with pancolitis or after 15 years in those with colitis involving only the left colon. The rationale for this frequency is the difficulty of detecting cancer or dysplasia in any single examination. However, there is no direct evidence that this practice reduces colorectal cancer mortality in these patients and none that it is more effective than colectomy based on extent and duration of disease.

II. BACKGROUND INFORMATION FOR RECOMMENDATIONS ON COLORECTAL CANCER SCREENING AND SURVEILLANCE

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death in the United States. In 1996, an estimated 134,000 new cases of CRC will be diagnosed and 55,000 people will die of the disease.[1] Delayed diagnosis of CRC can result in medical malpractice action.[2] Risk factors for CRC include older age, family history, certain hereditary conditions, a diet high in saturated fat and low in fiber, excessive alcohol, and sedentary life style.[3] Some of these risk factors such as advancing age cannot be changed; others such as diet require massive and long-term public educational strategies to effect change. In recent years, evidence has accumulated that the number of people developing and dying of CRC could be greatly reduced through appropriate screening and surveillance. However, there has been uncertainty about the choice of screening and surveillance tests, how frequently they should be performed, who should be tested, and the cost-effectiveness of various test strategies. In addition, the rate of CRC screening is low. (See page 603 for data on CRC screening rates.) Therefore, in 1994, the federal Agency for Health Care Policy and Research (AHCPR) entered into a contract with the American Gastroenterological Association (AGA) to evaluate the evidence on CRC screening and surveillance and to develop appropriate clinical practice guidelines based on this evidence. AGA produced this document on behalf of a consortium of organizations that were (in addition to AGA) the American Society for Gastrointestinal Endoscopy, the American Society of Colon and Rectal Surgeons, American College of Gastroenterology, and the Society of American Gastrointestinal Endoscopic Surgeons.

How These Guidelines Were Developed

AHCPR and the consortium established a multidisciplinary expert panel in 1994 to develop the guidelines. Two panel members (S.J.W. and R.H.F.) jointly chaired the panel. All panel members provided written disclosure of any potential conflicts of interest to AHCPR. (No such conflicts were present.) A group designated as the "Research Design Team" (consisting of the co-chairs, several panel members, and outside experts in gastroenterology, radiology, gastrointestinal surgery, and health care economics) was given the task of preparing a preliminary list of questions to be answered by the guidelines. They also designed and directed the literature search and review process that would be the basis for the initial work of the guideline panel. A subcontractor to AGA, Abt Associates, Inc. of Cambridge, Massachusetts, conducted the literature search. This search utilized Medical Subject Headings (MeSH) terms to search MEDLINE from 1966 to 1994 and Cancerlit from 1980 to 1994. Other articles published during the writing of the guideline were reviewed by the co-chairs who consulted with panel members as necessary to determine the articles' significance and relevance. MeSH terms used in the literature search were: colonic neoplasms, rectal neoplasms, colorectal neoplasms, sigmoidoscopy, colonoscopy, barium, genetic screening, hereditary diseases, and occult blood. The search yielded more than 3500 citations. An "Abstract Review Form" was completed for each citation and used to document disposition of the citation. The form noted if the article was rejected for further consideration and the reason for the rejection, if the article was to be retained for further consideration and the reason for retention, if it had a useful bibliography, and any other comments that might be relevant. The Research Design Team reviewed these forms and from them selected approximately 350 key articles. A 16-page "Data Collection Form" was used to summarize the key articles. It included data such as the number of people in the study, the specific research questions it addressed, the study design, and the results. This information was used by the Research Design Team to prepare a set of evidence tables concerning CRC natural history and epidemiology, risk factors, screening test performance characteristics, effects of screening and surveillance, test cost and cost-effectiveness, and patient and provider participation. The evidence tables summarized the following attributes of the key studies for the panel: location and time period, outcome measure used, results, and conclusions. Brief comments from the Research Design Team about the study were also included in the table as appropriate.

Development of the actual practice recommendations and presentation and analysis of the evidence behind them was the responsibility of the aforementioned multidisciplinary panel. Its members included specialists in behavioral medicine, colorectal surgery, epidemiology, family practice, gastroenterology, general internal medicine, health care economics, nursing, oncology, osteopathy, preventive medicine, public health, and radiology, as well as a physician assistant and a consumer representative. Under the supervision of the co-chairs, an initial working draft of the guideline was prepared by a writer who is a physician and journal editor.

The panel met for 2 days in December, 1994, to establish the scope of the guideline, develop a common understanding of the main concepts and data bearing on CRC screening, surveillance, and diagnosis, decide on the specific research questions to be addressed, and review the key clinical research literature on CRC screening and surveillance. It also agreed on the following mission statement to serve as the fundamental objective of the project: **To develop practical screening and surveillance guidelines for clinicians so as to decrease colorectal adenocarcinoma morbidity and mortality in average- and high-risk populations.**

The panel met again in April, 1995, to discuss the main evidence on which guidelines would be based, hear public testimony on the issues, and draft preliminary guidelines. In addition to these meetings, individual members of the panel performed in-depth analyses of the evidence base for specific questions and the panel co-chairs held numerous discussions

with panel members by telephone and in writing to obtain answers to specific questions, clarify recommendations, and resolve differences of opinion. In June 1995, a draft of the guideline was sent to the entire panel for review. The following month, the panel co-chairs and project staff met to discuss unresolved questions raised by members of the panel and to plan the best way to address them. During the following months, the co-chairs consulted frequently by telephone with panel members to discuss these questions. The results of these discussions were incorporated in a revised draft.

At the aforementioned July meeting, it was also decided that a decision analysis on the clinical consequences of various screening strategies would be conducted. This analysis was conducted in the fall of 1995 and reviewed by the panel. The methods and results of the analysis are described in Appendix 2. Briefly, the analysis was based on a simulation of a population cohort followed from ages 50 to 85 years, with "perfect" compliance. The results can be thought of as an estimate of the results of a screening program on an average person in terms of (1) the likelihood of developing a case of CRC and of having it detected; (2) having false positive or false negative test results; (3) developing complications; (4) increasing his/her life expectancy, and (5) the expected number of tests to be conducted. The ranking of the screening programs, however, is not obvious from the results because it is possible that different individuals will value the possible outcomes differently. The analysis showed that all screening and surveillance strategies recommended by the panel resulted in reduced mortality from CRC.

In May 1996, AHCPR notified the panel co-chairs that, as a result of the restructuring of the AHCPR guideline program, it would not support completion of the guideline. The panel elected to complete the guideline themselves, under AGA auspices. Another revised draft of the guideline was prepared and sent to the panel for comment in May 1996. Their comments were incorporated into a revised report that was reviewed by the panel in August. It also was sent to the sponsoring medical societies and several other organizations for comment. A few unresolved issues were addressed by a subcommittee of the panel, and the final report was approved by the panel in November 1996. The overall developmental process is summarized in Figure 2.

While this report is issued on behalf of the consortium organizations, the panel members had final authority over the content and wording. Decisions were reached by consensus; a majority view was taken in instances where the opinions of a few individual members differed from those of the rest of the panel and a revision of the guideline that was acceptable to the majority could not resolve the difference.

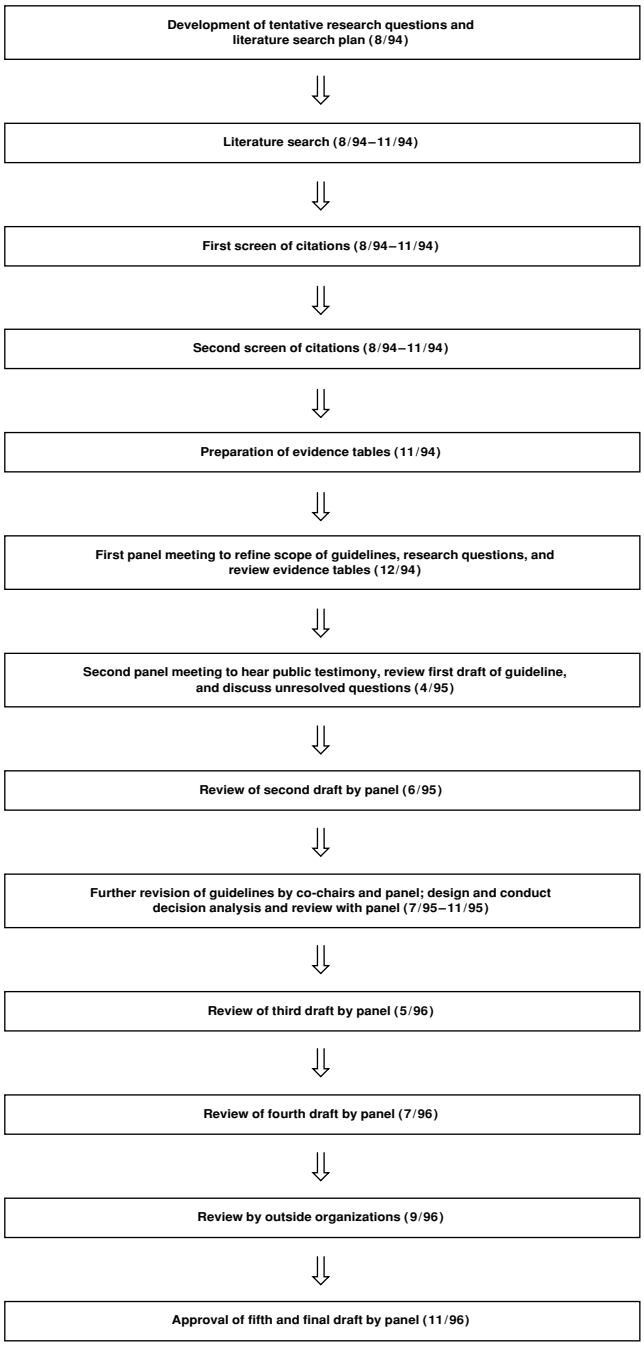

Figure 2. Summary of the guideline process and timeline.

Definition of Screening, Diagnosis, and Surveillance

Screening, diagnosis, and surveillance serve three different purposes. *Screening* (in the context of colorectal cancer) identifies individuals who are more likely to have CRC or adenomatous polyps from among those without signs or symptoms of the disease. *Diagnosis* classifies people who are suspected of having CRC or adenomatous polyps (in this case because of a positive screening test) into those with and without the disease. *Surveillance* monitors people with previously diagnosed colorectal disease; e.g., patients who have had polyps, CRC, or inflammatory bowel disease. Definitions of other terms used in this report are included in the Glossary.

Scope of the Guidelines

These guidelines address screening for CRC and adenomatous polyps in people without symptoms of the disease,

subsequent diagnostic workup in those with positive tests, and surveillance of people with colorectal disease.

The effectiveness of screening for CRC and its antecedents should be seen in the context of other preventive interventions. Diet, drugs, nutritional supplements, and other lifestyle factors might also prevent this cancer. The authors recognize that these are part of an overall strategy to prevent CRC and deaths but did not review this evidence and make no recommendation for or against these other forms of prevention. The guidelines also do not cover investigation of gastrointestinal symptoms or treatment and general follow-up of patients after treatment for CRC. Lastly, the specific qualifications and training needed to perform a given screening test properly or to measure proficiency are beyond the scope of the panel's charge.

How to Use These Guidelines

The guidelines in this report set out several options for screening, diagnosis, and surveillance for CRC. The panel concluded that there was strong evidence to support screening and that several tests, either alone or in combination, offer high enough levels of performance and effectiveness to be included among the options for screening. Decisions about which test or tests to use should take into account the patient's preferences, the patient's age, any existing comorbidity, and local resources and expertise. The panel considers planning of CRC screening an ideal opportunity for clinicians to share the decision making process with their patients as well as for exercising their own clinical judgment.

Rationale and Strength of Evidence for Screening

Reasons to Screen for Colorectal Cancer

In general, screening is justified when (1) a disease is common and associated with serious morbidity or mortality; (2) screening tests are sufficiently accurate in detecting early stage disease, are acceptable to patients, and are feasible in general clinical practice; (3) when treatment after detection by screening has been shown to improve prognosis relative to treatment after usual diagnosis; and (4) evidence exists that the potential benefits outweigh the potential harms and costs of screening.[4,5] CRC fulfills all of these criteria. First, it is common and serious: it is the second leading cause of death from cancer in the United States, affecting women and men about equally. Treatment of patients with advanced CRC is largely unsuccessful. In 1996, an estimated 134,000 new cases of CRC will be diagnosed and 55,000 people will die of the disease.[1] Second, various screening tests have been shown to achieve accurate detection of early stage cancers.[6–8] Third, evidence from controlled trials and case-control studies suggests, with various degrees of persuasiveness, that removing adenomatous polyps reduces incidence of CRC and detecting early-stage cancers reduces mortality from the disease.[9–14] Finally, the decision analysis conducted as part of producing this guideline report also shows that screening benefits outweigh its harms. The various ways of screening for CRC all have cost-effectiveness ratios comparable to those of other generally accepted screening tests.[15]

The natural history of CRC also suggests that screening can be effective. Most cancers develop from benign adenomatous polyps and develop slowly over many years,[16–18] providing a window of opportunity for detecting and removing precancerous polyps and early-stage cancers. Thus, screening strategies can be directed toward detecting cancers early to reduce morbidity and mortality and detecting and removing premalignant polyps to reduce the incidence of CRC.

Screening Rates in the U.S. Population

Most Americans are not currently screened for CRC. The best information on screening rates in the general population comes from the National Health Interview Survey (NHIS), a household survey in which personal interviews were conducted on a national sample of the civilian, noninstitutionalized population of the United States. The survey contained questions about cancer screening in 1987 and 1992. Screening rates increased between 1987 and 1992, but in 1992 only 17.3% of people aged 50 years or older had undergone FOBT in the previous year and 9.4% had undergone sigmoidoscopy in the previous 3 years.[19,20] CRC rates were somewhat higher for whites than for blacks and Hispanics. A 1993 telephone survey conducted through the Behavioral Risk Factor Surveillance System (BRFSS) of 38,000 people age 50 or older found that $<40\%$ reported having a sigmoidoscopy during the preceding 5 years. A 1992 BRFSS survey in four states found that $<35\%$ of respondents reported having had an FOBT.[21] These rates were higher than the NHIS data but, nevertheless, did not exceed 40% for any of the population subgroups that were surveyed.

Evaluation of Evidence

The panel considered only evidence from research that had been reported in full in peer-reviewed journals or for which full reports were available for critical review. Abstracts alone were not considered. The opinions of experts (separate from the evidence itself) and descriptions of usual practice were given relatively little weight; when they were included in the evidence base, this was explicitly stated.

Outcomes. The most appropriate outcome for studies of CRC screening is a reduction in the rate of death from CRC. For trials of interventions aimed at finding and removing adenomatous polyps, a reduced incidence of CRC is an appropriate intermediate outcome because an individual who is prevented from developing CRC cannot die of it. However, because not all incident CRCs progress to causing symptoms and death, reduction in incidence is an imperfect measure of reduction in mortality. Finding cancers at earlier stages (stage shift) or observing increased survival from the time of diagnosis from screening are consistent with effectiveness but, nevertheless, are fallible. This is because screening tends to find slower-growing tumors (length time bias) and may identify cancers

earlier in their natural history without necessarily changing the time at which an adverse health outcome such as death appears (lead time bias).

The authors sought to include evidence on the effects of screening on morbidity from CRC. Screening may improve quality as well as length of life by reducing the extent or urgency of surgery and the need for colostomy, by decreasing the need for chemotherapy, and by ameliorating suffering in those who die of the disease. However, if mortality from CRC were delayed rather than reduced, screening might lead to a longer and more distressing disease process. The authors found little direct evidence on the effect of screening on morbidity. Published case-control studies have not examined only morbidity and mortality because they included people who did and did not die of CRC, whereas randomized trials have taken mortality as their main outcome and have reported little on morbidity. Indirect evidence of an effect on morbidity would include evidence that screening reduced the number of patients undergoing emergency operations or increased the proportion of detected cancers that had less advanced pathology (stage shift).

Research design. The strongest possible evidence for the effectiveness of screening for CRC would come from large, well-conducted, randomized controlled trials. Observational studies, in which people do or do not undergo screening in the course of usual patient care, generally provide weaker evidence of effect than randomized trials, but for some screening strategies they are the only direct evidence available. Controlled cohort studies, one type of observational study, are convincing to the extent that screened and unscreened groups can be shown to be comparable. Case-control studies of screening have numerous potential weaknesses but can provide important evidence if careful attention has been paid to controlling bias. Simple descriptions of the onset of disease, stage at detection, and death rates in screened patients, without a concurrent comparison group, are the weakest useful evidence, mainly because one cannot be certain what the patients' cancer incidence and death rates would have been without screening and because patients who have sought screening tend to have a better prognosis than those who do not (compliance bias). Survival from the time of diagnosis may be misleading because of "lead time bias" (see above). This hierarchy of evidence applies to studies in general; individual studies can overcome some of the inherent weaknesses of their design.

This report describes the scientific strengths and weaknesses of the best studies bearing on each question. The following terms are used to describe individual studies (not the evidence as a whole): "strong" refers to randomized controlled trials, "intermediate" to cohort and case-control studies, and "weak" to all other study designs. (It is assumed that the studies were appropriately designed and executed.)

Weighing the evidence. The panel's recommendations with regard to screening and surveillance strategies are based on the totality of evidence. This includes the results of the strong and intermediate strength studies and the pattern of evidence from all well-conducted studies that are relevant, as well as biological plausibility, consistency of the evidence across different studies under different conditions, and analogy with other cancers in which screening has been shown to be of value. The authors chose to describe the strength of the evidence in words rather than creating an ordinal classification system similar to that used by other groups such as the U.S. Preventive Services Task Force and the Canadian Task Force on the Periodic Health Examination[5,22] because they believed that this provided a more complete description of the evidence and rationale used. The authors' relied on the totality of the evidence, with the results of the scientifically strongest studies being only one important part of the information base for the decision.

When the term "direct evidence" is used, it refers to strong and intermediate strength studies, specifically, controlled comparisons with incidence or CRC death as an outcome. "Indirect evidence" includes biological plausibility, extrapolations from studies that were not designed to investigate the issue in question, uncontrolled studies, natural history studies, and computer modeling studies.

For many important components of these guidelines, adequate direct evidence was not available. Where recommendations could not be based on the best possible kind of evidence (e.g., randomized trials of the effects of screening on CRC mortality), the panel provided the explicit reasoning behind its judgments. This frequently included indirect evidence such as the decision analysis conducted to estimate and compare the clinical consequences of various screening strategies.

Evaluation of New Test Technologies

Evidence for the value of early detection of CRC and the detection and removal of adenomatous polyps is based on currently available screening tests. New technologies were not considered if their effectiveness had not been rigorously tested in clinical studies by the time this report was prepared.

The authors believe that it might be appropriate in the future to substitute a newer test (such as virtual colonoscopy) for currently recommended ones if there is convincing evidence that the new test has (1) comparable performance (e.g., sensitivity and specificity) in detecting cancers or adenomatous polyps at comparable stages; (2) is equally acceptable to patients, and (3) has comparable or lower complication rates and costs. Provided this is the case, the authors feel that it would not be necessary to submit each new technology to the original standard of proof, i.e., a randomized controlled trial with death from CRC as an outcome measure.

Epidemiology and Biology of Colorectal Cancer

Incidence and Prevalence

Adenocarcinoma of the colon and rectum is the second most common cause of death from cancer in the United States, accounting for 14% of cancer deaths. In 1996, about 134,000

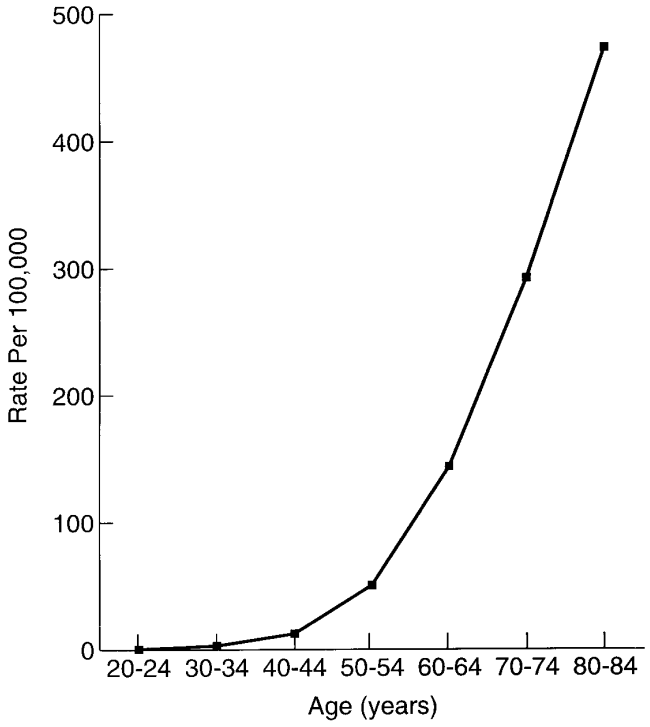

Figure 3. Age-specifi incidence of CRC in the general population; SEER Program (total, male and female, all races, colon and rectum, 1988–1992). (Reprinted with permission.[217])

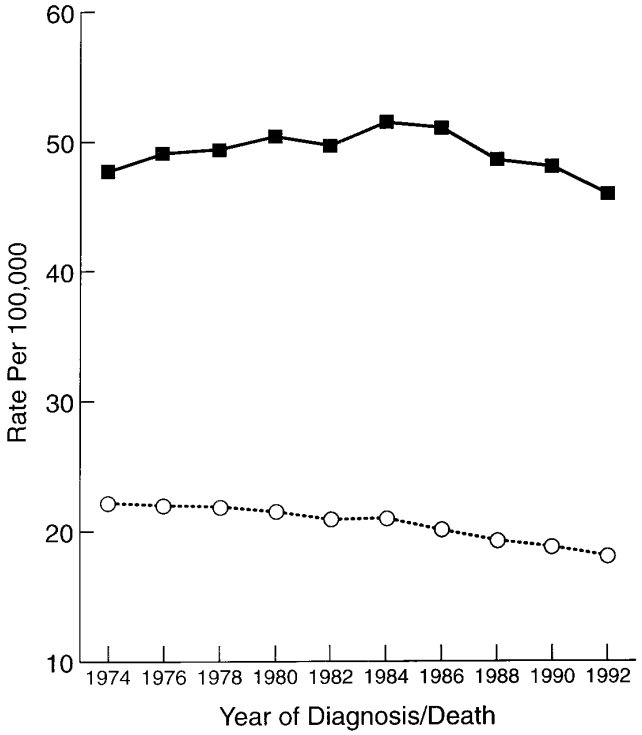

Figure 4. Age-adjusted incidence (■) and mortality (○) of CRC in the general population over time; SEER program (total, male and female, all races, colon and rectum, 1973–1992). (Reprinted with permission.[217])

Americans will be found to have the disease and about 55,000 will die of it.[1] The cumulative lifetime risk is approximately 5%. Other kinds of cancer comprise only 1% of all cancers of the large bowel.

