

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale—Update Based on New Evidence

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We have updated guidelines for screening for colorectal cancer. The original guidelines were prepared by a panel convened by the U.S. Agency for Health Care Policy and Research and published in 1997 under the sponsorship of a consortium of gastroenterology societies. Since then, much has changed, both in the research literature and in the clinical context. The present report summarizes new developments in this field and suggests how they should change practice. As with the previous version, these guidelines offer screening options and encourage the physician and patient to decide together which is the best approach for them. The guidelines also take into account not only the effectiveness of screening but also the risks, inconvenience, and cost of the various approaches. These guidelines differ from those published in 1997 in several ways: we recommend against rehydrating fecal occult blood tests; the screening interval for double contrast barium enema has been shortened to 5 years; colonoscopy is the preferred test for the diagnostic investigation of patients with findings on screening and for screening patients with a family history of hereditary nonpolyposis colorectal cancer; recommendations for people with a family history of colorectal cancer make greater use of risk stratification; and guidelines for genetic testing are included. Guidelines for surveillance are also included. Follow-up of postpolypectomy patients relies now on colonoscopy, and the first follow-up examination has been lengthened from 3 to 5 years for low-risk patients. If this were adopted nationally, surveillance resources could be shifted to screening and diagnosis. Promising new screening tests (virtual colonoscopy and tests for altered DNA in stool) are in development but are not yet ready for use outside of research studies. Despite a consensus among expert groups on the effectiveness of screening for colorectal cancer, screening rates remain low. Improvement depends on changes in patients' attitudes, physicians' behaviors, insurance coverage, and the surveillance and reminder systems necessary to support screening programs.

Eight years ago, an expert panel was assembled by the U.S. Agency for Health Care Policy and Research to prepare clinical practice guidelines for colorectal cancer screening and accompanying rationale based on the best available evidence. The Panel was convened by a consortium of gastroenterology societies, all of which provided logistic support throughout and financial support during the latter part of the Panel's work.

The Panel's report, published in 1997,¹ highlighted a substantial body of research evidence favoring colorectal cancer screening, much of which had accumulated in the few years preceding the report. Guidelines subsequently published by the American Cancer Society and others^{2–5} consolidated a national consensus favoring colorectal cancer screening. Medicare began paying for colorectal cancer screening and other payers have followed. National programs to raise public awareness of colorectal cancer prevention have been initiated. Nevertheless, colorectal cancer screening rates in the United States population remain low.⁶

Recognizing that guidelines can become out of date, especially in rapidly evolving fields, the medical societies that sponsored the original guidelines decided that the 1997 guidelines should be reviewed and updated to take into account a substantial body of evidence published in the past 5 years (Table 1).

Abbreviations used in this paper: AAPC, attenuated adenomatous polyposis coli; APC, adenomatous polyposis coli; CT, computerized tomography; DCBE, double-contrast barium enema; FAP, familial adenomatous polyposis; FOBT, fecal occult blood test; HNPCC, hereditary nonpolyposis colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability.

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Table 1. Modifications From Prior GI Consortium Guidelines

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| <p>Screening</p> <ul style="list-style-type: none"> No rehydration when testing for FOBT. Use of colonoscopy and not barium enema for diagnostic evaluations. Shortened interval for DCBE screening to 5 years in average-risk people. More detailed recommendations for genetic testing in FAP and HNPCC. Reliance on colonoscopy for screening of people with close relatives who have colorectal cancer or adenomatous polyps at age ≤ 60 years or 2 affected close relatives. Reliance on colonoscopy for HNPCC screening. Detailed recommendations for genetic testing in FAP and HNPCC. <p>Surveillance</p> <ul style="list-style-type: none"> More use of risk stratification in deciding surveillance intervals after polypectomy; first follow-up colonoscopy in 5 years rather than 3 years for patients at low risk for new adenomas. Reliance on colonoscopy for postpolypectomy surveillance. Reliance on colonoscopy for follow-up surveillance in patients who have had a resection for colorectal cancer. |
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Process

The original GI Consortium Panel was comprised of experts in primary care, gastroenterology, surgery, oncology, epidemiology, behavioral science, clinical economics, and nursing, as well as a patient advocate. The panel responsible for the current guidelines was comprised of representatives from the original panel and of the U.S. Multisociety Task Force on Colorectal Cancer, a combined effort of the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, the American Gastroenterological Association, and the American College of Physicians/Society of Internal Medicine. This group was asked to review the original guidelines, prepare appropriate revisions with rationale, highlight new evidence since 1997, and suggest research questions—the answers to which seem critical to progress in colorectal cancer screening and surveillance. Societies with representatives on the panel included the American Academy of Family Practice, American College of Gastroenterology, American College of Physicians—American Society of Internal Medicine, American College of Radiology, American Gastroenterological Association, American Society of Colorectal Surgeons, and American Society for Gastrointestinal Endoscopy.

Appropriate members of the guidelines panel, based on their individual interests and expertise, were assigned 1 or more sections of the guidelines previously published by the GI Consortium. They conducted a literature search on the assigned topic and prepared evidence tables summarizing scientifically strong studies that were relevant to colorectal cancer screening and surveillance.

These tables, with associated citations, were circulated to the panel for comments. Then, a meeting was held at which the important new evidence was presented and critiqued. Following this, guidelines were drafted based on the meeting consensus, with an accompanying discussion of the rationale, new evidence (since close of evidence gathering for the earlier guidelines in 1996), and recommendations for future research. The document was then edited by the Panel Co-Chairs (S.J.W., R.H.F.) and the Task Force Chair (D.K.R.) and circulated to the members for comments. The final draft was then circulated to appropriate committees of the sponsoring organizations. The final draft was also reviewed and endorsed by the American Cancer Society.

The following recommendations are intended for the U.S. context. Other countries with similar rates of colorectal cancer, clinical practices, resources, and values might also find these guidelines appropriate for their setting.

General Recommendations

People with symptoms or signs that suggest the presence of colorectal cancer or polyps fall outside the domain of screening and should be offered an appropriate diagnostic evaluation (Table 2).

Screening programs should begin by classifying the individual patient’s level of risk based on personal, family, and medical history, which will determine the appropriate approach to screening in that person.

Men and women at average risk should be offered screening for colorectal cancer and adenomatous polyps beginning at age 50 years.

They should be offered options for screening, with information about the advantages and disadvantages associated with each approach, and should be given an opportunity to apply their own preferences in selecting how they should be screened.

If the result of a screening test is abnormal, physicians should recommend a complete structural examination of the colon and rectum by colonoscopy (or flexible sigmoidoscopy and double contrast barium enema if colonoscopy is not available).

Table 2. Key Elements in Screening Average-Risk People

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|--|
| <ul style="list-style-type: none"> Offer screening to men and women aged 50 years and older Stratify patients by risk Options should be offered Follow-up of positive screening test with diagnostic colonoscopy Appropriate and timely surgery for detected cancers Follow-up surveillance required after polypectomy and surgery Providers need to be proficient Encourage participation of patients |
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Surveillance with colonoscopy should