As shown in Figure 3, the incidence of CRC increases with age and occurs with about equal frequency in women and men. However, racial differences in CRC survival have been observed.[23,24] The 5-year relative survival for colon cancer for 1983–1989 was 61% among white men, 59% among white women, 48% among black men, and 49% among black women.[25] Analyzing the National Cancer Institute Black/White Cancer Survival Study, Mayberry et al. found that black men and women with CRC had a 50% greater probability of dying of colon cancer than did white men and women.[24] Colorectal cancer mortality is low in American Indians and high in native Alaskans.[26] Factors including differences in stage of disease at diagnosis, aggressiveness of therapy, and sociodemographic and cultural characteristics have been postulated to contribute to the observed disparity in survival. However, none of these factors completely explains this observed incongruity.

African-Americans may have a more proximal distribution of adenomas and carcinomas than the general population; if this is true, full colonic examination would be more important in screening for CRC in this population.[27]

In recent years, the incidence and mortality rates of CRC have decreased, after having consistently increased over the past few decades (Figure 4). These trends could be explained by removal of premalignant polyps, earlier detection, more accurate diagnosis, lower incidence, or more effective treatment; it is uncertain in what proportions each of these contribute.

Clinical Features

Symptoms and signs of CRC may include abdominal pain, change in bowel habits, bleeding, an abdominal or rectal

Table 1. Comparison of TNM and Dukes' Staging Systems for CRC

Stage	TNM designation			Dukes' designation
0	Tis	N0	M0	—
I	T1	N0	M0	A
	T2	N0	M0	
II	T3	N0	M0	B
	T4	N0	M0	
III	Any T	N1	M0	C
	Any T	N2, N3	M0	
IV	Any T	Any N	M1	D

Tis, in situ; T1, tumor invades submucosa; T2, tumor invades muscularis propria; T3, tumor invades through muscularis propria; T4, tumor invades serosa, nodes, and adjacent organs; N0, negative lymph nodes; N1, 1–3 positive nodes; N2, >3 positive nodes; N3, positive nodes on vascular trunk; M0, no distant metastases; M1, distant metastases.

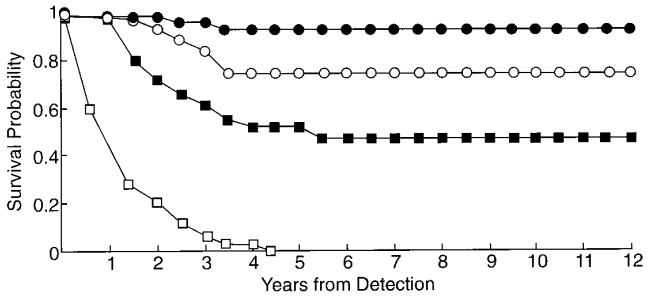

Figure 5. Correlation of survival with stage of CRC. See Table 1 for description of stages. ●, Stage I (63); ○, stage II (49); ■, stage III (55); □, stage IV (32). (Reprinted with permission. [218])

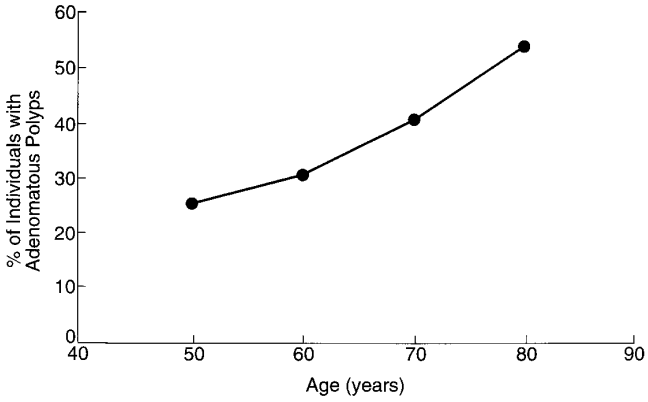

Figure 7. Prevalence of adenomatous polyps by age in the general population. (Reprinted with permission. [40])

mass, abdominal tenderness, and evidence of bowel obstruction.[28] Anemia and weight loss are also common. It is generally believed that symptoms are related to the site of the cancer, e.g., overt bleeding and obstruction are more common with rectosigmoid cancers, whereas weakness and abdominal mass occur more often in right-sided cancers.[29] These symptoms and signs are nonspecific indicators of CRC because they are also common in people with other diseases.

Cancers are found throughout the colon and rectum, with about half occurring proximal to the splenic flexure.[30,31] Currently, cancers appear to be found more often in the proximal colon than they were earlier in this century.[32] This observation triggered a vigorous debate about whether cancer had truly become more proximal over time or whether better methods of examining the proximal colon (principally colonoscopy) resulted in higher rates of detection of proximal cancers. There is no strong evidence to distinguish between better methods of detecting proximal lesions or biological change in distribution as an explanation. Changes in cancer incidence over time by site in the colon and rectum suggest that risk factors may operate differently at different sites.[32]

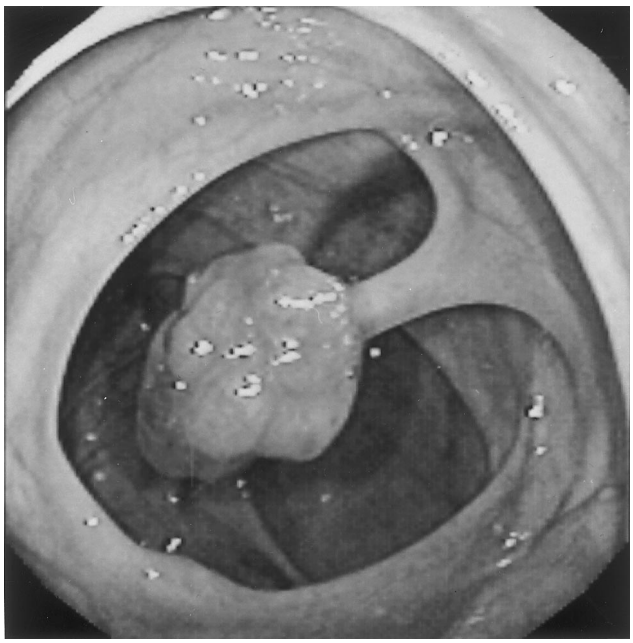

Figure 6. Photograph of a pedunculated benign polyp obtained by colonoscopy. (Courtesy of Arnold Markowitz, M.D., Memorial Sloan-Kettering Cancer Center, New York, NY.)

CRC is classified in stages according to the extent to which it has extended from its origin in the mucosa through the wall of the bowel, to regional lymph nodes, and to distant sites, especially the liver (Table 1). Survival from CRC is closely related to the clinical and pathological stage of the disease at diagnosis (Figure 5). Up to 90% of patients with cancer limited to the bowel wall will be alive 5 years after diagnosis[9] compared with 35%–60% of those with involvement of the lymph nodes and <10% of patients with metastatic disease.[33] Cancers with more advanced histological grade are associated with more rapidly progressing disease.

Polyps

Mucosal masses in the colon and rectum are described clinically as "polyps" (Figure 6). They represent several kinds of histology with different clinical importance. They include adenomatous polyps, which are premalignant and account for about half to two thirds of colorectal polyps; hyperplastic polyps (10%–30% of all polyps), which are generally small (<0.5 cm), of no clinical importance, and tend to be in the distal bowel; mucosal tags, which are also small and of no clinical importance but account for 10%–30% of all polyps; and a variety of other histological types such as lipomas and hamartomas, which are uncommon.[34,35]

Adenomatous polyps are found in about a quarter of people by age 50 years, and the prevalence increases with age (Figure 7). An estimate based on autopsy series, which are probably less susceptible to selection and detection bias than clinical series, is that the prevalence of adenomatous polyps is higher in men than women at any given age, reaching ~60% in men and ~40% in women by the age of 50 years.[36–41] Information on the prevalence of large polyps (>1 cm) by age is limited; one autopsy series reported a prevalence of large polyps of 4.6% at age >54 and 15.6% at 75 years.

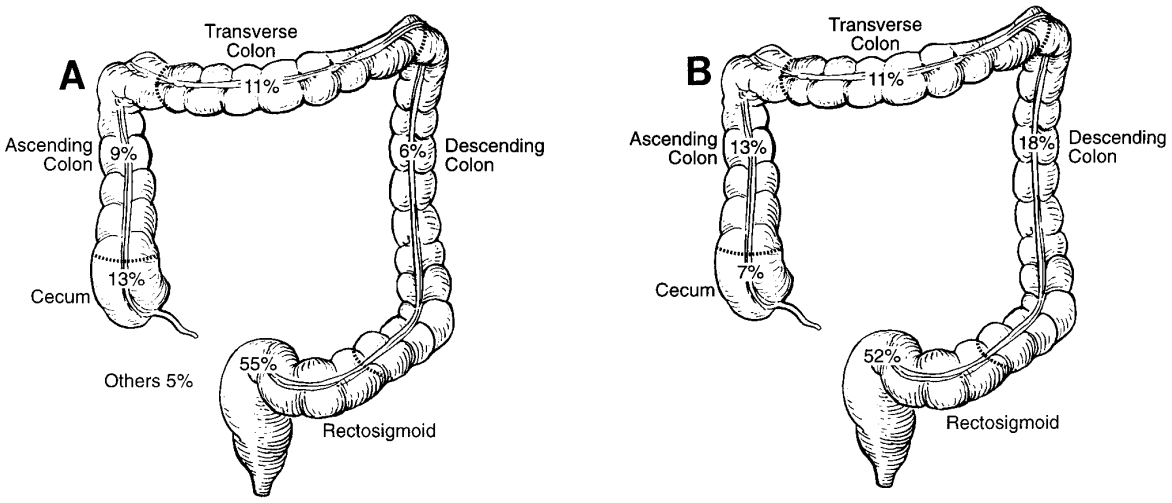

Figure 8. Frequency of (*A*) adenocarcinoma and (*B*) adenomatous polyps in different anatomic segments. (Reprinted with permission.[218])

As with cancers, adenomatous polyps are found throughout the colon and rectum (Figure 8), with approximately one-third occurring proximal to the splenic flexure.[30,31] At older ages, a larger proportion of adenomas are found in the proximal bowel.[34,41,42]

The probability that an adenomatous polyp will progress to cancer, and the probability that the patient will develop other adenomatous polyps or cancer elsewhere in the colon and rectum, can be estimated from characteristics of the polyp at the time it is first examined. The size of an adenomatous polyp (usually estimated at the time of endoscopic removal and not during subsequent pathological examination) is directly related to the probability that: (1) it will have high-grade dysplasia and (2) the patient will develop other adenomatous polyps and cancer elsewhere in the colon or rectum. In one study, 1.1% of adenomatous polyps <5 mm in diameter, 4.6% of those 5–9 mm in diameter, and 20.6% of those ≥1 cm had high-grade dysplasia, considered to be the earliest indication of preinvasive cancer.[35] Studies suggest that <1% of small adenomatous polyps (those <1 cm in diameter) are malignant compared with >10% of larger polyps.[43]

The best information on the relationship between the characteristics of adenomas and the risk of cancer is from a British study of 1618 patients, all of whom had had adenomas removed from the rectum or sigmoid colon and who were followed up without additional testing for about 14 years/patient. Those whose original polyps had been tubulovillous, villous, or large (>1 cm in diameter) were more than three times more likely to develop colon cancer than people in the general population (odds ratio 3.6; 95% confidence interval [CI], 2.4–5.0).[44] If, in addition, there were multiple rectosigmoid polyps with advanced pathology, affected people were more than six times more likely to develop colon cancer (odds ratio 6.6; 95% CI, 3.3–11.8). On the other hand, in patients with small, tubular adenomas (whether single or multiple), the risk of subsequent cancer was found to be no more than in the general population. These same polyp characteristics, i.e., size >1 cm, tubulovillous or villous histology, and multiple occurrence, predict increased risk of developing further adenomatous polyps as well as cancers.[45]

In this report we define a "large" polyp as many investigators have done: ≥1.0 cm in its largest diameter when seen intact or first removed (not as a fixed pathological specimen).

The Adenoma-Carcinoma Sequence

It is generally accepted that most cancers of the colon and rectum develop from adenomatous polyps. Direct evidence for this assertion is sparse; for obvious reasons it is not ethical to study the natural history of polyps by leaving them in place and observing the consequences. However, several kinds of indirect evidence support this belief: cancers and adenomatous polyps have the same anatomic distribution; cancers rarely arise in the absence of adenomatous polyps; the average age of onset of adenomatous polyps precedes that of cancer by several years[46]; patients with one or more large polyps (>1 cm in diameter) have been found to be at increased risk of future cancer[44,47]; most of these cancers arise at the site of large polyps left in place[47]; patients with familial adenomatous polyposis have hundreds to thousands of adenomatous polyps and a greatly increased risk of cancer; and finally, detecting and removing adenomatous polyps significantly reduces the incidence of CRC.[17,48]

Polyp Dwell Time

Few adenomatous polyps progress to cancer; the rate is estimated at about 2.5 polyps per 1000 per year.[49] In those that do, the transformation from small adenoma to cancer seems to occur slowly over many years. The average time taken for this transformation ("polyp dwell time") and the distribution of progression rates is not precisely known. There are no studies reporting observations of progression of small adenomas to large adenomas to local cancer to invasive cancer. Estimates

of the average dwell time can be derived from several kinds of indirect evidence.

- "Portrait studies" record the mean ages of people with adenomatous polyps of varying pathological stages and with invasive cancer. In one such study, the average age difference between people with the earliest stage adenomatous polyps and those with invasive cancer in surgical specimens was 18 years.[50] A similar time interval was observed for patients with familial polyposis.[18]
- Direct observations of a small number of biopsied benign polyps and their transformation to cancer support a time interval of 10–15 years.[18]
- Direct observation of patients who had adenomatous polyps excised strongly suggests that adenomatous polyps rarely arise and progress to cancer over periods of <3 years.[17,51–53] For example, in a large cohort of patients who had polyps removed, only 5 of 1418 patients followed up for 6 years developed CRC, all of which were asymptomatic and early-stage.
- A case-control study suggests that the protective effect of screening sigmoidoscopy lasts for up to 10 years.[11]
- Finally, the duration of time between the initial development of malignancy and the subsequent occurrence of a clinical problem has been estimated, using available data on incidence and prevalence, and the epidemiological relationship Prevalence = Incidence × Duration, to be at least 4.8 years.[54]

Based on these observations, the panel estimated that it takes an average of about 10 years for an adenomatous polyp, particularly one <1 cm in diameter, to transform into invasive cancer.

Pathogenesis

The progression from normal mucosa to adenomatous polyp to cancer appears to be associated with an accumulation

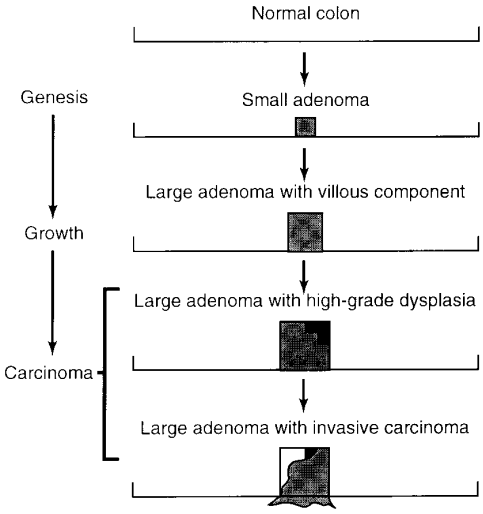

Figure 9. Pathogenesis of CRC. (Reprinted with permission.[219])

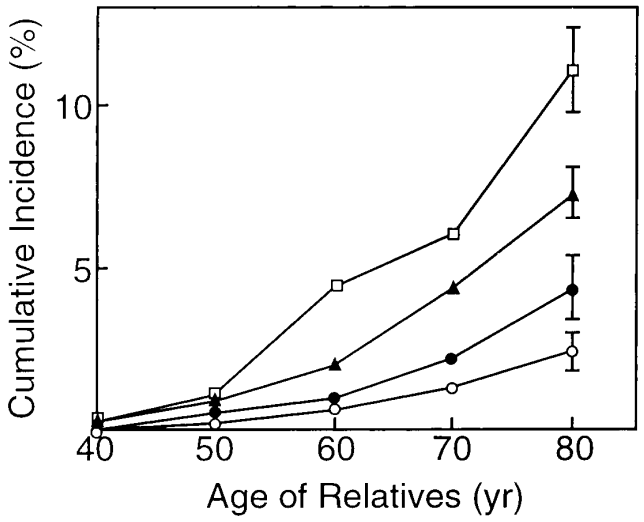

Figure 10. Cumulative incidence of CRC in relatives of probands with CRC. Age at diagnosis of CRC for case subjects: □, < 45 years; ▲, 45–54 years; ●, 55+ years. Controls: ○, all ages. (Reprinted with permission.[63])

of genetic alterations that are acquired after birth, resulting in genes that promote the development of cancer (oncogenes) as well as loss of genes that suppress tumor development (Figure 9). Several specific genetic abnormalities have been identified, and it is likely that more will be found. It is hypothesized that genetic alterations cause the development of adenomatous polyps and that additional genetic changes cause adenomatous polyps to progress to cancer. Environmental factors such as fat and fiber intake may also play a role in CRC pathogenesis.

Individuals vary in their propensity to form adenomatous polyps and cancers. People with adenomatous polyps are more likely to have other adenomatous polyps and to develop new ones if the original ones are removed.[55] Also, patients with CRC are more likely to develop second ("metachronous") CRCs than those who have never had a cancer.

Risk of Colorectal Cancer

About 75% of all new cases of CRC occur in people with no known predisposing factors for the disease.[56] Incidence increases with age, beginning around age 40 years, as summarized in Figure 3. People with no predisposing factors are considered to be at average risk for CRC.

The remaining cases occur in people who are at higher than average risk of the disease. This group includes people with a family history of CRC, previous adenomatous polyps or CRC, or a disease such as inflammatory bowel disease that predisposes to CRC. People with a family history of CRC (those with one or more parents, siblings, or children with the disease) but without any apparent defined genetic syndrome account for most of those at high risk (15%–20%). Hereditary nonpolyposis colon cancer accounts for 4%–7% of all cases and familial adenomatous polyposis about 1%. The remainder, about 1%, are attributed to a variety of uncommon conditions: inflamma-

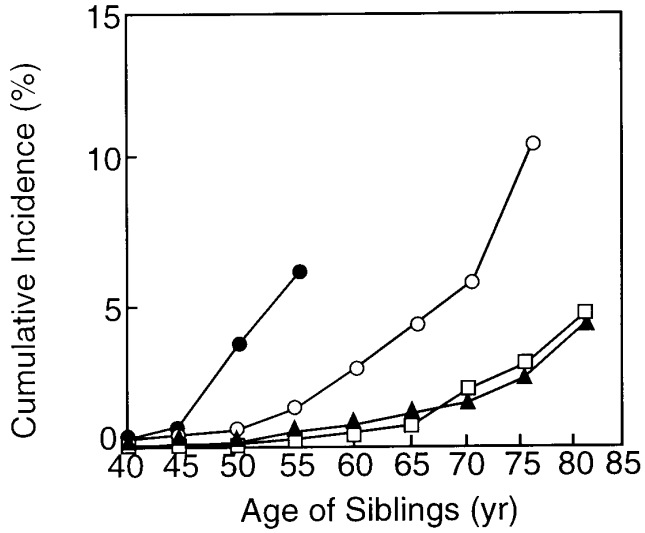

Figure 11. Cumulative incidence of CRC in siblings of patients with adenomas. Age of patient at diagnosis: ●, <50 years; ○, 50–59 years; ▲, ≥60 years. □, spouse. (Reprinted with permission.[58])

tory bowel disease, Peutz–Jeghers syndrome, familial juvenile polyposis, in which CRC risk is elevated but not as highly as in HNPCC and FAP.[56]

Family history. People with one or more first-degree relative (parent, sibling, or child) with CRC, but without one of the specific genetic syndromes (FAP, HNPCC), have approximately twice the risk of developing CRC as otherwise average-risk individuals without a family history. In those with a single affected first-degree relative, the risk significantly increases in the fourth decade and continues to increase with age.[57] The risk seems to be further increased if more than one first-degree relative has CRC and if the relative's cancer occurred relatively early in life (before approximately 55 years of age).[58] A similar increase in risk is found in close relatives of people having an adenomatous polyp diagnosed below age 60.[59] Most of this increased risk seems to be inherited, not environmental.[60] The cumulative incidence of CRC by age in people with a family history of adenomatous polyps or CRC is shown in Figures 10 and 11.

Specific genetic syndromes. Two specific forms of hereditary CRC in which the majority of affected persons develop CRC (Figure 12) are well characterized as both clinical syndromes and inherited abnormalities.[61–63]

Familial adenomatous polyposis. FAP accounts for approximately 1% of the new cases of CRC in the United States.[60] Affected individuals develop adenomatous polyps in the second and third decades of life, have hundreds to thousands of polyps throughout the colon by their 30s, and have an almost 100% chance of developing CRC by their 40s. The distribution of polyps and cancers throughout the colon is the same as in people at average risk.[61]

Syndromes once thought to be distinct but now known to be variants of FAP include Turcot's syndrome (familial colorectal cancer and brain cancer) and Gardner's syndrome (familial colorectal cancer, osteomas, and benign soft tissue tumors). The genetic defect is a mutation of the adenomatous polyposis coli (*APC*) gene on the long arm of chromosome 5, which leads to cytokinetic abnormality of the bowel wall and is inherited as an autosomal dominant syndrome.

Because many different mutations of this gene have been found in the kindreds studied and because FAP accounts for so few cases of CRC, it is not feasible to use genetic identification as a screening test in the general population, although it is useful to identify the gene carriers within kindreds.

Hereditary nonpolyposis colon cancer. HNPCC, also known as Lynch syndrome, accounts for about 5% of new cases of CRC each year. The clinical syndrome has two main forms: one without a family history of other cancers (Lynch syndrome I) and the other with an increased familial occurrence of other types of cancers, typically of the ovary and uterus (Lynch syndrome II). In both variations of the syndrome, CRCs occur at an early age, in the fourth and fifth decades, and the cancers are predominantly proximal to the splenic flexure. Adenomatous polyps precede the development of cancer but do not occur in unusually large numbers as in FAP and have unique features.

People with HNPCC develop adenomatous polyps with higher frequency and at a younger age than people without HNPCC, and the polyps have more advanced pathology and are often multiple and flat and precede the cancers.[62,64] In addition, there seems to be a more rapid transformation of adenomas to cancer in HNPCC compared with the general population even with respect to small adenomas. However, CRC in these patients has a better prognosis.[23,64,65,199,200]

The clinical distinction between patients with HNPCC and those with a family history of CRC in the absence of a genetic syndrome is sometimes unclear. Because HNPCC is not marked by polyposis of the entire colon or other clinically apparent abnormalities, if genetic testing is not performed, the syndrome must be defined by family history. A common standard is the existence of three or more relatives with histologically documented CRC, one of whom is a first-degree relative of the other two; one or more cases of CRC diagnosed before age 50 years in the family; and CRC involving at least two generations (the Amsterdam criteria).[66] Because these criteria are strict, defining HNPCC in this way is unlikely to

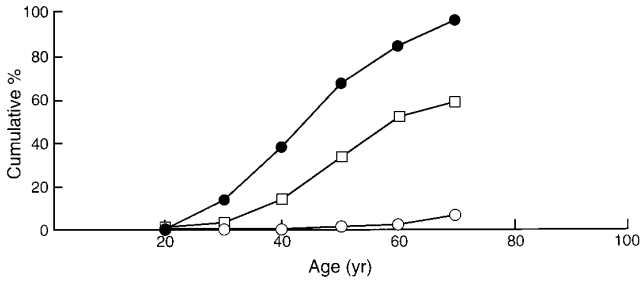

Figure 12. Cumulative incidence of CRC by age in subjects with genetic syndromes compared with the general population. ●, FAP; □, HNPCC; ○, general population.

result in false positive diagnoses. However, people with HNPCC may not meet the criteria, for example, if family members have died before age 50 years for other reasons or their health status is not known. The gene for HNPCC is an autosomal dominant with almost complete penetrance. A strong family history, therefore, carries approximately a one in two risk of having HNPCC.

Mutations primarily in four genes on chromosomes 2, 3, and 7 (*hMLH1, hMSH2, hPMS1,* and *hPMS2*) are associated with 70%–80% of cases. Some families, therefore, may not have currently known genetic mutations but may be gene carriers. For reasons similar to those described for FAP, it is not presently feasible to use genetic identification as a screening test in the general population, although it may be useful to identify the majority of gene carriers within kindreds. A negative genetic test has uncertain significance, as is the case with FAP.

Hamartomatous polyposis syndromes. In some uncommon conditions, with autosomal dominant inheritance, there are hamartomas in the small and large bowel. Risk of CRC is increased; the magnitude of increase is clearly less than for HNPCC or FAP but not precisely known. In Peutz–Jeghers syndrome, hamartomas throughout the small bowel and mucocutaneous pigmentation develop in childhood and colonic adenomas may occur. In juvenile polyposis, colonic hamartomas also develop in childhood, without abnormal pigmentation, and adenomatous features can occur in some of these polyps.

Inflammatory bowel disease (IBD). Patients with IBD are at substantially greater risk of cancer than people in the general population, although the disease contributes only a small proportion (<1%) of all new cases of CRC. The risk associated with ulcerative colitis and Crohn's colitis is similar for comparable extent, duration, and age of onset of inflammatory disease.[67]

Cancers that develop in people with IBD are generally flat and infiltrating. They do not often arise from polyps but from areas of precancerous dysplasia. Patients with moderate or severe dysplasia have a high probability of having cancer somewhere in the colon.[68] The degree of risk depends on the extent and duration of the inflammatory bowel disease and on the age of onset.[68–70] The strongest predisposing factor for cancer is the anatomic extent of the inflammation, with patients most at risk if they have pancolitis or ulceration extending proximally to the splenic flexure and least at risk if the disease is limited to the rectum and sigmoid colon.[68,71] The cumulative incidence of CRC in patients with pancolitis is 30% in 35 years.[71,72] The longer a patient has the disease, the greater the risk of cancer, but most cancers do not occur until after about 8 years of pancolitis.[73,74] Patients who develop ulcerative colitis early in life are also at increased risk of cancer,[72] but it is not clear that this is independent of duration and extent of disease.

Prior colorectal cancer. People who have had CRC are at increased risk of developing another (metachronous) CRC (apart from recurrence of the original cancer). In one study, 4119 patients at St. Mark's Hospital, London, were followed for up to 40 years.[18] Risk was low (1.9%) in the first 10 years, then increased to about four times the lifetime risk of average-risk people. CRCs were more common in people with double (synchronous) cancers at the first surgery. In a retrospective analysis of 5476 average-risk individuals entered in a tumor registry in Nebraska, the risk of a metachronous lesion was constant over 20 years from the first cancer.[75] In comparison with CRC incidence data in the general population, the ratio of observed to expected CRCs was 1.45 ($P < 0.01$). The risk of developing a metachronous lesion was 0.35% per year, reaching 6.3% at 18 years.

Risk factors for CRC, other than age, are summarized in Table 2. The contribution of the various risk factors to the total incidence of CRC is shown in Figure 13.

Table 2. Risk Factors for CRC

Average risk
Age 50 ≥ yr asymptomatic
Increased risk
Inflammator bowel disease
Chronic ulcerative colitis
Chronic granulomatous colitis
Adenomatous polyposis
Familial polyposis
Gardner's syndrome
Turcot's syndrome
Oldfield' syndrome
Juvenile polyposis
HNPCC
Lynch I
Lynch II
Family history
Colorectal adenomas < age 60 yr
CRC
Past history
Colorectal adenomas
CRC
Breast, ovarian, and uterine cancer

Screening People at Average Risk for Colorectal Cancer

General Recommendation for Screening

All women and men without symptoms of CRC or other relevant risk factors should be offered screening for CRC beginning at age 50 years. This general recommendation is based on strong evidence, although the evidence supporting individual screening methods varies in strength.

The panel believes that all of the screening strategies presented in this section are acceptable options. For each of the currently available tests, the panel assessed evidence on performance (the ability of the test to correctly identify people with and without CRC or adenomatous polyps), effectiveness (the ability to change outcomes of CRC), frequency of testing, acceptability, and potential harms of screening. These measures may be different in the three different contexts in which the

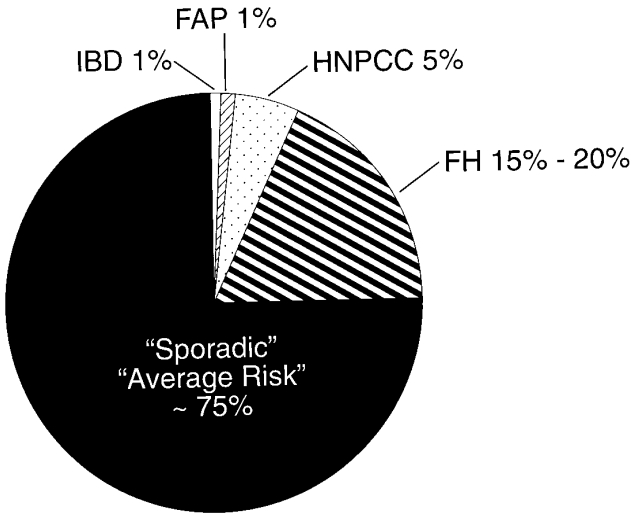

Figure 13. Factors associated with annual new cases of CRC. Sporadic, men and women age 50 and older with no special risk factors; FH, positive family history. (Reprinted with permission.[220])

tests can be used: screening, surveillance, and diagnosis. The following discussion relates specifically to screening.

Dimensions of Evaluation

Screening test performance. The performance of a screening test for CRC is described at the simplest level by its ability to distinguish those individuals likely to have adenomatous polyps or early CRCs from those less likely to have them. Test performance is commonly described in terms of *sensitivity* (e.g., the proportion of all cancers that are detected by the test), *false positive rate* (e.g., the proportion of all people without cancer who have a positive test), *specificity* (e.g., the proportion of all people without the disease who have a negative test), and *predictive value* (e.g., the proportion of all individuals with positive/negative tests who do/do not have cancer). Ideally, these measures should be expressed separately for CRC at various stages and for large and small adenomas because they have different clinical importance. Estimates of the performance of screening tests, derived from published studies, are limited in several ways. Most studies report performance only for neoplasia (either polyps or cancer) or for CRC alone. The studies are biased, as a basis for national screening policy, by including symptomatic and referred patients tested by unusually proficient and motivated examiners. Many studies describe performance in a small number of patients, so that differences in their results may result from random variation. True performance probably varies substantially from one to another examiner and location, but little information exists on the magnitude of this variation.

Screening test effectiveness. Screening tests, even very accurate ones, cannot in themselves prevent cancer. Positive tests must be followed up by diagnostic evaluation to confirm or exclude disease and by effective treatment. (In the case of screening colonoscopy, all three activities can be achieved during the same procedure.) This sequence of activities taken together comprises the preventive strategy. The effectiveness of this strategy is established by studies that compare outcome rates, such as death or incidence of CRC, in people who are and are not exposed to the strategy.

A distinction is made between *efficacy* (how well the intervention works under ideal conditions, such as in most randomized controlled trials) and *effectiveness* (how well it works under ordinary conditions in practice). Most of the information base for these guidelines comes from research in relatively favorable circumstances. This required the panel to extrapolate the results of research to conditions of usual practice. This dilemma is shared by all who would base clinical practice on research evidence and adds to the uncertainty when establishing these and other guidelines.

Screening frequency. Decisions about the frequency with which screening tests should be performed are based on two kinds of evidence. Direct evidence, such as from randomized, controlled comparisons of the effects of screening at various intervals, is best. For CRC, strong direct evidence exists for FOBT, whereas screening sigmoidoscopy is supported by intermediate strength evidence. These studies give direct information on the clinical consequences of varying the screening interval.

Judgments about screening interval can also be developed from indirect evidence, e.g., estimates of polyp dwell time. The time required for a polyp to arise and develop into cancer is central to this decision; however, as noted previously, this interval is not known precisely. If sensitivity of the screening test is low, it is advantageous to repeat it as frequently as possible so that there are many opportunities for the test to be positive during the period between when a polyp can be recognized and an incurable cancer has formed. If specificity is low, this weighs against frequent testing because of the large number of false positives. To the extent the procedure involves risk and cost, these factors also argue against frequent screening. Screening intervals for colonoscopy are supported only by indirect evidence.

Complications. Evaluation of a test must also account for the potential physical and psychological effects of screening. The latter include the anxiety produced in individuals undergoing testing or waiting for results; the stress of undergoing further tests or of being labeled with a presumptive diagnosis (especially if the diagnosis is wrong because of a false positive test); the risk that reassurance by a negative test might cause the patient to forgo further testing; and the benefits of reassurance by negative tests. The physical complications of both the screening test and of subsequent diagnostic workup must also be considered. Screening and diagnostic tests for CRC, especially endoscopic procedures, can produce severe complications such as perforation, bleeding, and death. These, and the remote possibility of transmitting infections, must be considered along with the immediate discomfort, inconvenience, and embarrassment the procedures might cause.

Acceptability. A screening program will not be implemented if the public and clinicians do not believe it is desirable or feasible. Adequate attention to the issues discussed under "Implementing the Guidelines" is extremely important to the success of any CRC screening program.

The ultimate success of a screening strategy depends on the participation of individuals and health care providers in the initial screening procedure, the diagnostic workup of positive cases, and, in some cases, surveillance. The behavioral dynamics are different in each of these situations. What little information there is on participation rates in screening for CRC relates to FOBT and sigmoidoscopy. The high rates of compliance recorded in some studies are difficult to replicate in everyday practice, but they do at least show that high rates are possible when compliance is given sufficient emphasis and attention.

Fecal Occult Blood Testing

The concept of detecting cancers of the colon and rectum by testing for blood in the stool is based on the observation that cancers bleed more than normal mucosa. About two thirds of cancers bleed in the course of a week,[76] and a higher proportion, perhaps more than 90%, will be detected with repeated testing over several years.[9] Bleeding tends to be intermittent, and blood is distributed unevenly in the stool. The amount of bleeding increases with the size of the polyp and the stage of the cancer. People with small polyps bleed scarcely more than those without polyps, whereas those with very large polyps ($\geq$2.0 cm) often bleed.[77] Testing for fecal occult blood will therefore lead to detection of cancers; however, it also will lead to the detection of polyps because they are much more common.

FOBT provides only an indication of the possible presence of cancers and large polyps. Patients with positive results must undergo some form of diagnostic evaluation, consisting of either double contrast barium enema, with or without flexible sigmoidoscopy, or colonoscopy. In this respect, FOBT differs from sigmoidoscopy and colonoscopy, which can act as both screening and diagnostic tests. The performance and especially the effectiveness of FOBT must be considered in the context of any subsequent diagnostic evaluation.

The test process. The test most widely used for detecting blood in the stool is the guaiac-based test for peroxidase activity. The positive reaction with blood results from the pseudoperoxidase activity of hemoglobin. The test gives no indication of the amount of blood being lost. It is not specific for cancer since non-neoplastic lesions, such as gum disease, gastritis, peptic ulcer disease, and hemorrhoids can also cause gastrointestinal bleeding. Nor is the test specific for blood per se, because other substances with peroxidase or pseudoperoxidase activity (red meat, bacteria, and hyperoxides in some fruits and vegetables) can cause false positive reactions if they are present in the stool.[77a] Some commonly used drugs such as aspirin and other nonsteroidal anti-inflammatory drugs can cause occult gastrointestinal bleeding; therefore, these and other medications that are gastric irritants should be avoided.

Table 3. Factors Affecting FOBT

Avoid	Examples	False positive	False negative
Heme	Rare red meat	+	
Peroxidase activity	Turnips, horseradish	+	
Salicylates		+	
Vitamin C			+

NOTE. Ingestion of fiber for example in fruits and vegetables, increases stool transit time and may avoid false-negative test results. Begin 24 hours before and continue through time of stool collection.

False negative tests may result because the cancer did not bleed while the sampled stool was being formed or because the type of guaiac test being used was not sensitive enough to detect small amounts of blood. Vitamin C, an antioxidant, can also interfere with the reaction and cause a false negative test. Dietary iron supplements do not directly interfere with the test, but by turning the stool dark, they can make it difficult to interpret the blue color change of a positive test.

Typically several days elapse between collecting the stool and testing it for the presence of blood. The slides should be kept at room temperature during the testing to preserve the stability of the hemoglobin, if present. The sensitivity of guaiac based tests is increased if the test slide is rehydrated with a few drops of water before adding the hydrogen peroxide reagent. However, the trade-off for increased sensitivity is a reduction in specificity.

The sensitivity of FOBT increases with the number of samples per stool and the number of stools sampled. Therefore, to minimize the risk, it is recommended that the individual provide several specimens from several consecutive stools.

Elements of an ordinary diet, because of their peroxidase activity, can cause false positive reactions of the guaiac-based tests. The person being tested, therefore, is asked to observe certain dietary restrictions for 2 days before the test and throughout the test period; these include avoiding red meat and certain vegetables (Table 3).

The person using the test completes it by taking samples of stool from two different sites, using a wooden applicator stick, and smearing them thinly onto separate windows on the card incorporating the guaiac reagent. They then repeat the procedure for the next two bowel movements and return the cards, either in person or by mail, to the screening center, preferably within 4 days. A single specimen obtained by digital rectal examination has questionable value and is not a substitute for the test method described here. The version of the test most commonly used, and the one to which most of the available evidence relates, is the Hemoccult II test (Smith Kline Diagnostics, Inc., San Jose, CA). A more sensitive version, the Hemoccult II Sensa (SmithKline Diagnostics Inc., San Jose, CA) is also available. A positive result is registered if a blue color appears when the hydrogen peroxide reagent is added to the stool on the card. This must be observed immedi-

ately because the color may fade. The test is considered positive if any one of the six windows turns any degree of blue. A performance monitor on each slide should be tested to verify the reactivity of the slide.

The best available evidence that FOBT is effective in preventing death caused by CRC relates to rehydrated tests on two samples from each of three consecutive stools in individuals who were advised to follow a restricted diet.[9]

Performance characteristics. Although a simple test, FOBT may be inaccurately interpreted, usually resulting in false negatives. In one study, only 38% of moderately positive samples (relative to a laboratory standard) were read correctly by program coordinators for a large, multicenter trial. Training improved performance, with correct interpretation increasing to 90% after a 1-hour instructional seminar.[78] Negative samples were usually read correctly.

The sensitivity and specificity of FOBT for CRC reported in different studies vary considerably.[79] This variation may be due to several factors: the different type of test used in different studies; whether or not the slides were rehydrated; the number of samples taken from each patient and how they were obtained; whether the recommended diet was followed; the standard for the presence or absence of cancer against which the FOBT was compared; the kinds of patients tested; and whether the test is used for a prevalence (first time) screen or an incidence (repeated) screen. Also, the sensitivity of a test at one point in time is less than that of a program of testing over several years, because a program of testing offers several opportunities to detect the polyps and cancers that did not bleed on earlier occasions.

Five prospective controlled trials of screening using the Hemoccult test have been reported.[9,10,14,80,81] Results from these trials reflect the performance of a program of repeated screening rather than of a single test. In its nonhydrated form, Hemoccult achieved sensitivities for detecting cancer ranging from 72% to 78% and a specificity of 98%. Rehydrating the slides, as was done in the trials from Minnesota and Sweden, increased the sensitivity of the test to a range of 88%–92%, but with loss of specificity (down to 90%–92%) and positive predictive value for cancer (from 10% to 17% down to 2%–6%). Stated another way, for every case of cancer detected, 6–10 patients need to undergo colonoscopy or barium enema as a result of the nonhydrated test compared with 17–50 patients with the rehydrated test.

In an attempt to increase the sensitivity for cancer without significant loss of specificity, in one study, two newer tests were combined (Hemoccult II Sensa and HemeSelect; Smith Kline) in sequence. Sensitivity increased from 38% to 65%; specificity remained unchanged at 97%.[82] Both tests were more sensitive than the nonhydrated Hemoccult test.[79] FOBT is far less sensitive for polyps than for cancers because most polyps do not bleed. However, the FOBT screening strategy as a whole does detect many adenomas in part because large adenomas, those most likely to be precancerous, often do bleed and in part because false positive FOBTs, which are common, lead to diagnostic testing that discovers polyps whether or not they had bled.[83,84]

Rehydration increases the proportion of cancers found by FOBT screening but also increases the proportion of patients who have a positive test and must undergo diagnostic testing but do not have colorectal cancer. The Minnesota trial, a randomized controlled trial showing that screening with FOBT decreases mortality, used rehydration during most of the study period, whereas two other trials also showing reduction in CRC mortality with screening did not.[85,86]

Reported sensitivities of FOBT for cancer range from 38% to 92%. Given this range, estimates of 40%, 60%, and 80% were used for the sensitivity analysis of the simulation model conducted for the panel. The base case used 60%. The prospective controlled trials using Hemoccult II reflected the performance of a program of repeated screening rather than a single test and, therefore, will tend to overestimate sensitivity for a single test. However, with multiple opportunities to detect cancer, even a low-sensitivity single test may achieve high overall program sensitivity. In the base case, which used a single-test sensitivity estimate of 60%, annual FOBT with follow-up colonoscopy for positive tests found nearly 93% of cancers. Using a lower estimate of 40% sensitivity still resulted in 85% of cancers being found. Similarly, specificity estimates from the trials ranged from 90% to 98% (for the nonhydrated test). The simulation model used a range of 90%–94% because it assumed the test to have the sensitivity of the hydrated slide.

Effectiveness. A growing body of evidence has established that testing for fecal occult blood with complete diagnostic evaluation of the colon, primarily with colonoscopy, and treatment in those testing positive reduces mortality from CRC.

Early studies, community trials and case series, found that screening for fecal occult blood led to cancers being detected at an earlier pathological stage[87–88] and to patients surviving longer after their diagnosis.[14] Because it was recognized that these findings, however promising, might result from biases (especially lead time bias; see Glossary), controlled trials with mortality as their end point were begun. Five such controlled trials have been conducted, four of which were randomized,[9,10,80,89] and one unrandomized.[14] Three randomized[9,85,86] and one nonrandomized trial[14] had been completed and reported at the time of the panel's evaluation of the data.

The first completed randomized trial was conducted in Minnesota.[9] The investigators randomized 46,551 people aged 50–80 without symptoms of CRC into three groups: one to be screened annually, the second to be screened every 2 years, and the third to receive usual care. Participants were at first tested with unhydrated slides and later, for most of the trial, with rehydrated slides. Participants were followed up for up to 13 years. Those with positive tests for fecal occult blood were investigated with colonoscopy; if colonoscopy was incom-

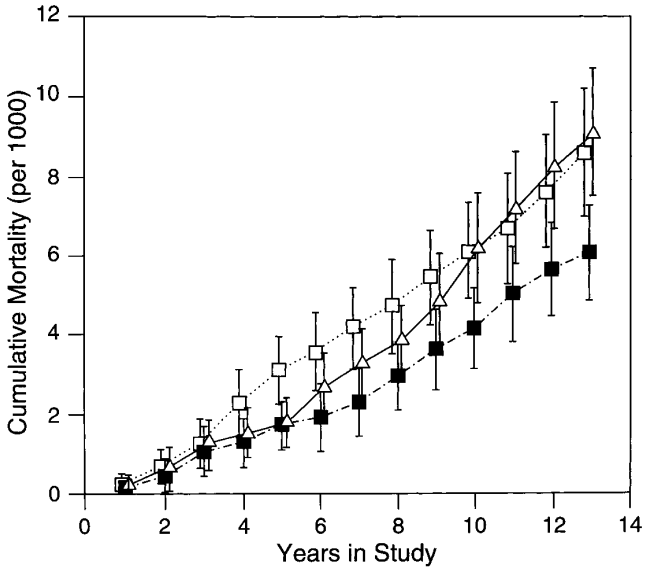

Figure 14. FOBT screening and CRC mortality. ■, Annual screening (n = 15,570); □, biennial screening (n = 15,587); △, control (n = 15,394). (Reprinted with permission.[9])

plete, a double contrast barium enema was performed. The 13-year cumulative mortality per 1000 from CRC was 5.88 in the annually screened, 8.33 in the biennially screened group, and 8.83 in the control group, a 33% reduction in the group offered annual screening compared with controls (Figure 14). The small reduction in mortality in the group screened every 2 years was not beyond what was likely by chance alone. The reduction in incidence in the annually screened group was 2.95 per 1000 per 13 years; expressed another way, 339 people had to be screened for 13 years to prevent one CRC death. The incidence of CRC was not different in the three groups after 13 years of follow-up, consistent with the long lead time from polyp to cancer.

In a randomized controlled trial in England, 150,251 patients aged 45–74 years registered with general practitioners in the Nottingham area were randomly allocated to be offered FOBT (Hemoccult) without hydration every 2 years or to receive usual care (i.e., no intervention). Positive tests were evaluated with colonoscopy. After a mean follow-up of 7.8 years, the investigators found a reduction in mortality of 15% (odds ratio, 0.85; 95% CI, 0.74–0.98) in the screened group.[85] In a randomized controlled trial in Denmark, 61,993 people aged 45–75 years sampled from the population were randomly allocated to be offered FOBT (Hemoccult II) without hydration every 2 years or usual care. Positive tests were evaluated by colonoscopy. Ten years after the study was begun, the investigators had observed an 18% reduction in CRC mortality in the screened group (mortality ratio, 0.82; 95% CI, 0.68–0.99).[86]

The findings of the randomized trials are supported by results from a case-control study conducted in the United States.[12] In addition, a nonrandomized controlled trial has been completed in the United States.[14] In this trial, FOBT was added to sigmoidoscopy and compared with sigmoidoscopy alone. This trial also showed a mortality reduction associated with FOBT screening followed by diagnostic evaluation of positive tests with colonoscopy. This study is discussed in more detail in another section of this report that addresses the combination of the sigmoidoscopy and FOBT for screening.

The results of these studies reflect the combined effectiveness of screening for fecal occult blood followed by diagnostic evaluation with colonoscopy.[6,9] There is debate as to how much of the observed benefit in the Minnesota trial resulted from the diagnostic evaluations received by more than a third of the patients, many because of the high rate of false positive FOBT.[90] The following evidence from the Minnesota trial supports an independent effect of FOBT: a significant percentage of patients with an initially positive FOBT were subsequently found to have cancer (2.7% of those screened biennially) and the increased likelihood of finding cancer as the number of positive slide tests obtained from an individual increased.[84]

Indirect evidence of the effectiveness of FOBT was generated by the decision analysis commissioned for this report that modeled the effects of the clinical practice recommendations on a population basis. The simulation model used to assess these effects indicates that for a population of 100,000, annual FOBT with appropriate follow-up would reduce incidence of colon cancer by 2378 cases, from 4988 cases to 2610 cases.* The number of expected cancer deaths would decrease by 1330. This reduction in incidence and mortality would be accompanied by increases in complications: the population could expect 52 complication deaths from colonoscopy, 304 colonoscopy perforations, 741 major bleeding episodes, and 767 cases of minor complications. An individual whose death by cancer was prevented would have an increased life expectancy of 9.3 years.

There is only indirect evidence that screening with FOBT improves the quality of life in patients who develop CRC. One study reported more cancers treated by polypectomy alone in screened patients compared with unscreened patients (10% vs. 2%) and more elective operations.[6] A stage shift (more localized and fewer advanced cancers in the screened group) has also been reported in nearly all studies of CRC. All of these factors are linked to reductions in at least short-term morbidity. No studies report the effects of screening on patients' functional status, quality of life, or morbidity over long-term follow-up.

Frequency. Although screening every other year may reduce mortality, annual screening leads to a greater reduction

*These results assume an FOBT sensitivity and specificity of 60% and 92%, respectively, and colonoscopy complication rates of 8.5/1000 tests: 1.3 perforations, 0.2 deaths, and 3.4 major bleeding episodes with the remainder being minor complications. Colonoscopy sensitivity was assumed to be 96.7% for cancer, 85% for large polyps, and 78.5% for small polyps, while colonoscopy specificity was assumed to be 98% for all. Colonoscopy sensitivity is influenced by the percentage of examinations that are complete to the cecum.

in mortality. The Minnesota study found a reduction in mortality for CRC in the annually screened group but no reduction in the group screened every second year compared with controls.[9] In the British and Danish trials,[85,86] screening every other year resulted in a reduction in mortality though less than in the Minnesota trial, which might have also been partly explained by not rehydrating stool samples before FOBT. A case-control study by Selby et al. found reduced mortality in people screened every second year, but the confidence intervals were wide and this result could be due to chance.[12]

Complications. Complications of FOBT result mainly from the diagnostic evaluation of people with positive tests, either with barium enema or colonoscopy. In addition to these risks, there may be, as with all screening tests, negative effects such as anxiety in people with false positive tests and the danger of misleading reassurance in people with false negative results. Little information exists on the frequency and severity of these possible effects.

Participation and acceptability. Compliance rates in studies of screening for fecal occult blood vary widely for both the individuals and health care providers. Reported patient compliance has ranged from 30% to 90%.[9,91–93] In most of these studies, however, the rates tended to decline as the study progressed: for example, from 70%–80% at the beginning of one trial to 20% at 1 year and 16% at 2 years.[14] Younger participants are especially likely to abandon screening.[92] Generalizations should, however, be made with caution given the scarcity of data on these issues.

Factors linked to higher rates of compliance with FOBT include knowledge of CRC[20,94]; higher educational level[95]; having relatives or friends with the disease[93]; and believing in the importance of health checks in general and early diagnosis of CRC in particular.[96,97] Women are more likely to complete FOBT than men.[93,97]

Reasons most often given for not completing FOBT are the absence of symptoms, the embarrassing or unpleasant nature of the test, not wanting to know about health problems, and technical difficulties with the test.[98]

Health care providers play a key role in boosting compliance. Clinicians who give high priority to preventive services tend to achieve higher rates of compliance among their patients.[99] Compliance is higher among individuals who belong to health maintenance organizations.[20] Educational interventions and reminders have been shown to increase compliance, both for patients (from 27%–48% in one study)[100] and clinicians.[101]

Conclusions. Among all of the screening tests discussed in this report, strong, direct evidence that screening (with appropriate diagnostic follow-up and treatment) reduces mortality from CRC exists only for FOBT. However, it is also clear that this strategy has limitations. Few adenomatous polyps (only a small proportion of large ones) bleed, so the test is mainly aimed at detecting cancer after it develops rather than at finding and removing precancerous lesions. Because cancers bleed intermittently, there is an upper limit to how successful early detection using FOBT can be. Finally, there is a high false positive rate with the more sensitive rehydrated test. This commits larger numbers of patients to undergo the anxiety, inconvenience, and risks associated with full diagnostic evaluation by colonoscopy or barium enema. They may incur additional financial costs as well.

- **Recommendations and rationale for screening with FOBT:** **see page 596.**

Sigmoidoscopy

As a screening method, sigmoidoscopy has three important advantages over testing for fecal occult blood: (1) it allows clinicians to visualize the bowel directly; (2) lesions can be biopsied as part of the procedure, and (3) it has high sensitivity and specificity for polyps in the part of the bowel examined. Thus, in addition to detecting early-stage cancers, it offers the possibility of reducing the incidence of CRC through the detection and subsequent removal of adenomatous polyps. An important limitation of sigmoidoscopy as a single screening strategy, however, is that it can visualize at most about half of all polyps and cancers, those in the left side of the colon. As with FOBT, full diagnostic evaluation of the entire colon is needed in patients in whom adenomatous polyps or cancers are found.

Description of the test. Three types of sigmoidoscopes have been used for screening: the rigid 25-cm scope and the flexible 35- and 60-cm scopes. Flexible sigmoidoscopes have largely replaced rigid ones because they provide clearer visualization of the mucosa, allow examination of more of the bowel, and are more comfortable for the patient. The 60-cm flexible scope visualizes more of the colon than the 35-cm scope without clinically important increases in discomfort or complication rates.[102] The distal bowel is usually prepared by giving a saline laxative enema or a similar preparation 1–2 hours before the procedure. Patients are not sedated, and approximately 10%–15% experience at least moderate discomfort during the procedure.[103] Patients may also find the procedure embarrassing, so it is important to provide privacy and reassurance.

The procedure takes 8 minutes on average (range, 6–20 minutes), depending on the clinician's experience.[104–111] However, clinicians who are not specialized in lower endoscopy have been shown to take as long as 15–20 minutes with the 60-cm scope.[112] Adequate experience is acquired during 24–30 examinations under instruction, but even after that, skill varies substantially among physicians.[113] There is good evidence that nonphysician health professionals can be trained to use both the 30- and 60-cm flexible scopes for screening, with detection of polyps and cancers and complication rates equivalent to those achieved by medical endoscopists.[114–116]

Biopsy specimens can be obtained during sigmoidoscopy. However, polypectomy during sigmoidoscopy is not commonly performed. It is best accomplished using electrocautery. Explosions can occur when electrocautery ignites hydrogen or methane in an inadequately cleansed bowel; full bowel preparation is therefore preferable if polypectomy is planned.

Antibiotics to prevent endocarditis as a complication of endoscopy are recommended for some patients. The American Society for Gastrointestinal Endoscopy, American Heart Association, and American Society of Colon and Rectal Surgeons recommend that patients at high risk for developing endocarditis because of prosthetic heart valves, a previous history of endocarditis, or surgically constructed systemic-pulmonary shunts or conduits should be considered for antibiotic prophylaxis during the procedure on a case-by-case basis.[117–119]

Definition of a positive sigmoidoscopy. What kind of finding on sigmoidoscopy should be considered positive, requiring further action? It is clear that polyps that are shown on biopsy to be hyperplastic or to consist of normal mucosa are not premalignant and need not be followed up. A sigmoidoscopy should be considered to be positive if a cancer or any polyp >1 cm in diameter is found. More controversial is whether an adenoma <1.0 cm in diameter, especially if tubular and without high-grade dysplasia, constitutes a positive test requiring subsequent examination of the entire colon.

Some clinicians and patients believe that discovery of any adenoma, no matter how small, is a cause for examination of the entire bowel. The probability of finding a clinically important lesion can be estimated from characteristics of the polyp at the time of sigmoidoscopy. Small, tubular adenomas are uncommonly associated with more advanced lesions proximally and are associated with a risk of CRC no greater that the general population.

The consequences of not following up small (<1.0 cm) adenomas by colonoscopy are described in several studies. In a study from the Mayo Clinic,[120] people in whom polyps of <1 cm were found on sigmoidoscopy had a risk of future cancer no greater than the general population. However, the polyps were fulgurated (coagulated) and the histological characteristics were therefore unknown. Many of the polyps could have been hyperplastic and therefore not associated with an increased risk for CRC. A study from St. Mark's Hospital in London[44] delineated the future risk of CRC in people who had adenomas removed at sigmoidoscopy and who did not undergo colonoscopy. (This study was in the precolonoscopy era.) The risk of subsequent colon cancer was increased 1.7-fold when a single adenoma was detected and 4.8-fold if multiple adenomas were present but was not increased when only a single small (<1 cm) tubular adenoma was detected. If this adenoma had no high-grade dysplasia, the risk for future colon cancer was no higher than in the general population. In a study relating the characteristics of polyps found on sigmoidoscopy to those found on subsequent colonoscopy in 226 people with and without symptoms, patients with small (≤1.0 cm) tubular adenomas on sigmoidoscopy had a <1% occurrence of an advanced, synchronous lesion.[121]

Decisions about which lesions to follow up by colonoscopy must be made both in the interest of the patient and of society in general. Limited societal resources must be allocated to where they will do the most good. Patients should be protected from future CRC; on the other hand, they should be spared the risk, discomfort, and inconvenience of low-yield procedures. The issue is still an open question.

Performance. The performance of sigmoidoscopy is described in relation to three questions: (1) how well does the examination perform in the area it can visualize; (2) what percent of all cancers of the colon and rectum can be reached by the instrument, and (3) what is the performance of the overall screening strategy that begins with sigmoidoscopy and follows up abnormal sigmoidoscopic examinations with examination of the entire bowel?

The flexible scopes of different length apparently do not differ in accuracy for the part of the bowel examined by each because the technology is similar. By analogy, the performance of sigmoidoscopes is in part established by what is known of the performance of colonoscopes, for which the information base is more extensive. This suggests that nearly all cancers and all polyps >1 cm in diameter and 70%–85% of small polyps are identified.[122] False positive findings (reporting a mass lesion when none is present) are rare, but many polyps that are biopsied or removed are not adenomatous and will never progress to cancer. There is every reason to believe that the performance of the flexible sigmoidoscope would be better than the rigid one: the potential and actual reach is higher, the optics are better, and the comfort of both patient and examiner is greater. A study directly comparing the performance of the two confirms the superiority of the flexible instrument.[107]

The three types of sigmoidoscopes, the 25-cm rigid scope and the 30- and 60-cm flexible scopes, each have different potential depths of penetration.[123] The proportion of polyps and cancers that can be detected is greatest with the 60-cm flexible scope, which reaches up to or beyond the proximal end of the sigmoid colon in 80% of examinations and should, therefore, detect 40%–60% of adenomatous polyps and CRCs.[123,124] The 35-cm scope can reach 30%–40% of lesions at full insertion and the rigid scope 20%–30%.[32]

If an adenomatous polyp is found on sigmoidoscopy, there is an increased probability that others are present elsewhere in the bowel.[16,125,126] Detecting and removing an adenomatous polyp in the rectosigmoid not only eliminates a possible source of cancer but the presence of the polyp suggests that other adenomas may exist beyond the reach of the sigmoidoscope. It is common practice to follow up an abnormal screening sigmoidoscopy with full colonoscopy, not only to excise the lesions already found but to look for more proximal lesions. When adenomatous polyps are found in the rectosigmoid, patients have about a one in three chance of having additional adenomas more proximally in the colon.[16,125,126] Several studies have compared the performance of the 60-cm flexible sigmoidoscope with that of full colonoscopy in the same group of asymptomatic patients.[31,127,128] Studies that compared the number of polyps found in the first 60 cm of colonoscopy with the number found on full colonoscopy suggest that the 60-cm flexible sigmoidoscope would correctly identify 40%–60% of all adenomas detected by colonoscopy. The characteristics of the proximal adenoma seem to correlate with the characteristics of the rectosigmoid

adenoma; i.e., when adenomas <1 cm in diameter are found in the rectosigmoid, it is unlikely that adenomas with advanced pathology (those >1 cm or with high-grade dysplasia or invasive cancer) will be found proximally.[121]

About a third of patients with proximal adenomatous polyps had no distal polyps.[31,128] If these patients had undergone only flexible sigmoidoscopy, they would not have been identified as being at increased risk of CRC. That is, the sensitivity of the overall strategy of following up abnormal sigmoidoscopy with complete examination of the colon is about two-thirds.

Effectiveness. There has been no randomized controlled trial addressing the effectiveness of screening sigmoidoscopy. Screening sigmoidoscopy is included in a set of randomized controlled trials of screenings for several types of cancer (the Prostate, Lung, Colon, and Ovary Trial) supported by the National Cancer Institute. Begun in 1992, this study is not expected to yield results on mortality until 2008.[129]

The best available evidence on the effectiveness of sigmoidoscopy in reducing death from CRC comes from three case-control studies.[11,13,130] Within the limitations of the case-control design, the study by Selby et al. is strong (Table 4). It compares the screening histories of people who died of CRC (case subjects) with age- and sex-matched controls. Case and control subjects were average-risk people sampled without bias at three sites of the Kaiser Permanente Health Plan in California. Only screenings with rigid sigmoidoscopes were included, and sigmoidoscopies were counted from records rather than relying on patients' recall. The investigators adjusted the results for differences in compliance with preventive care in general, taking as their marker the number of periodic health examinations participants in the study had undergone, and adjusted for the effect of FOBT. They found that rigid sigmoidoscopy was associated with a 59% (odds ratio, 0.41; 95% CI, 0.25–0.69) reduction in mortality from cancers in the part of the colon reached by the rigid sigmoidoscope. To test the internal validity of their findings, they analyzed those case subjects (and their controls) who died of cancers that were beyond the reach of the rigid sigmoidoscope and found that the protective effect of having had a screening sigmoidoscopy was not present for these proximal cancers. Finding no effect where none was expected makes selection bias an unlikely explanation for their main results.

A case-control study by Newcomb et al.[13] reported an 80% reduction in the risk of death from rectosigmoid cancer in patients who had undergone one or more sigmoidoscopic examinations compared with those who had never done so (odds ratio, 0.21; 95% CI, 0.08–0.52). A study by Muller and Sonnenberg[130] included 4411 U.S. veterans dying of CRC and both living and dead controls without CRC. Proctosigmoidoscopy was associated with an odds ratio of 0.41 and 0.40 (living and dead controls, respectively), an approximately 60% reduction in CRC mortality. Although it was not possible in this study to correct for bias related to compliance or the performance of proctosigmoidoscopy for nonscreening reasons, the results are consistent with the other two studies.

Another case-control study by Muller and Sonnenberg showed that patients with CRC were less likely to have undergone sigmoidoscopy than matched controls (odds ratio, 0.56; 95% CI, 0.46–0.67.[48] Although the investigators were unable to take into account whether the procedures were for screening or symptoms, the most likely potential biases (that people underwent sigmoidoscopy because of symptoms of CRC and that people with sigmoidoscopy are more likely to have cancers found) would tend to increase the odds ratio. This study bears on the hypothesis that removing polyps prevents CRC, complementing the other case-control studies of sigmoidoscopy in which CRC mortality is the outcome and early detection of cancer is the more likely mode of action.

Table 4. Odds of Having Had at Least One Screening Sigmoidoscopy During the 10-Year Period Before Diagnosis of Fatal Cancer in Case Subjects

Adjustment	No. of case subjects (%) (n = 261)	No. of Controls (%) (n = 868)	Odds ratio (95% CI)[a]
Cancer within reach of sigmoidoscope			
Unadjusted	23 (8.8)	210 (24.2)	0.30 (0.19–0.48)
History of CRC or polyp, family history of CRC[b]	—	—	0.25 (0.16–0.42)
History of CRC or polyp, family history of CRC, no. of periodic health checkups[c]	—	—	0.41 (0.25–0.69)
Cancer above reach of sigmoidoscope			
Unadjusted	56 (22.9)	67 (25.0)	0.80 (0.54–1.19)
History of CRC or polyp, family history of CRC[b]	—	—	0.80 (0.54–1.19)
History of CRC or polyp, family history of CRC, no. of periodic health checkups[c]	—	—	0.96 (0.61–1.50)

[a]Odds ratios and 95 percent CI were obtained from matched conditional logistic-regression models.
[b]The odds ratio was adjusted by entering a history of CRC or polyp before the 10-year period and a family history of CRC noted before diagnosis in the case subject as dichotomous variables.
[c]The odds ratio was further adjusted by entering the number of periodic health checkups during the 10-year period as a continuous variable.
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Although case-control studies are by their very nature vulnerable to bias and so can be misleading, the Selby et al. study seems to avoid many biases and the Newcomb and Muller[48] studies provide independent corroboration of a possible effect of screening sigmoidoscopy on deaths from CRC.

Two of these case-control studies are with rigid rather than flexible sigmoidoscopy, and the third apparently mostly with rigid scopes as well. Therefore, they provide only indirect evidence of effectiveness of flexible sigmoidoscopy in reducing mortality from CRC. Other indirect evidence comes from studies comparing the performance of rigid and flexible scopes that found that the flexible scopes detect more polyps and cancers[104–111] and from the panel's decision analysis on the clinical consequences of CRC screening. The model used in this analysis indicates that for a population of 100,000, flexible sigmoidoscopy every 5 years with appropriate follow-up would reduce incidence of colon cancer by 1976 cases, from 4988 cases to 3013 cases. The number of expected cancer deaths would decrease by 967. This reduction in incidence and mortality would be accompanied by increases in complications: the population could expect up to 3 complication deaths from colonoscopy, 20 colonoscopy perforations, 49 major bleeding episodes, and 49 cases of minor complications. The population would also expect up to 6 complication deaths from flexible sigmoidoscopy. An individual whose death by cancer was prevented would have an increased life expectancy of 8.6 years.*

Screening frequency. The case-control study of screening sigmoidoscopy by Selby et al.[11] found that the effectiveness of screening sigmoidoscopy was just as great for patients who had undergone the procedure 9–10 years before as for those who had undergone it more recently.[12] However, this estimate was based on a retrospective study with a small number of patients. Results of the case-control study by Muller and Sonneberg are consistent with a protective effect of at least 6 years.[130] In a study by Rex et al.,[131] 259 asymptomatic, average-risk persons (age, ≥50 years) with negative flexible sigmoidoscopy underwent a second examination an average of 3.4 years after the first. The second examination found adenomas in 6% of the screenees but no cancers or large polyps.

Complications. The major complication of sigmoidoscopy is perforation of the colon. Data from large series of sigmoidoscopies show perforation rates ranging from 1 to 2 per 10,000 examinations.[108,132–134] Slightly higher complication rates apply when biopsy or polypectomy is performed. No direct evidence of mortality from flexible sigmoidoscopy was found in the literature.

*These results assume a flexible sigmoidoscopy sensitivity of 96.7% for cancer and large polyps and 73.3% for small polyps within the reach of the 60-cm flexible instrument. Specificity is assumed to be 94% for cancer and large polyps and 92% for small polyps. Flexible sigmoidoscopy is assumed to produce three complications/10,000 tests, with 2.8% of these complications ending in death. Colonoscopy complication rates used were 8.5/1000 tests: 1.3 perforations, 0.2 deaths, and 3.4 major bleeding episodes, with the remainder being minor complications. Colonoscopy sensitivity was assumed to be 96.7% for cancer, 85% for large polyps, and 78.5% for small polyps, and colonoscopy specificity was assumed to be 98% for all.

Fiberoptic scopes (both sigmoidoscopes and colonoscopes) have the potential to transmit infection. Even with the best methods of disinfection it is not possible to completely sterilize all components of the instrument, although it is possible to reduce the density of infectious agents to a very low level if proper procedures are followed. A few case reports describe bacterial infection transmitted by lower gastrointestinal endoscopy, but there are are no reports of infections transmitted in recent large prospective series of sigmoidoscopy. It is generally believed that the risk of transmitting infection by sigmoidoscopy or colonoscopy is low and that transmission of viruses in particular is highly unlikely.[135,136]

Participation and acceptability. Rates of patient participation in screening sigmoidoscopy vary widely in different studies. Rates as high as 100% have been reported in people older than 50 years with a family history of CRC,[137] whereas, in another study of people older than 50 years with no family history who were invited by letter to participate, rates were as low as 1.3%.[138] Rates of adherence in studies performed in the workplace range from 31% to 53%.[98] This variation is due in part to differences in study populations, recruitment methods, and types of sigmoidoscopes. Factors positively associated with having ever had a sigmoidoscopy include older age, female gender, white race, higher income, greater degree of optimism and knowledge of the disease, and a medical visit within the past 2 years.[20] Some studies have also found that participation is higher in those with a family history of cancer.[139–140] The health care provider also plays an important role. Rates of patient participation are higher if the procedure is recommended by a physician,[141] and in one study, individuals in whom sigmoidoscopy was performed by nurse practitioners were significantly more likely to attend again than those screened by physicians.[114] However, studies on the effect of interventions on participation have major methodological limitations; most of them used nonrandomized designs or were conducted with nonrepresentative population samples. As with participation rates for other screening procedures, rates for sigmoidoscopy can be improved if health care professionals give the matter sufficient emphasis.

• **Recommendation and rationale for screening with flexible sigmoidoscopy: page 597.**

Combined Fecal Occult Blood Testing and Sigmoidoscopy

There are theoretical reasons for combining FOBT with sigmoidoscopy. In one randomized controlled trial, two thirds of the interval cancers, those missed by FOBT, were found in the rectosigmoid area.[6] In addition, sigmoidoscopy is more accurate than FOBT for detecting adenomatous polyps; therefore, sigmoidoscopy offers the possibility of reducing the incidence of CRC as well as detecting cancers at an earlier stage.

Only one controlled trial has studied the additional benefit of adding FOBT to screening sigmoidoscopy.[14] Investigators at the Sloan-Kettering Institute and the Strang Clinic, a busy

prevention clinic in New York, allocated 12,479 people 40 years of age and older, using calendar periods (nonrandom allocation), to annual screening either with rigid sigmoidoscopy combined with FOBT or with rigid sigmoidoscopy alone. After 5–11 years of follow-up, mortality from CRC was lower in those receiving FOBT as well as sigmoidoscopy (Table 5). This was associated with earlier stage cancers and longer survival in the FOBT group compared with the control group (70% vs. 48%).

Indirect evidence supporting the combination strategy comes from the panel's simulation model. The model indicates that for a population of 100,000, the combination of annual FOBT with flexible sigmoidoscopy every 5 years (with appropriate follow-up) would yield the following outcomes: (1) the incidence of colon cancer would be reduced by 3087 cases from 4988 cases to 1901 cases and (2) the number of expected cancer deaths would decrease by 1609. This reduction in incidence and mortality would be accompanied by increases in complications: the population could expect up to 53 complication deaths from colonoscopy, 312 colonoscopy perforations, 757 major bleeding episodes, and 772 cases of minor complications. The population would also expect up to 5 complication deaths from flexible sigmoidoscopy. People whose death by cancer was prevented would have an increased life expectancy of 7.3 years. These results assume sensitivity, specificity, and complication rates identical to those used for FOBT and flexible sigmoidoscopy individually.

- **Recommendation and rationale for screening with both FOBT and flexible sigmoidoscopy:** **see page 598.**

Barium Enema

Description of the test. Barium enema can be performed in two ways: as a single contrast study using barium alone, which reveals filling defects, or as a double contrast (DCBE, also called air-contrast barium enema) study, in which air is instilled after most of the barium has been removed and lesions in the mucosa are outlined by the retained barium. DCBE is slightly more difficult and expensive but is better at detecting mucosal lesions, including small polyps. It has tended to replace single contrast procedures as a test for cancer and polyps, except in the very young, the very old, and the seriously ill or disabled patient who may be less able to tolerate the more complicated procedure. The following comments concern DCBE.

Patients usually begin preparation 24 hours before the procedure, with a low residue or liquid diet followed by laxatives and enemas. Patients are encouraged to drink clear fluids to avoid dehydration. The examination takes 20–30 minutes. Patients may be given an intravenous antispasmodic drug but are not usually given sedation. With the patient lying prone, a soft tube 2 cm in diameter is inserted 3–5 cm into the rectum and liquid barium is instilled. The barium's progress is monitored fluoroscopically as the patient rolls to the left and right and is then tilted to a standing position to fill the colon as far as the cecum. Air is instilled to assist the progress of the barium through the bowel and to provide a double contrast examination. This can cause some discomfort,[142] especially if the air is instilled too quickly. Radiographs of the bowel are then taken.

Patients can leave the hospital immediately after the examination. They pass barium from the rectum for 1–2 days and may experience temporary constipation. Laxatives may be prescribed to prevent impaction of barium. Some patients experience a colicky discomfort after the examination, especially once the antispasmodic wears off. A double-blind prospective study found that instilling carbon dioxide rather than air reduced the incidence of severe pain after the procedure from 27% to 7%.[143]

Performance. Barium enema images the entire colon in most completed examinations. However, studies show that 5%–10% of barium enemas are unsatisfactory, requiring another attempt or colonoscopy to visualize the entire colon.[144–146] The performance characteristics of DCBE are not precisely known because of methodological shortcomings of existing studies. Foremost among these are difficulties in identifying a gold standard for the presence or absence of polyps and cancer. Colonoscopy, a commonly used gold standard, may itself miss lesions. In addition, detection rates during follow-up examination vary depending on the interval since the previous examination, and most published studies are of symptomatic patients rather than people being screened. There are also clinical reasons for variation in performance such as the skill of the examiner and differences in patients' anatomy.

Results from the studies with the fewest biases[122,147–149] suggest that the sensitivity of DCBE is 50%–80% for polyps <1 cm, 70%–90% for polyps >1 cm, and 55%–85% for Dukes' stage A and B cancers. Insensitivity is mainly related to inadequate visualization of parts of the bowel and to errors of interpretation. False positive findings are mainly caused by adherent stool and non-neoplastic mucosal irregularities, with rates ranging from <1% for cancers, 5%–10% for large polyps,[145,148,150] and about 50% for small polyps.[148] Thus, most studies suggest that performance of DCBE, although lower than colonoscopy, is sufficient to detect the

Table 5. FOBT Screening and CRC Mortality

	Study group	Control group
Person-years	33534	34675
Total deaths	259	270
Mortality rate[a]	7.7	7.8
CRC deaths	12	22
Mortality rate[a]	0.36	0.63

The study group was offered FOBT and sigmoidoscopy; the control group was offered only sigmoidoscopy.
[a]Mortality rate equals number of deaths per 1000 per year in the study and control groups. $P = 0.053$.
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majority of clinically important lesions. Single contrast barium enema is substantially less sensitive and specific than DCBE in detecting clinically important lesions during screening.

Performance of barium enema combined with sigmoidoscopy. Traditionally, patients have undergone sigmoidoscopy before barium enema because barium enema was considered an inaccurate examination of the sigmoid colon and rectum.[151–153] With improved double-contrast techniques, the accuracy of the procedure in the rectosigmoid has been considered better and some radiologists no longer recommend prior sigmoidoscopy.[154–157] A randomized trial of DCBE plus flexible sigmoidoscopy vs. colonoscopy in 383 patients with gastrointestinal bleeding suspected to be from the colon found that colonoscopy detected more cases of polyps <9 mm than DCBE plus sigmoidoscopy.[158] However, there was no difference between groups in the number of patients detected with cancers or polyps ≥9 mm. DCBE and sigmoidoscopy together have been the first-line diagnostic evaluation for a large ongoing Swedish randomized, controlled trial of screening FOBT. In this study, DCBE alone missed 25% of cancers and a similar proportion of polyps >1 cm in the rectosigmoid, with the true presence of these lesions conservatively estimated by findings of flexible sigmoidoscopy and follow-up for the appearance of CRC.[159] The flexible sigmoidoscope performed better than DCBE in this region, but this method overlooked 5% of carcinomas and 10% of adenomas >1 cm in the rectosigmoid (sensitivity, 95% and 90%, respectively). The combination of flexible sigmoidoscopy and DCBE had a sensitivity of 98% for carcinomas and 99% for adenomas.

The panel's decision analysis also indicates a modest net benefit from the addition of sigmoidoscopy to DCBE.

Effectiveness. The panel found no controlled comparisons of the effectiveness of barium enema in screening for CRC in which death or any other adverse health outcome from CRC was measured. Indirect evidence of the effectiveness of barium enema in screening comes from the fact that detecting polyps and early cancers by other screening tests reduces the incidence and mortality from CRC cancer and that air-contrast barium enema detects many of these lesions. Barium enema screening is also supported by the decision analysis on the clinical consequences of CRC screening that was performed by the authors. This simulation model estimates that for a population of 100,000, screening with air-contrast barium enema at 5-year intervals (with appropriate follow-up) would reduce incidence of colon cancer by 3384 cases, from 4988 cases to 1604 cases. The number of expected cancer deaths would decrease by 1663. This reduction in incidence and mortality would be accompanied by increases in complications: the population could expect up to 16 complication deaths from colonoscopy, 97 colonoscopy perforations, 248 major bleeding episodes, and 259 cases of minor complications. The population would also expect up to 18 complication deaths from barium enema. An individual whose death by cancer was prevented would have an increased life expectancy of 7.6 years.

For a 10-year interval, incidence is reduced by 2812 cases to an expected 2176 cases. The number of expected cancer deaths would decrease by 1442. The expected number of complications is reduced from that for a 5-year interval: the population could expect up to 12 complication deaths from colonoscopy, 69 colonoscopy perforations, 178 major bleeding episodes, and 181 cases of minor complications. The population would also expect up to 12 complication deaths from barium enema. An individual whose death by cancer was prevented would have an increased life expectancy of 7.7 years.*

Screening frequency. There are no studies that directly address the question of how frequently barium enema should be performed in screening for CRC. The rationale for performing a DCBE every 5–10 years is based on indirect evidence reflecting current knowledge of the natural history of the disease and existing data on the performance and relative cost and safety of the procedure. It generally is considered that evolution from normal mucosa to invasive carcinoma takes place over approximately 10 years. This would indicate a screening interval of at least every 10 years. However, some neoplasms may be overlooked on any given examination, and there may also exist some tumors that progress more rapidly. Therefore, a 5-year interval also appears reasonable. Given the relatively low cost and the safety of the procedure, this frequency would be acceptable. Additional supportive evidence is also derived from the case-control mortality studies pertaining to sigmoidoscopy in which the protective effect of this procedure persisted during such screening intervals. If it is assumed that the benefits from the barium enema relate to its ability to detect adenomatous polyps and early cancers (similar to sigmoidoscopy), then a similar screening frequency is suggested.

Complications. The most serious complication of barium enema is bowel perforation. However, data on perforation rates and other serious complications are sparse. The few data in the literature are not current and relate to single contrast barium enemas. A recent study in the United Kingdom[160] using a retrospective, self-administered mail questionnaire estimated the perforation rate at 1 in 25,000 and cardiac complications at 1 in 46,000. However, the study has the weakness of self-reporting.

Patients are exposed to 300–500 mrem of radiation during a barium enema examination. For comparison, the estimated effective dose of radiation from mammography is about 300

*These results assume a DCBE sensitivity of 84% for cancer, 82% for large polyps, and 67% for small polyps. Specificity is assumed to be 97.5% for cancer, 83.3% for large polyps, and 75% for small polyps. Barium enema is assumed to produce three complications/10,000 tests, with 10% of these complications ending in death. Colonoscopy complication rates used were 8.5/1000 tests: 1.3 perforations, 0.2 deaths, and 3.4 major bleeding episodes, with the remainder being minor complications. Colonoscopy sensitivity was assumed to be 96.7% for cancer, 85% for large polyps, and 78.5% for small polyps; specificity was assumed to be 98% for all.

mrem. Considering the age and frequency at which screening is commonly recommended, a screening strategy using barium enema would deliver a lifetime dose lower than that for screening mammography. There is no direct evidence that barium enema examinations, or other radiation of similar dose, frequency, and anatomical coverage, cause clinically important increases in the risk of cancer or other tissue damage.

Participation and acceptability. Studies of the acceptability of barium enema among patients being investigated for suspected colonic disease give inconsistent results. One found that 94% of patients rated barium enema as an acceptable procedure, whereas in another, nearly half of patients found barium enema distressing and uncomfortable.[161–163] Little is known about patients' participation with barium enema for screening.

- **Recommendation and rationale for screening with double-contrast barium enema: see page 598.**

Colonoscopy

Colonoscopy is the only technique currently available that offers the potential to both find and remove premalignant lesions throughout the colon and rectum. Screening for fecal occult blood detects only those polyps and cancers that bleed; sigmoidoscopy allows inspection of only the distal half of the large bowel; and DCBE, although it can image the entire large bowel, does not allow biopsy or polypectomy.

The test. Colonoscopy requires preparation of the bowel using laxatives with or without enemas or large volumes of an oral cathartic solution. Patients usually receive intravenous sedation that maintains consciousness so that they can provide feedback to the operator about pain or discomfort and cooperate with the procedure, yet subsequently remember little about the procedure.[164–166] It is extremely uncommon for patients without known heart or lung disease to develop clinically important cardiorespiratory complications during colonoscopy. However, elderly patients or others at risk of cardiorespiratory abnormalities may need monitoring of, for example, blood pressure or oxygenation, during the procedure. Patients at increased risk of endocarditis may receive antibiotic prophylaxis, as described under sigmoidoscopy earlier.

The endoscopist maneuvers the scope within the bowel, monitoring its progress on a videoscreen. Distending the bowel with air is necessary for visualization of the bowel mucosa. Polyps are removed by a combination of electrocautery and traction by forceps or a wire snare. The procedure takes 15–20 minutes for an experienced endoscopist, but much longer for beginners.[167] Patients may experience transient pain during and after the procedure. Colonoscopy is currently performed only by physicians. Although patients require sedation, they can return home within 1–2 hours of the procedure.

Performance characteristics. Colonoscopic techniques have improved since the procedure was first introduced in the early 1970s. Nevertheless, procedural competence varies across endoscopists.[168] The cecum is reached in 80%–95% of procedures,[31,128,169] the depth of penetration depending mainly on the experience of the endoscopist and the adequacy of the preparation.[170,171] Most available data on performance are from diagnostic evaluations and surveillance, not from screening settings. In a study of screening colonoscopy, 98.6% of examinations reached the cecum.[128] Incomplete colonoscopies require either a repeat colonoscopy or supplemental barium enema.

Colonoscopy can detect both cancers and polyps, although, like barium enema, it is less accurate when the polyps are small. A limitation of many studies of performance of colonoscopy is that colonoscopy itself is often taken as the gold standard for the presence or absence of polyps and cancers. A retrospective review of 429 patients who had CRCs and polyps resected after undergoing preoperative colonoscopy found that the findings at colonoscopy correlated with the pathological specimen in 97% of cases but that colonoscopy missed the lesion in the remaining 3% of cases.[8] In a retrospective study[172] of 235 patients in a cancer referral center who had undergone colectomy for primary CRC (1980–1987), all of whom had undergone preoperative colonoscopy, 36 of 46 polyps $\geq$10 mm located in the area examined during colonoscopy were found by colonoscopy (78%; 95% CI, 73%–93%). A prospective study, in which 90 patients underwent colonoscopy by two experienced examiners, concluded that large polyps ($\geq$1 cm) were rarely missed but that the operators missed about 15% of smaller polyps.[122] However, it is possible that anatomic "blind spots" may have existed for both examiners. Other studies have used follow-up colonoscopy within a short time frame (6 months or 1 year) as the gold standard.[51,55] These suggest that colonoscopy misses 25% of polyps $<$5 mm and 10% of polyps $>$1 cm.

False positive results, i.e., reporting a lesion when none is present, are as rare with colonoscopy as they are with sigmoidoscopy, although about a third of the polyps removed at colonoscopy are not adenomatous.[41]

Effectiveness. There are no published studies that directly examine the effectiveness of colonoscopy as a screening test for CRC in terms of CRC deaths. There is indirect evidence; i.e., it has been shown that detecting and removing polyps reduces the incidence of CRC,[17] that detecting early cancers lowers the mortality from the disease, and that colonoscopy detects most of these lesions. A case-control study showed fewer CRCs developing in people who had undergone colonoscopy (odds ratio, 0.61; 95% CI, 0.48–0.77) or polypectomy (odds ratio, 0.48; 95% CI, 0.35–0.66).[48] To the extent that colonoscopy is an essential part of the intervention in the trials of FOBT, these trials strengthen the evidence for the effectiveness of colonoscopy.[9] Indirect support for screening colonoscopy is also found in the results of the decision analysis conducted for this report. The results of the simulation model indicate that for a population of 100,000, screening with colonoscopy at 10-year intervals would reduce incidence of colon cancer by 3570 cases, from 4988 cases to 1418 cases. The number of expected cancer deaths would decrease by 1763.

This reduction in incidence and mortality would be accompanied by increases in complications: the population could expect 73 complication deaths from colonoscopy, 445 colonoscopy perforations, 1075 major bleeding episodes, and 1101 cases of minor complications. An individual whose death by cancer was prevented would have an increased life expectancy of 7.3 years.*

Complications. Colonoscopy can be complicated by perforation, hemorrhage, respiratory depression due to sedation, arrhythmia, transient abdominal pain, and ileus, and nosocomial infection. Most studies reporting rates for these complications represent early experience with the procedure rather than current practice and may overestimate current rates. On the other hand, there are several reasons why rates reported in published articles may be lower than those in practice: (1) the studies are retrospective reviews, which may suffer from underreporting[173]; (2) they are reports of experience in major health care centers, where complication rates are likely to be lower than in general medical practice; and (3) they may not include late complications.

Data from six prospective studies of colonoscopy indicate that approximately 1/1000 patients have perforation, 3/1000 have major hemorrhage, and 1–3/10 000 die as a result of the procedure.[128,169,174–177] Complication rates may be higher if polypectomy is performed.[178]

Older patients do not seem to be at greater risk of complications than younger patients,[179] but they may tolerate the procedure less well. About 5/1000 patients experience clinically significant respiratory depression.[180] Arrhythmias could theoretically be triggered by the procedure, but clinically significant rhythm disturbances are very rare. Colonoscopy also carries the theoretical risk of infection, the magnitude of which is extremely small but not precisely known. (See the section on complications from sigmoidoscopy.)

Frequency of screening. There are no studies that directly address the question of how frequently colonoscopy should be performed in screening for CRC. However, on the basis of the high accuracy of colonoscopy, the length of time taken for polyps to develop into cancers in the grossly normal colon, and estimates from a case-control study of proctosigmoidoscopy,[11] screening colonoscopy every 10 years seems to be adequately protective, provided no polyps or cancers are detected.

Participation in screening colonoscopy. Data on compliance with screening colonoscopy are sparse. When physicians and nurses and their spouses were invited by letter to undergo free screening colonoscopy, <15% accepted.[131] In the National Polyp Study, 80% of people reattended after previous polypectomy.[181] Opinions of acceptability vary. Williams et al. found that 88% of patients rated colonoscopy as an acceptable procedure.[162] Nearly a quarter of patients studied by Durdey et al. found the procedure distressing and uncomfortable.[163]

- **Recommendation and rationale for screening with colonoscopy:** **see page 598.**

Comparison of Barium Enema and Colonoscopy

Colonoscopy and DCBE offer alternative ways of examining the entire colonic mucosa. Each procedure has advantages and disadvantages.[173] Studies exist that compare the two procedures, but most suffer from methodological flaws. Of the controlled trials comparing the two procedures,[167,182–86] all relate to patients with symptoms or previously detected polyps and only two incorporate some form of randomization.[184,185] These show that while colonoscopy detects more small polyps, there is little difference in the ability of these tests to detect large polyps (>1 cm in diameter). False positive rates and rates of inadequate examinations are about the same for the two procedures.

It is not clear which procedure patients consider most acceptable. Steine found that patients who underwent both procedures rated pain significantly worse during colonoscopy compared with barium enema.[161] Williams et al. found patients' preferences for the two procedures to be broadly similar,[162] whereas Durdey et al.[163] and Van Ness et al.[187] found that more patients preferred colonoscopy. It is likely that individual patients might prefer one or the other of the procedures.

Although colonoscopy is more accurate than barium enema for small polyps, both may miss clinically important lesions. It is seldom useful to perform both because a second procedure after either has been conducted initially contributes only marginal additional information. However, a positive barium enema (or sigmoidoscopy) usually is an indication for a subsequent colonoscopy.

The two procedures can also be seen as alternatives for examining the colon and rectum. Because they have different advantages and disadvantages, individual physicians and patients may choose either over the other in given circumstances. As noted elsewhere in this report, factors such as cost and complication rates can influence decisions on which option is selected. Models of diagnostic strategies for people with a positive screening FOBT have shown that barium enema and colonoscopy have comparable cost-effectiveness, within the limits of the assumptions used in the models.[188,189]

Digital Rectal Examination

It has been common practice to screen for CRC by digital rectal examination, followed by tests for fecal occult blood if stool is present in the rectum. Some expert groups have recommended this practice.[190,191] Only a small proportion (5%–10%) of all cancers are within reach of the examining finger,[192] and stool samples obtained during the examination provide only a single specimen for fecal occult blood that may be falsely negative because of inadequate sampling. Digital

*These results assume a colonoscopy sensitivity of 96.7% for cancer, 85% for large polyps and 78.5% for small polyps, whereas colonoscopy specificity was assumed to be 98% for all. Colonoscopy complication rates used were 8.5/1000 tests: 1.3 perforations, 0.2 deaths, and 3.4 major bleeding episodes, with the remainder being minor complications.

rectal examination by itself has not been shown to be an effective way of screening for CRC. However, it is part of other screening examinations for CRC (sigmoidoscopy, colonoscopy, and barium enema) and may be included in a comprehensive program of preventive health care for other reasons.

Summary: Screening Strategies for Average-Risk People

The clinical recommendations presented in this report are summarized in the algorithm shown in Figure 1. It shows the screening and surveillance options for the average- and high-risk populations considered by the panel. Table 6 summarizes the characteristics of the screening test procedures discussed in this report (FOBT, flexible sigmoidoscopy, DCBE, and colonoscopy). The text should be consulted for complete information on the use of these tests in average- and high-risk populations.

When to Stop Screening

There is no direct evidence relating to the time at which screening should stop, but indirect evidence supports stopping screening in people nearing the end of life. Polyps take about 10 years to progress to cancer, and screening to detect polyps may not be in the patients' best interest if they are not expected to live at least that long. Also, screening and diagnostic tests are, in general, less well tolerated by elderly people. Therefore, there will come a time in most people's lives when the rigors of screening and diagnostic evaluation of positive tests are no longer justified by the potential to prolong life. The age at which to stop screening depends on the judgment of individual patients and their clinicians, taking into account the lead time between screening and its benefits and the patient's life expectancy.

New Technologies for Screening

Several new technologies for CRC screening are in various stages of development. They have not yet been sufficiently evaluated to be recommended for widespread use.

Alternative tests for fecal occult blood. Other tests for fecal occult blood, based on different chemical reactions, have been developed. Preliminary assessments of their sensitivity and specificity have been published.[79] An immunochemical test (HemeSelect) reacts specifically with hemoglobin. It has the advantage of detecting bleeding only from the lower gastrointestinal tract, because blood protein from the upper gastrointestinal tract is digested. Studies suggest several advantages of the immunologic tests over guaiac-based tests, including higher sensitivity for colorectal bleeding, lower sensitivity to upper gastrointestinal bleeding, and no requirement for dietary restrictions or avoidance of medications.[193] They are, however, much more expensive, and some studies of screening have shown high rates of positive tests, raising concern about the tests' specificity.[194–196] A quantitative test for porphyrin derivatives (Hemoquant) has been shown to be less sensitive and less specific than the guaiac based test.[197] A version of the guaiac test called Hemoccult II Sensa may possess a high sensitivity, similar to that of the rehydrated Hemoccult test.[79,82] The newer tests are undergoing field testing to determine how well they perform relative to the usual standard, the guaiac-based test. As yet they have not been evaluated sufficiently to be included in the present recommendations.

Virtual colonoscopy. In virtual colonoscopy, data from spiral computerized tomographic scans are synthesized by computer to produce images of the entire colonic mucosa in apparent three-dimensions. Patients undergo bowel preparation but do not require sedation. Air is passed into the bowel, and cross-sectional computerized tomographic scans are taken at multiple levels. The procedure takes less than a minute, although reconstructing the images takes much longer. As yet there is no good evidence on the performance, effectiveness, complication rate, or patient acceptance of the method. This method is under development and is not yet ready for large-scale evaluation or widespread use.

Screening People at Increased Risk for Colorectal Cancer

A more aggressive approach to screening might be justified in people who are at higher than average risk of

Table 6. Summary of the Characteristics of Each Screening Test Discussed in This Report

Screening test	Overall performance	Complexity	Potential effectiveness	Evidence of effectiveness	Screening test risk
FOBT	Intermediate for cancers, low for polyps	Lowest	Lowest	Strongest	Lowest
Flexible sigmoidoscopy	High for up to half of the colon	Intermediate	Intermediate	Intermediate	Intermediate
FOBT + flexibl sigmoidoscopy	Same as flexibl sigmoidoscopy and FOBT	Intermediate	Intermediate	Intermediate	Intermediate
DCBE	High	High	High	Weakest	Intermediate
Colonoscopy	Highest	Highest	Highest	Weakest	Highest

NOTE. The costs of the screening tests themselves, also an important characteristic, vary, but the costs of the screening strategies (lifetime programs of screening and follow-up of abnormal test results) are comparable. Complexity involves patient preparation, inconvenience, facilities and equipment needed, and patient discomfort.

colorectal cancer. The higher a person's risk of disease, the greater the potential benefit from screening for that person and the lower the cost of screening per cancer detected. (The actual benefit depends, however, on the effectiveness of early detection of the disease and prevention of the cancer.)

Screening high-risk people could take several forms: patients could enter screening at an earlier age if polyps and cancers arise at an earlier age; they could be screened more frequently if the evolution from small polyps to cancer is more rapid; they could be screened by tests that reach the right colon if their cancers occur more proximally; or they could be screened with more sensitive methods such as colonoscopy or DCBE rather than FOBT or sigmoidoscopy, if the risk is high.

Patients already found to have adenomatous polyps are at increased risk but are candidates for surveillance rather than screening; this issue will be discussed later.

Family History of Colorectal Cancer

This group is comprised of individuals having one or more first-degree relative with CRC; people with HNPCC or FAP are excluded. There is good evidence that cancers arise at an earlier age in these people than in average-risk persons. In effect, the risk of a 40-year-old person with a family history of CRC is comparable to that of an average-risk 50-year-old person[57] (see Figures 10 and 11 for comparative incidence data).

It is also clear that the incidence of CRC in this group is increased about twofold and that this increase seems to be greater in young adults than later in life.[57] Risk is higher if the relative developed CRC at a young age.[57,197]

There is no evidence that cancers develop more rapidly in people with a family history of CRC. Similarly, the distribution of cancers in the colon and rectum is apparently not substantially different in patients with a family history of CRC compared with average-risk people.

In addition to the increased risk associated with having a family member with CRC, siblings and parents of patients with adenomatous polyps are also at increased risk for CRC. The risk is increased when the adenoma in the relative is diagnosed before age 60 or, in the case of siblings, when a parent has had CRC.[59]

- **Recommendation and rationale for screening in people with a family history of colorectal cancer or adenomatous polyps: see page 598.**

Genetic Syndromes

Genetic abnormalities for two inherited colorectal cancer syndromes, FAP and HNPCC, have been identified. In both cases, specific genetic mutations have been found in the kindreds examined. It has been estimated that 80% of individuals in FAP and HNPCC families (by the Amsterdam criteria) are carriers of the known gene mutations. Because of the rarity of these syndromes and the technical difficulties of identifying all possible mutations, it is not presently feasible or appropriate to screen the general population for these familial syndromes. However, if blood is available from a clinically affected relative in either syndrome and a genetic mutation has been identified, it is possible to determine if other members of the kindred are carriers because the genetic mutation is constant within kindreds and so more easily identified. A negative test in an individual from a family that has an affected member with a positive test essentially rules out the disease. A negative test in an individual in the absence of a positive test in the family does not rule out the disease. At present HNPCC is being identified primarily by a family history that meets the Amsterdam criteria (see page 609).

In people affected by FAP, approaches to prevention are based on the biological behavior of the syndrome, which is well characterized. Screening is not an issue once it is known a person has the syndrome. There are too many polyps to be evaluated individually and the risk of cancer is high. Therefore, colectomy is the only feasible preventive strategy, and the main decision is when it should be performed.

For people at risk for HNPCC because of a family history of the syndrome and people who know from genetic testing that they carry the gene, screening is relevant. There is evidence (see section 4) that cancers develop at an earlier age and at a much higher rate with a more proximal distribution than in average risk people. Adenomas often are multiple and flat and precede the cancers.[64,198] Evidence for the effectiveness of screening is sparse. In one study, 251 people at risk for HNPCC because of family history underwent no screening or screening with colonoscopy or barium enema and sigmoidoscopy every 3 years, the allocation between the two groups being according to whether people accepted or declined an invitation to be screened.[199] After 9 years, the screened group had fewer CRCs (4.5% vs. 11.9%; $P = 0.03$) and fewer deaths ($P = 0.08$). The occurrence of interval cancers in the screened group suggested that a 3-year interval between examinations was too long for this high-risk group. Evidence exists that the pathological progression of small adenomas and their transformation to cancer is accelerated in HNPCC compared with the sporadic adenoma-adenocarcinoma sequence.[64,199,200]

- **Recommendations and rationale for testing in people with family history of FAP or HNPCC: see pages 599.**

Refer to Figure 1 for an algorithmic summary of screening in familial high-risk people.

Surveillance

Surveillance After Removal of Adenomatous Polyps

The main options for surveillance are colonoscopy and DCBE. With these surveillance strategies, as with screening tests, performance is judged in terms of the proportion of additional adenomatous polyps they detect (sensitivity), their ability to distinguish clinically important polyps and cancers from other lesions (specificity), and their effectiveness in terms of their ability to reduce incidence and deaths from CRC.

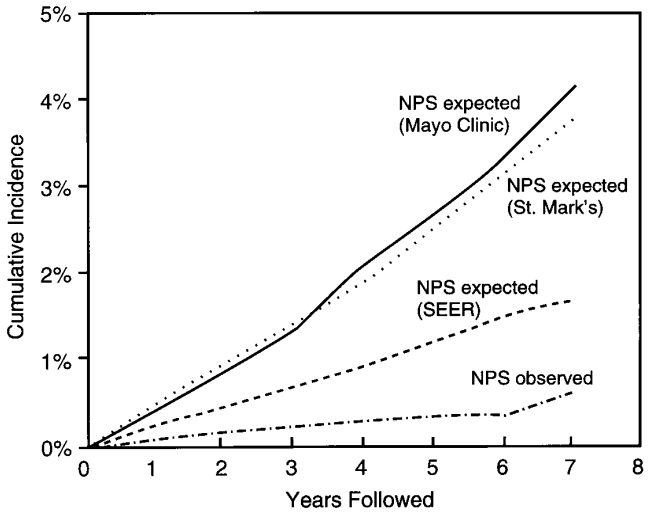

Figure 15. Observed and expected CRC incidence in National Polyp Study cohort after colonoscopic polypectomy. (Reprinted with permission.[17])

Evaluation must also take into account risk, convenience, and cost.

The performance characteristics (sensitivity and specificity) of both colonoscopy and barium enema have been described under screening and diagnosis. (Most of the information in fact applies more closely to surveillance since the studies were performed in that setting.)

The best evidence of the effectiveness of surveillance is for colonoscopy. In the National Polyp Study, a cohort of 1418 patients who had undergone complete colonoscopy and removal of one or more adenomatous polyps from the colon or rectum were followed up for an average of 5.9 years per patient with periodic colonoscopy. After adjusting for age, sex, and polyp size, rates of cancer were 76%–90% lower than expected ($P < 0.001$) from comparison with three reference groups who had not undergone surveillance (Figure 15).[17] It is not possible, however, to distinguish the benefits of surveillance from those of initial clearance of the bowel. If the first surveillance colonoscopy was negative, subsequent examinations were highly unlikely to reveal further adenomatous polyps. The study used reference groups as controls, with the assumption that patients undergoing polypectomy would have experienced the same incidence of cancer as the reference populations if they had not undergone polypectomy. However, the differences are so large that it is unlikely that bias could entirely account for them.

The optimal frequency of surveillance was also studied in the National Polyp Study. Patients who had all undergone prior polypectomy were randomized to undergo surveillance colonoscopy either 1 and 3 years or only 3 years after polypectomy. The two groups showed no difference in the proportion of detected adenomatous polyps with advanced pathology (3.3% in both groups; 95% CI, 0.8%–5.3%).[181] This suggests that the first follow-up screen after polypectomy can be deferred for at least 3 years.

There have been no reported studies of surveillance after polypectomy using barium enema and no reported studies comparing surveillance with barium enema vs. colonoscopy. The National Polyp Study included in its design a blinded comparison between DCBE and colonoscopy in the detection of polyps at follow-up; however, the final results of this analysis are not yet available.

There is no direct evidence relating to when to stop surveillance. As with screening, the age at which surveillance should stop will depend on the judgment of patients and their clinicians, taking into account the patient's medical history and comorbidity. The decision on when to stop will also depend on the characteristics of the polyps removed and the results of follow-up examinations. And, as noted previously, examinations subsequent to the first surveillance examination are unlikely to find adenomatous polyps.

- **Guideline and rationale for screening in patients with a history of adenomatous polyps: see page 599.**

Surveillance of People After Curative-Intent Resection of Colorectal Cancer

People who have had a CRC are at increased risk of a second (metachronous) cancer, apart from their risk of recurrence of the original cancer; this should be considered when making surveillance recommendations for these individuals. There are no controlled studies of the effectiveness of surveillance strategies in this situation. Available information suggests that the metachronous cancers have a biological behavior that is not, on average, different from initial cancers except in increased frequency of occurrence. Cancers are preceded by adenomatous polyps. Therefore, by analogy they should undergo surveillance comparable to that recommended after polypectomy. The choice of surveillance procedure (colonoscopy or barium enema) might be affected by distortions of normal anatomy and adhesions caused by the surgery and should be decided on an individual basis. Colonoscopy permits removal of polyps that occur with higher frequency in these patients. Flexible sigmoidoscopy increases the sensitivity of DCBE and can visualize the anastamosis in distal resections.

- **Recommendation and rationale for surveillance in patients after curative-intent resection of colorectal cancer: see page 600.**

Surveillance in People With Inflammatory Bowel Disease

Surveillance for CRC in patients with inflammatory bowel disease aims primarily to detect moderate to severe dysplasia and early cancers rather than polyps. It is usually performed by colonoscopy with biopsies of suspicious lesions. FOBT is not helpful because colorectal bleeding is a prominent feature of inflammatory bowel disease. Sigmoidoscopy does not reach all the areas of bowel likely to harbor cancers. Barium enema does not identify flat, infiltrating cancers; nor can it detect dysplasia, because this diagnosis relies on biopsy.

Although the need for surveillance is widely accepted, the evidence base that the practice is effective in reducing mortality, or better than timing a colectomy according to the extent and duration of disease alone, is weak. In one study of 401 patients with ulcerative colitis, all of whom were offered surveillance, most of the cancers detected during regular surveillance were at an early stage.[68] A recent decision analysis suggested that both surveillance and prophylactic colectomy increased life expectancy in patients with ulcerative colitis and that both are better than no surveillance.[201,202] Several investigators have questioned whether annual colonoscopic surveillance is cost-effective.[202–205]

It is common practice to repeat surveillance colonoscopy every 1–2 years, beginning after 8 years of disease in patients with pancolitis or after 15 years in those with colitis involving only the left colon. The rationale for this frequency is grounded in the difficulty of detecting cancer or dysplasia in any single examination. However, there is no direct evidence that this approach is effective in reducing mortality.

- **Recommendation and rationale for surveillance in patients with inflammatory bowel disease: see page 600.**

Clinical Consequences of the Screening Strategies

In deciding whether to screen for CRC and which strategies are preferred, patients and clinicians need to consider all clinically important consequences of screening as they accumulate over time. These include the prevention of CRC death and cost, the main elements of a recent government cost-effectiveness analysis (summarized in the next section). But the consequences go beyond these to include major procedures such as colonoscopy and DCBE that would be performed in the course of screening and follow-up, false positive test results, frequency of major complications, and prevention of CRC occurrence.

The consideration of evidence on individual strategies taken one at a time is limited in several ways. Many probabilities are uncertain, and the accumulation of a cascade of events, each with an uncertain probability, can result in substantial error. Results at the screening stage (for example, a positive FOBT) lead to diagnostic testing, which may in turn lead to surveillance. These complex events occur at various times, often over decades.

To describe the clinical consequences of the alternative screening strategies more comprehensively, the panel commissioned a study to model the effects of each strategy for average-risk people beginning screening at age 50 and continuing in the same strategy until age 85 or death. The model included not only the screening test but also the diagnostic and surveillance testing induced by the screening test. The assumptions in this model for testing, probabilities of results, and additional information about the model are summarized in Appendix 2. The model estimates are based on patients who accept and follow through with a screening option.

Table 7 summarizes the main consequences of the screening strategies based on the model. All of the screening strategies are more effective in saving lives than no screening. Individual strategies vary in the number of cancers prevented, tests undertaken, and risk. All strategies result in many false positive tests. All strategies include colonoscopy, to a greater or lesser extent, and much of the risk of all screening strategies is related to colonoscopy. Although this risk is relatively small for each procedure, it accumulates for a population, as some members undergo screening and diagnostic and surveillance testing repeatedly.

The risks and benefits of screening take place over many years, with the risks generally preceding the benefits. Events later in the life cycle may be of less value to the individuals involved because future events are discounted and because there are fewer years of life to be lost. The counts of CRC deaths avoided that are presented in Table 7 do not take this into account.

Modeling highlights the uncertainty surrounding the probabilities but can also yield insights into how much imprecision in estimates affects the results. For example, when the sensitivity of DCBE was varied over the range of plausible values, net gain in life-years was lower at lower sensitivities but the effectiveness of DCBE remained comparable to other strategies.

The results presented in Table 7 need to be interpreted with caution. It should be kept in mind that this is a computer simulation; data from actual clinical or epidemiological studies are much stronger evidence. Further, all figures presented are *estimates,* i.e., they are based on a simulation of a population in which randomness plays a part. For example, annual FOBT is presented as saving 12,325 life-years, *plus or minus 523.* One might think that annual FOBT performs better than FOBT plus flexible sigmoidoscopy every 5 years, based on a comparison of life-years saved, 12,325 vs. 11,760. However, if the confidence intervals around the life-years saved (approximately 500) are examined, it will be seen that the value for FOBT might be as low as 11,802 (12,325 − 523) or as high as 12,848 (12,325 + 523). Similarly, FOBT plus flexible sigmoidoscopy may range from 11,248 to 12,272. Because the ranges overlap—the low value for FOBT is 11,802 and the high value for FOBT plus flexible sigmoidoscopy is 12,272–one cannot say that FOBT performs "better" than FOBT plus flexible sigmoidoscopy in terms of life-years saved. Confidence intervals for all values are provided in Table A2 in Appendix 2.

The row labeled "cancer deaths prevented" in Table A2 needs to be considered in light of the fact that polypectomy prevents cancers from developing. Therefore, the more adenomatous polyps are removed, the fewer cancers (and cancer deaths) will occur. This is especially clear from reading across the row marked "cancer cases." Screening strategies that result in fewer adenomatous polyps being removed also result in a greater number of cancer cases.

Finally, the number of complication deaths associated with a screening strategy will affect the number of life-years saved.

Table 7. Clinical Consequences of 100,000 People Entering a Program of Screening for CRC at Age 50 Years and Remaining in it Until Age 85 or Death

Screening strategy	Annual FOBT	Sigmoidoscopy every 5 yr	FOBT + sigmoidoscopy every 5 yr	Ba enema every 5 yr	Ba enema every 10 yr	Ba enema + sigmoidoscopy every 5 yr	Colonoscopy every 10 yr
Screening tests	2,703,041	569,816	FOBT 2,704,501 Sigmoid 424,301	566,162	320,579	Ba Enema 568,223 Sigmoid 568,230	327,913
Consequences							
False positive screening tests	215,830	3897	218,964	26,346	13,857	30,985	1442
Diagnostic evaluations	226,295	14,996	231,627	73,711	52,963	74,214	N/A
Cancer cases	2610	3013	1901	1604	2176	1113	1418
Cancers detected	2422	568	1758	1285	1501	916	1095
Cancer deaths prevented	1330	967	1609	1663	1442	1889	1763
Complication deaths	52	9	58	34	24	46	73
Perforations	304	20	312	97	69	100	445
Major bleeding episodes	741	49	757	248	178	243	1075
Minor complications	767	49	772	259	181	249	1101
Years of life saved by screening	12,325	8328	11,760	12,568	11,035	14,655	12,904
(95% CI)	(± 523)	(± 500)	(± 512)	(± 506)	(± 526)	(± 526)	(± 522)

NOTE. The number of cancers detected varies because polyp removal reduces the incidence of CRC, therefore, the more frequently polyps are removed, the fewer cases of CRC occur to be detected. With no screening, the number of cancer cases expected is 4988 and the number of cancer deaths is 2391.

Comparing a screening strategy of barium enema every 5 years with a strategy of colonoscopy every 10 years, one can see that the number of life-years saved is approximately equivalent. However, more cancer cases occur in the 5-year barium enema strategy than in the 10-year colonoscopy strategy (1604 vs. 1418). At the same time, complication deaths are nearly twice as high in the colonoscopy strategy, which reduces the expected number of life-years saved.

Sensitivity analysis (varying the underlying parameters) of the results reveals that years of life saved by screening can vary by as much as 3000, although life-years saved are always greater than zero. Therefore, the totality of the evidence must always be considered in determining which screening strategy to use.

Table 8. Major Complication Rates of Screening Tests

Screening test	Complication rate (perforation and hemorrhage)	Death
Barium enema	1/10,000	1/50,000
Sigmoidoscopy	1–2/10,000	<1/10,000
Diagnostic colonoscopy	1–3/1,000	1–3/10,000

NOTE. Major complications with colonoscopy are more frequent if polypectomy is performed. Note that the decision analysis used more conservative, i.e., worst case, estimates of complication rates.

Patients may have a special interest in complications, particularly those that could result in an earlier death. Therefore, lives lost by screening may be weighed more heavily than lives saved. Table 8 summarizes the complication rates of the major procedures involved in CRC screening, sigmoidoscopy, colonoscopy and barium enema.

No screening program can be evaluated solely on the basis of any one statistic. Individual patients will be interested in the number of life-years they could expect to save through screening and, as noted, complications from screening. However, they also will want to know about their probability of developing CRC, the number of tests they will need to undergo, the likelihood of false positive and false negative results and, possibly, the cost of the screening procedures. In addition, if the clinicians in a patient's locale have abilities that vary from those assumed in this analysis, the results of screening will differ.

Cost-effectiveness of Screening People at Average Risk

Cost of Screening

The cost of a screening program reflects the diagnostic and surveillance tests generated by positive screening tests as well as the cost of the screening tests per se. Nevertheless, the screening test is the initiating event, and the cost that must be borne in the short run.

Current charges for the various screening tests for CRC vary greatly and should be interpreted with caution. Their actual cost may involve a complex set of variables, some of which are difficult to measure accurately. For example, the total true cost of a colonoscopy involves physician and nursing compensation, direct and indirect costs of the endoscopy facility and equipment, intravenous sets, drugs, biopsies, administrative expenses, etc. In addition, there is only an indirect relationship between cost of a procedure and its charge in many health care systems. The actual out of pocket expense to the patient for a screening test also varies greatly. In summary, generalizations about screening costs are difficult to make. However, charges probably affect CRC screening rates and participation.

Cost-effectiveness Analysis

Several models of CRC screening cost-effectiveness have been published.[206,207] The most recent and comprehensive study was performed by the Office of Technology Assessment (OTA) of the United States Congress.[15] OTA examined the cost-effectiveness of four screening strategies (FOBT, flexible sigmoidoscopy, DCBE and colonoscopy), individually and in combination, starting at age 50 and stopping at age 85 years. The analysis took into account the years of life lost because of the detection and treatment of cancers that would otherwise have remained harmlessly silent. It did not consider the effect of imperfect compliance with the screening, diagnostic, and surveillance schedules. The analysis was based on various assumptions regarding the sensitivity and specificity of the screening tests, the complication rates, the cost of the procedures and of treating detected cancers, and the length of time that polyps spend in the precancerous phase. These assumptions are shown in Appendix 1.

The main results of the analysis are summarized in Figure 16. The analysis reached several conclusions. First, screening for CRC in average-risk people is within the range of cost-effectiveness commonly accepted for other screening tests and many therapeutic interventions. All strategies cost <$20,000 per year of life saved and are within an acceptable range of cost-effectiveness by U.S. health standards. No strategy is ruled out on the basis of cost-effectiveness alone. Second, screening would represent a large life time investment, costing from $250 to 1200 per person entered into the program at 50 years of age. Third, the returns on this investment are high in terms of years of life saved. Fourth, there is not firm ground for choosing among the various tests on the basis of cost-effectiveness alone. The investigators acknowledged that the analysis was heavily dependent on estimates of dwell time, which were uncertain, and that it did not take into account all elements of the decision including acceptability, how costs are paid for, and the numbers and competency of the health professionals needed to accomplish the screening.

As shown in Figure 16, screening sigmoidoscopy alone (at any interval) is less effective than the other screening strategies. The cost-effectiveness of the other strategies for most screening intervals is comparable. For several strategies, there is a steep increase in cost, with only small increases in effectiveness, with shorter intervals between screening examinations.

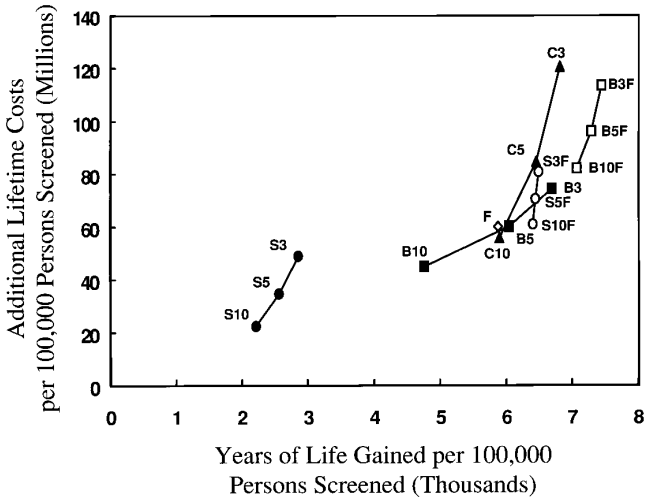

Figure 16. Effects and costs of CRC screening. S, sigmoidoscopy; B, DCBE; C, colonoscopy; F, annual FOBT. The number next to the letter indicated screening interval in years. (Data from Wagner et al.[15]) For example, S5F is sigmoidoscopy every 5 years combined with annual FOBT.

Implementing the Guidelines

Encouraging Patients' Participation

Informing patients. Ensuring that patients are fully informed about screening is an essential part of the screening strategy. Studies show a low level of awareness about the risk of CRC and its symptoms among adults in the United States.[20,208] They also indicate that patients who understand the nature of the disease are more likely to feel that they may be at risk, perceive fewer barriers to testing, and are more likely to participate in screening.[20,95] Good communication between patients and their health care providers and effective use of educational materials can greatly enhance patients' participation and satisfaction.[139,140,209,210] Health care providers should ensure that patients are aware of their risk of CRC and that they understand the importance of family history, age, and predisposing conditions. They should explain the importance of detecting cancer early, when death and morbidity can be prevented or reduced, and the possibility of preventing cancer from developing by detecting and removing precancerous polyps. (Potential primary prevention measures such as diet should also be explained.)

Deciding on a test and preparing the patient. Having several options for screening and follow-up allows the health care provider and the patient to consider which test is most appropriate and acceptable. Patients differ in the extent to which they want to be involved in clinical decisions. Health care providers should be prepared to give details of the advantages and disadvantages of the different screening strategies and to describe what is involved in terms of preparation, the

procedure itself, and follow-up of positive results. Patients should also be told the risks associated with different screening and follow-up investigations.

When a plan for screening has been decided, the clinician should explain what is involved, either in person or by providing patient education materials. The information should include how the patient needs to prepare for the test; what side effects, if any, can be expected from the preparation; a description of the test itself, including appropriate warnings about any discomfort during the procedure and afterwards; information on how and when he or she will be told the results; an explanation of the need for follow-up in some cases; and information about out of pocket cost to the patient.

Needs of special populations. When working with ethnically or culturally diverse populations, sensitivity to differences in cultural values, traditions, and beliefs will enhance participation in and adherence to screening recommendations. A complete discussion of the impact of cultural traditions on screening is beyond the scope of this guideline; however, some general recommendations and caveats can be offered. Additional information can be found in several publications.[211–213]

At least four aspects of the screening experience should attend to cultural relevance and sensitivity: risk assessment, education and counseling, the examination experience, and access to care. During risk assessment, providers should attend to issues of verbal and nonverbal interpersonal communications. Cultures emphasizing social harmony are less likely to be frank, question authority, or ask for clarification. For certain traditional Native Americans, discussions about family members are taboo. Some traditional Asian patients will be reluctant to discuss rectal bleeding, considering it "dirty." Tailored educational messages enhance the potential that a message will be attended to. Materials should transmit information via culturally familiar mediums (e.g., story telling fotonovellas, television), picture individuals of the targeted culture, be linguistically and reading level appropriate, and respect traditional taboos.

Intimate screening examinations and tests should attend to modesty and traditional beliefs. During the procedure, providers (preferably of the same gender as the patient if that is a concern to the patient) should minimize exposure of the patient's genitals, maintain the patient's sense of dignity, minimize embarrassment, prevent chilling (considered a source of illness in some cultures), and be aware of beliefs and values about sexuality and intimacy. Some patients may find rectal examinations embarrassing and insulting and, therefore, will avoid them. Home stool collection may require creative thought in cases in which patients lack adequate sanitation facilities (e.g., migrant camps, reservations, rural homes). In such situations, patients may never see their stool to be able to describe it correctly.

Finally, access to care issues should be considered for all special populations. Providers should explore options for evening and weekend appointments, outreach activities in medically underserved neighborhoods, and collaborative ventures with respected and frequented community organizations such as churches, senior citizen centers, and free clinics.

Referrals, communication, follow-up, and documentation. For several of the recommended procedures, the primary health care provider or the patient may choose a clinician with documented specialization in a technique. Primary care providers should set up a system for timely appointments and for communicating with the specialists involved. Similarly, the specialist must promptly provide the patient's primary care physician with test results and recommendations.

Timely, reliable, and accurate communication of test results is vital to minimize patients' anxiety and ensure their participation in subsequent screening. Effective communication is especially important when the test indicates the need for follow-up investigation. Patients have substantial anxiety when they have to return for additional tests or be referred to a specialist.

In view of the various, and for some screening strategies long, intervals between procedures, tracking and reminder systems and flow sheets, chart stickers, comprehensive implementation programs, and clinician education initiatives are advised wherever possible. These increase patients' participation as well as improve documentation by health care providers.[214,215]

Strategic Considerations

Considering the direct and indirect evidence in support of CRC and surveillance, the panel believes that widespread adoption of the recommendations in this guideline could yield major reductions in the mortality from CRC, saving up to 30,000 lives per year. Achieving such widespread adoption will require a substantial commitment on the part of clinicians, professional organizations, insurers, and those responsible for the organization and management of health care systems.

A workforce to carry out screening programs must be present. This could require expanded training of primary care physicians and paramedical personnel to perform flexible sigmoidoscopy. The current supply of clinicians with rigorous training and expertise in performing colonoscopies and barium enemas (mainly gastroenterologists, colorectal surgeons, and radiologists) may be sufficient to cover the additional load from screening and diagnostic investigation. However, this will need to be formally assessed. Because recommendations are presented as options and the various modalities of screening can be performed by different kinds of clinicians, the impact of these recommendations will not fall on any one segment of the clinical workforce. Programs to train clinicians in the performance of the screening procedures and ensure competence and quality must be evaluated.

This effort will undoubtedly increase the current cost of CRC screening for the country as a whole. However, gains from these expenditures are expected to occur for many years afterwards. CRC screening is probably cost-effective relative to other medical services now considered usual care. However, because of the present mechanisms for financing medical care, with concern for current dollar costs over long-term benefits,

health care managers and payers have insufficient incentives to initiate CRC screening programs. An incentive for health care systems to include programs for CRC screening may be patient demand once the public becomes informed that there is evidence of their effectiveness. Presumably, if CRC screening prevents advanced-stage cancer, costs to health care payers will be decreased and, ultimately, market forces will favor screening.

The Need for Additional Research

Conclusive answers to many important questions regarding CRC do not currently exist. The following are some of the questions that require further research.

- How long does it take for adenomatous polyps to arise de novo and progress to cancer, in both average- and high-risk people? The frequency of screening and surveillance tests and the cost-effectiveness of various screening strategies depend heavily on estimates of these transition times. The difficulty of obtaining this information is obvious: adenomatous polyps are removed when found, destroying the opportunity to observe their natural history directly. More imaginative and credible ways of estimating and characterizing polyp dwell times are needed.
- How do screening and subsequent diagnostic procedures and treatment affect quality of life? Randomized trials now underway offer an excellent opportunity to study how screening affects morbidity, functional status, and the affective response to screening and its sequelae.
- How effective is flexible sigmoidoscopy? Evidence is needed on the performance of flexible sigmoidoscope screening, ideally by randomized controlled trials, but if not feasible, by well conducted observational studies, in different settings with different methods.
- What is the risk of CRC in people in whom small adenomatous polyps are found on sigmoidoscopy or when a small adenomatous polyp is the sole finding on colonoscopy?
- Do screening colonoscopy or DCBE in average-risk people improve health outcomes such as CRC incidence and mortality? Because these strategies are potentially so effective (especially colonoscopy) or cost-effective (especially barium enema), there is an urgent need for better evidence on their effects from prospective controlled trials. In particular, radiologists and endoscopists have an important responsibility to collaborate in providing sound evidence for future clinical policy.
- What is the sensitivity of DCBE? The performance of DCBE in screening for CRC and adenomatous polyps, relative to a credible gold standard for the presence or absence of lesions, has yet to be established.
- How can individual risk be more precisely characterized? The feasibility and cost-effectiveness of screening and follow-up depend heavily on tailoring the strategy to the patient's risk, taking into account age, screening history, family history and genetic make-up, and patient preferences. Studies of risk have shown large differences according to easily elicited characteristics of patients. These studies need to be extended to allow more precise estimates of individual risk.
- How do different screening protocols each affect CRC incidence and mortality in people with a family history of the disease?
- Does screening in inflammatory bowel disease change the outcome of disease?
- What is the prevalence of the genetic high-risk syndromes, especially HNPCC, in the general population and what are the benefits of genetic screening and their effects on family members?
- How can competence in screening procedures be improved? Our recommendations are contingent on competent performance of screening. It is known that some tests require considerable skill to be performed correctly and that proficiency varies among clinicians. More effort and imagination must be invested in training clinicians in screening techniques and in studying and assuring their technical competence.
- What is the optimal interval between screening tests for each test method? Current recommendations for screening intervals are based almost entirely on indirect evidence.
- Can better screening tests be developed? None of the present strategies for screening is ideal in terms of cost, safety, patient discomfort and acceptability, sensitivity and specificity, and availability. New screening and surveillance tests need to be developed and their performance and effectiveness studied.
- Can findings from research in the molecular biology of colorectal pathogenesis be translated into clinically useful tests and interventions and these tests and interventions in turn be subjected to strong clinical evaluation of performance and effectiveness?
- How do patients' understanding of CRC, risk factors, available screening options for prevention, and their personal preferences affect participation in CRC screening?
- What educational interventions are most effective in raising public, patient, and clinician awareness of the magnitude of the risk of CRC, its natural history, the significance of adenomatous polyps, familial risk factors, and the available interventions for screening, diagnosis, and treatment?
- What are the most effective strategies that health care professionals can employ to increase screening rates among various populations?

Appendix 1: Summary of Assumptions Used in OTA Study

Parameter	Base case value	Range
Sensitivity/specificit of screening and diagnosis		
Sensitivity of FOBT for polyps	10%	
Sensitivity of FOBT for cancer	40%	40%–85%
Sensitivity of colonoscopy for polyps/cancer	90%	
Sensitivity of DCBE for polyps/cancer	70%	60%–80%
Sensitivity of FSIG for polyps/cancer	90%	85%–95%
Reach of FSIG	50%	35–70%
Specificit of FOBT	90%	90%–98%
Specificit of colonoscopy	100%	
Specificit of FSIG	98%	
Specificit of DCBE	98%	
Natural history of polyp/cancer sequence		
Prevalence of polyps at age 50 yr	30%	
Annual polyp incidence rate	Age specific 50–65 yr, 1.33%/yr 66–70 yr, 2%/yr 70+ yr, 1%/ yr	
Percent of cancers originating as polyps	70%	56%–90%
Annual cancer incidence with no screening	Age-specifi	
% of cancers detected in early stages with no screening	40%	
Dwelling time of cancer in early stages	2 yr	
% of total dwelling time in early stages before clinical detection (0%–100%)	100%	
Dwelling time of cancer in late stages	2 yr	
5-yr all-cause survival for early cancer	Age-specifi	
5-yr all-cause survival for late cancer	Age-specifi	
For polyps destined to be clinically detected as cancers in absence of screening:		
Precancerous polyp dwelling time detectable as FSIG, DCBE, and colonoscopy	5 yr	1–20 yr
Precancerous polyp dwelling time detectable by FOBT	5 yr	1–20 yr
Complications and unintended consequences		
Rate of perforation of colon colonoscopy	0.1%	
Death rate from perforated colon	0.02%	
Surgical mortality rate from colonic resection	4%	
Prevalence of lifetime-latent cancers at age 50	0.02%	
Annual incidence of lifetime-latent cancers	Age specific 50–65 yr, 0.02% 65–85 yr, 0.05%	
Rate of perforation from DCBE and FSIG	0	
Costs		
Unit cost of screening FOBT	$10	
Unit cost of screening flexibl sigmoidoscopy	$80	+100%
Unit cost of screening DCBE	$131	+100%
Unit cost of screening colonoscopy	$285	+100%
Unit cost of diagnostic colonoscopy	$285	+100%
Unit cost of diagnostic colonoscopy with polypectomy	$434	+100%
Unit cost of surveillance colonoscopy	$285	+100%
Unit cost of tissue pathology for polyps and lesions	$64	+100%
Lifetime cost of treating early cancer	$35,000	
Lifetime cost of treating late cancer	$45,000	
Lifetime cost of treating perforated colon	$35,000	
Discount rate	5%/yr	

FSIG, flexibl sigmoidoscopy.

Appendix 2: Decision Analysis of the Clinical Consequences of Screening

This appendix provides additional information on the decision analysis requested by the panel to develop quantitative estimates of the clinical consequences of various screening strategies in average-risk populations. The analysis estimated the likely consequences for an individual or physician considering various screening methodologies. Results of interest included the number of CRC cases detected and missed, false negative and false positive test results, CRC deaths, CRC deaths prevented by screening, and years of life saved by screening.

Table A1 in this appendix shows the input values used for the analysis, including "base case" or best estimates of values for sensitivity, specificity, complications, mortality, etc. These values are within the ranges indicated in the guideline and are also consistent with all values used in the OTA analysis cited in this guideline.[15] Table A2 shows results for the base case under the following assumptions:

- CRC rates and cancer deaths are expected to occur as indicated in Surveillance, Epidemiology, and End Results (SEER) Program incidence and mortality data published in 1994.
- Other deaths are based on the U.S. life table for the total population, 1992 (Monthly Vital Statistics Report 43(6), 3/22/95.
- The initial population in any screening methodology is 100,000.
- Patients in the screening/surveillance programs are expected to have two thirds of the CRC mortality rate of the unscreened population (given CRC), given that the cancer is *found* in the program.

Screening methodologies are as follows:

- FOBT screening annually, with any positive result being followed up by a colonoscopy. A positive colonoscopy (for either CRC or a large polyp) results in the individual patient transferring to the surveillance program.
- Flexible sigmoidoscopy screening with a 60-cm instrument every 5 years, with any positive result (CRC, large polyp, or adenomatous small polyp) being followed up by a colonoscopy. Although this guideline recommends that patients decide with their physician whether to have colonoscopy or no further diagnostic tests if only a small (<1 cm) single tubular adenoma is found, patients were modeled as all having a follow-up colonoscopy. A positive colonoscopy (for either CRC or a large polyp) results in the individual patient transferring to the surveillance program.
- FOBT annually plus sigmoidoscopy every 5 years. Any positive results for FOBT is followed up with colonoscopy; negative results are followed up with flexible sigmoidoscopy every fifth year. A positive result on flexible sigmoidoscopy (CRC, large polyp, or small adenomatous polyp) is also followed up with colonoscopy. As with flexible sigmoidoscopy alone, patients were assumed to decide on follow-up colonoscopy for a single small (<1 cm) tubular adenoma. Positive colonoscopy results (either CRC or a large polyp) result in the patient becoming part of the surveillance program.

Table A1. Simulation Parameters

	Used (%)	Range (%)
Complication rates		
Colonoscopy complication rate	0.85	0.85 – 0.85
Colonoscopy perforation rate given complication	15.87	3.41 – 15.87
Colonoscopy mortality rate given complication	2.78	0.29 – 2.78
Minor colonoscopy complications given complication	40.48	40.48 – 40.48
Major bleeding episodes given colonoscopy complication	39.68	39.68 – 39.68
Barium enema complication rate	0.03	0.03 – 0.03
Mortality rate given barium enema complication	10.00	5.00 – 25.00
Flexible sigmoidoscopy complication rate	0.03	0.03 – 0.03
Flexible sigmoidoscopy mortality rate given complication	2.78	0.29 – 2.78
Sensitivity/specificit estimates		
FOBT sensitivity for cancer	60.00	40.00 – 80.00
FOBT specificit for cancer	92.00	90.00 – 94.00
Flexible sigmoidoscopy reach	50.00	50.00 – 60.00
Flexible sigmoidoscopy sensitivity		
Cancer	96.70	88.00 – 98.00
Large polyps	96.70	88.00 – 98.00
Small polyps	73.30	73.30 – 88.00
Flexible sigmoidoscopy specificit		
Cancer	94.00	92.00 – 96.00
Large polyps	94.00	92.00 – 94.00
Small polyps	92.00	92.00 – 92.00
DCBE sensitivity		
Cancer	84.00	78.00 – 90.00
Large polyps	82.00	73.00 – 91.00
Small polyps	67.00	52.00 – 82.00
DCBE specificit		
Cancer	97.50	97.50 – 99.80
Large polyps	83.30	69.70 – 91.80
Small polyps	75.00	60.00 – 83.30
Colonoscopy sensitivity		
Cancer	96.70	90.00 – 96.70
Large polyps	85.00	85.00 – 90.00
Small polyps	78.50	73.00 – 84.00
Colonoscopy specificit		
Cancer	98.00	96.00 – 100.00
Large polyps	98.00	96.00 – 98.00
Small polyps	98.00	96.00 – 98.00
Biopsy sensitivity for adenoma	98.00	98.00 – 98.00
Biopsy specificit for adenoma	100.00	100.00 – 100.00
Underlying distribution parameters		
Large polyps as a percentage of all polyps	10.00	10.00 – 10.00
Adenomatous polyps as a percentage of polyps	50.00	20.00 – 50.00

Table A2. Results for Base Case

	No screening		Annual FOBT		FS, 5-yr interval		Annual FOBT + FS, 5-yr interval		BE, 5-yr interval		BE, 10-yr interval		Sigmoidoscopy + BE, 5-yr interval		Sigmoidoscopy + BE, 10-yr interval		Colonoscopy, 10-yr interval	
	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI	Estimated mean	95% CI
Cancers	4988	12.79	2610	9.47	3013	10.63	1901	9.00	1604	7.77	2176	10.40	1113	6.47	1875	12.37	1418	7.68
Cancer patients	4902	12.34	2599	9.36	2985	10.21	1893	9.01	1596	7.71	2168	10.33	1110	6.39	1866	12.22	1414	7.60
Cancer deaths	2391	9.51	1061	5.41	1424	6.33	782	5.36	728	5.95	949	6.79	502	4.21	827	7.68	628	4.76
Other deaths	61,733	31.23	62,115	29.97	62,076	28.37	62,416	29.85	62,429	27.88	62,354	29.92	62,462	30.40	62,443	36.60	62,452	28.48
Colonoscopy complication deaths	0	0.00	52	1.36	3	0.36	53	1.39	16	0.68	12	0.72	18	0.86	13	1.02	73	1.47
Colonoscopy perforations	0	0.00	304	3.32	20	0.92	312	4.04	97	1.96	69	1.56	100	2.12	74	2.41	445	3.71
Major bleeding episodes	0	0.00	741	5.86	49	1.51	757	5.80	248	3.30	178	2.49	243	2.89	174	3.14	1075	6.34
Minor complications	0	0.00	767	5.44	49	1.48	772	5.98	259	3.44	181	2.51	249	3.32	181	3.57	1101	5.58
Colonoscopies	0	0.00	226,295	103.11	14,996	34.56	231,627	99.41	73,711	59.71	52,963	56.23	74,214	58.90	54,598	70.67	327,913	61.29
Cancers found	0	0.00	2422	9.25	568	4.82	1758	8.84	1285	7.47	1501	7.94	916	5.85	1347	10.87	1095	6.03
False positives, cancer	0	0.00	120	1.93	9	0.63	126	2.44	43	1.10	35	1.35	47	1.31	36	1.62	159	2.46
False positives large polyp	0	0.00	119	2.11	6	0.49	120	2.02	40	1.09	31	1.13	43	1.25	31	1.38	142	2.52
False positives, small polyp	0	0.00	731	5.84	22	0.93	756	5.65	161	2.66	103	1.91	161	2.21	105	2.86	1140	7.19
Polyps	47,226	40.93	47,513	43.13	47,452	44.55	47,636	47.12	47,594	39.17	47,648	41.39	47,501	45.43	47,494	57.96	47,575	44.91
Large polyps	4993	13.17	3181	10.86	3543	11.61	2654	9.07	2757	9.95	3021	10.92	2091	8.97	2799	13.95	2442	10.02
Small polyps removed	0	0.00	23,731	33.95	9262	21.83	26,515	36.28	31,772	33.05	26,475	32.66	33,227	38.89	27,625	48.32	32,650	37.41
Large polyps removed	0	0.00	1562	7.72	947	5.92	1562	7.39	2028	8.43	1901	8.63	1604	8.04	1878	11.30	1779	7.89
Large adenomas removed	0	0.00	1562	7.72	947	5.92	1562	7.39	2028	8.43	1901	8.63	1604	8.04	1878	11.30	1779	7.89
Small adenomas removed	0	0.00	10,412	19.75	8000	17.98	13,032	25.24	17,800	24.76	11,762	20.62	15,808	24.26	12,852	32.98	14,881	24.01
FOBT false positives	0	0.00	215,830	100.39	0	0.00	216,144	100.07	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
FOBT true positives	0	0.00	2482	9.61	0	0.00	1717	9.10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
FOBT false negatives	0	0.00	1653	11.88	0	0.00	1129	9.30	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
FOBT true negatives	0	0.00	2,483,077	490.20	0	0.00	2,485,511	513.45	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
FOBTs performed	0	0.00	2,703,041	537.05	0	0.00	2,704,501	539.42	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
FS complication deaths	0	0.00	0	0.00	6	0.54	5	0.37	0	0.00	0	0.00	8	0.49	3	0.45	0	0.00
FS false positives	0	0.00	0	0.00	405	4.46	258	3.38	0	0.00	0	0.00	400	3.96	230	3.87	0	0.00
FS true positives	0	0.00	0	0.00	496	4.55	88	1.88	0	0.00	0	0.00	387	3.87	592	7.55	0	0.00
FS false negatives	0	0.00	0	0.00	3691	20.28	162	2.74	0	0.00	0	0.00	581	5.48	821	7.77	0	0.00
FS true negatives	0	0.00	0	0.00	565,243	92.67	423,788	142.39	0	0.00	0	0.00	566,856	103.92	319,098	88.17	0	0.00
FS false positives large polyp	0	0.00	0	0.00	437	3.81	303	3.39	0	0.00	0	0.00	434	4.51	243	3.97	0	0.00
FS false positives, small polyp	0	0.00	0	0.00	3056	10.18	2260	8.90	0	0.00	0	0.00	3465	12.34	1797	12.95	0	0.00
FSs performed	0	0.00	0	0.00	569,816	89.48	424,301	141.88	0	0.00	0	0.00	568,230	102.57	320,742	86.32	0	0.00
BE complication deaths	0	0.00	0	0.00	0	0.00	0	0.00	18	0.80	12	0.59	21	0.98	12	0.97	0	0.00
BE false positives	0	0.00	0	0.00	0	0.00	0	0.00	276	3.43	161	2.65	300	3.15	165	3.22	0	0.00
BE true positives	0	0.00	0	0.00	0	0.00	0	0.00	1153	7.16	1352	7.36	815	5.34	1180	9.68	0	0.00
BE false negatives	0	0.00	0	0.00	0	0.00	0	0.00	229	3.15	251	3.21	152	2.38	231	4.24	0	0.00
BE true negatives	0	0.00	0	0.00	0	0.00	0	0.00	564,487	89.96	318,803	56.25	566,935	104.16	319,151	88.37	0	0.00
BE false positives, large polyp	0	0.00	0	0.00	0	0.00	0	0.00	2189	8.77	1247	7.17	2234	9.22	1251	10.61	0	0.00
BE false positives, small polyp	0	0.00	0	0.00	0	0.00	0	0.00	23,881	29.35	12,449	20.05	24,152	32.46	12,475	29.69	0	0.00
BEs performed	0	0.00	0	0.00	0	0.00	0	0.00	566,162	89.37	320,579	56.20	568,223	102.55	320,739	86.39	0	0.00
Life-years	2,673,591	638.56	2,685,916	552.77	2,681,920	493.08	2,685,351	524.53	2,686,160	507.80	2,684,627	558.58	2,688,247	559.40	2,685,603	841.16	2,686,495	549.26
Total complication deaths	0	0.00	52	1.36	9	0.63	58	1.43	34	0.96	24	0.93	46	1.43	27	1.59	73	1.47
Total deaths	64,124	30.23	63,227	29.11	63,509	27.89	63,256	30.17	63,190	28.08	63,327	28.43	63,011	30.41	63,297	37.54	63,153	28.92
Cancers "prevented"			2378	9.86	1976	10.30	3087	9.69	3384	9.27	2812	10.22	3875	8.88	3113	11.03	3570	9.25
Cancer deaths prevented			1330	6.78	967	7.08	1609	6.77	1663	6.96	1442	7.24	1889	6.45	1564	10.71	1763	6.59
			55.64%		40.45%		67.29%		69.55%		60.31%		79.01%		65.41%		73.74%	
Life-years saved			12,325	523.47	8328	500.04	11.760	512.19	12.568	505.67	11,035	525.84	14,656	526.17	12,012	925.69	12,904	522.05
Years per life saved			9.26		8.61		7.31		7.56		7.65		7.76		7.68		7.32	
Net deaths prevented			897	26.01	615	25.49	868	26.47	934	25.58	797	25.72	1114	26.58	827	29.88	971	25.93
Maximum	Deaths	yr/life	1,337	9.71	974	9.19	1616	7.66	1670	7.89	1449	8.06	1896	8.06	1575	8.33	1770	7.64
Minimum	Deaths	yr/life	1324	8.83	960	8.03	1602	6.96	1656	7.22	1435	7.25	1883	7.45	1553	7.04	1757	7.00
Maximum	Life-years		12,848		8828		12,272		13,074		11,561		15,182		12,937		13,426	
Minimum	Life-years		11,802		7828		11,248		12,063		10,509		14,130		11,086		12,382	
Cancer cases	4988		2610		3013		1901		1604		2176		1113		1875		1418	
Cancers detected			2422		568		1758		1285		1501		916		1347		1095	
Percent			92.79%		18.84%		92.46%		80.11%		68.98%		82.30%		71.85%		77.24%	
Cancers missed			188		2445		143		319		675		197		528		323	
Percent			7.21%		81.16%		7.54%		19.89%		31.02%		17.70%		28.15%		22.76%	
False positive tests			216,800		3935		219,966		26,590		14,025		31,237		16,332		1442	
Screening tests			215,830		3898		218,964		26,346		13,857		30,985		16,161		0	
Colonoscopies			970		37		1002		244		168		252		171		1442	
Life-years, no cancer death	2,695,439																	
Life-years lost to cancer	21,848																	

BE, barium enema; FS, flexibl sigmoidoscopy.

- Colonoscopy every 10 years, with any positive result (CRC or large polyp) transferring the patient to the surveillance program.
- DCBE every 5 years, with any positive result (CRC or large polyp) being followed up with colonoscopy. A positive colonoscopy (CRC or large polyp) results in the patient being transferred to the surveillance program.
- DCBE every 10 years, with any positive result (CRC or large polyp) being followed up with colonoscopy. A positive colonoscopy (CRC or large polyp) results in the patient being transferred to the surveillance program.
- DCBE every 5 years, with flexible sigmoidoscopy. The patient is assumed to have both procedures and be followed up with a colonoscopy for a positive result on either one (CRC or large polyp for DCBE; large polyp, or adenomatous small polyp for flexible sigmoidoscopy). Again, a positive colonoscopy for CRC or a large polyp results in the patient leaving the screening program and entering the surveillance program.

Under these assumptions and given the range of input variables used, all screening modalities seem to have some advantages and disadvantages. For the base case, lives saved range from about 40% of unscreened CRC deaths to nearly 80%. Interestingly, an increase in colonoscopy complication rates makes all different screening strategies less attractive, because positive results are followed up by colonoscopy for all strategies in similar numbers.

Differences in the number of CRCs found by a screening strategy are strongly affected by changes in incidence resulting from prevention of CRC by colonoscopic polypectomy. Each strategy results in a different probability of colonoscopy and therefore of CRC incidence following screening; CRC cases range from 1130 to 3010. Those strategies for which incidence is greatly reduced do not have the opportunity to detect a large number of colorectal cancers (e.g., FOBT plus flexible sigmoidoscopy is estimated to detect only 1758 cancers in the base case). In contrast, FOBT alone is estimated to detect 2422 colorectal cancer cases. However, the number of opportunities to detect colorectal cancer is limited by CRC incidence, which is affected by the screening strategy.

All screening strategies are expected to result in increases of between 8000 and 15,000 life-years per 100,000 population. Complication deaths are in the same range for many strategies, although the 5-year interval barium enema plus flexible sigmoidoscopy and screening colonoscopy resulted in the largest screening complication mortality rates. The maximum possible increase in life-years is approximately 23,600 because this is the estimated total number of life-years lost due to CRC in the 35-year span from age 50 to 85 in a cohort of 100,000 people. This number was estimated by running the simulation model with no screening but explicitly removing the possibility of cancer death while keeping death from other causes. The resulting number of life-years was compared with that of an unscreened population in which cancer death was allowed.

Results

The OTA's cost analysis resulted in 3000–7500 years of life gained (per 100,000 people screened), assuming a 10-year polyp dwell time. While the answers produced by this analysis are not comparable because no discounting is completed, the results of this analysis are within the same order of magnitude.

Flexible sigmoidoscopy alone as a screening procedure is the least desirable screening methodology in terms of life-years saved. In determining years of life saved, the analysis followed a cohort of 100,000 people from age 50 to age 85, using annual CRC incidence and mortality rates derived from SEER data as well as other mortality rates derived from the U.S. life tables. CRC mortality rates for the surveillance population were estimated at precisely two-thirds the mortality rate for the unscreened population, whereas CRC mortality was assumed to remain constant for those individuals whose CRC was not found by the screening program. For each year of the screening (and surveillance) program, the number of individuals remaining in the population at the end of the year was used as a proxy for life-years, and all years (from age 50–85) were added to obtain total life-years. This was contrasted with total life-years for an unscreened population, and the difference is the number of life-years gained by the screening methodology.

Of interest is the last line on each of the individual case result pages: years/life saved. This number divides total life-years gained by net lives saved to obtain the estimated increase in life-span for each individual with a prevented CRC death. Years per life saved ranges from a low of 7.3 to a high of 9.2, indicating that preventing a CRC death may increase an individual's life span by approximately 8 years.

The input variables which most strongly impact the results are the following: complication and mortality rates for colonoscopy; incidence of nonadenomatous polyps (which when detected, trigger a diagnostic follow-up), and sensitivity of screening procedures for large polyps. Results are also extremely sensitive to the underlying epidemiology, particularly with respect to the likelihood of small vs. large polyps to develop into carcinoma.

The adenoma to carcinoma sequence is modeled by a probabilistic sequence that is age dependent. At any age, an individual has a chance of developing a polyp, and any adenomatous polyp has the potential to transform into cancer. As noted in the text, the vast majority of polyps do not actually become cancerous, suggesting a relatively long dwell time.

All cancers were assumed to arise from adenomatous polyps via the adenoma-to-carcinoma sequence described in the text. The transformation from polyp to cancer was modeled as a γ distribution based on the age of the adenomatous polyp (since formation). The estimated mean value of 30.88 years was based on the criterion of matching actual incidence rates as closely as possible. Using the probabilistic model of polyp formation and this transformation function, a probability of CRC by age

was calculated. This model estimates that about 10% of all adenomas are expected to become cancerous within 10 years and 20% within 15 years.

In the base case results shown in Table A2, each strategy comprises two columns: the first is the estimated mean value for the strategy, and second is the 95% confidence interval.

A detailed description of the research with all results is available from Laura Miller, Ph.D., c/o American Gastroenterological Association, 7910 Woodmont Avenue, Bethesda, Maryland 20814.

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Glossary

(The terms are defined in terms of their relation to colorectal cancer screening.)

Acceptability: the extent to which clinicians and patients find a preventive intervention desirable and feasible.

Bias: a process at any stage of inference tending to produce results that depart systematically from the true values.

Case-control study: a study in which relative risk associated with a patient characteristic or relative protection from an intervention is estimated by comparing exposure to them in people with and without the outcome of interest (e.g., colorectal cancer death).

Cohort study: a study in which people who are and are not exposed to a potential risk factor or intervention are observed over time and outcomes (e.g., colorectal cancer incidence or deaths) are compared.

Compliance: the extent to which a patient follows medical advice or physicians follow recommendations for patient care. (Sometimes referred to as adherence.)

Compliance bias: systematic difference in the observed effectiveness of an intervention, relative to the true one, because people who seek out preventive care tend to have a better prognosis than those who do not.

Confidence interval: the range of values that is likely to include the true value if chance alone (and not bias) were responsible for variation in the results of a study.

Cost-effectiveness analysis: a quantitative analysis of the monetary costs of an intervention relative to the health effects, such as reducing mortality from colorectal cancer.

Diagnosis: classifying people who are suspect of having colorectal cancer or adenomatous polyps (because of a positive screening test) into those with and without these conditions.

Dwell time: the period of time for a benign polyp to evolve into cancer.

Effectiveness: the benefits of an intervention to a population under ordinary circumstances.

Efficacy: the effects of an intervention under ideal circumstances, as is common in clinical research.

False negative test: a test result that suggests a cancer or polyp is not present when it is.

False positive test: a test result that suggests a cancer or polyp is present when it is not.

Lead time bias: the tendency for survival to appear to be

lengthened by screening because the diagnosis was made earlier rather than because death was delayed.

Length time bias: systematic difference in the observed effectiveness of an intervention, relative to the true one, that can result because screening tends to preferentially detect slower growing neoplasms.

Metachronous: colorectal cancers arising at a later time than the index lesion.

Neoplasia: a term for both adenomatous polyps and colorectal cancers.

Performance: for purposes of this guideline, performance is a measure of how well a screening test distinguishes between people with and without colorectal neoplasia (commonly described by sensitivity and specificity).

Polyp: a mass protruding from the colorectal mucosa into the bowel lumen.

Predictive value: a *positive* predictive value is the probability that a positive test result represents the lesion sought (such as adenoma or cancer). A *negative* predictive value is the probability that a negative test result represents the absence of what is being sought (such as adenoma or cancer).

Randomized controlled trial: study of the effects of a preventive or therapeutic intervention that includes random assignment of the participants so as to minimize systematic differences between people who do and do not receive it, thereby obtaining an unbiased estimate of effect.

Risk factor: a characteristic that is associated with the development of an outcome of disease such as colorectal cancer incidence or death.

Screening: identification of people who are more likely to have colorectal cancer or adenomatous polyps from among people without symptoms of the disease.

Sensitivity: the proportion of all people with cancer (or an adenoma) that are detected by a screening or diagnostic test.

Specificity: the proportion of all people without cancers (or adenomas) that are correctly classified by a screening or diagnostic test.

Surveillance: monitoring people known to have colorectal disease.

Synchronous: a cancer present elsewhere in the bowel at the time a colorectal cancer is found.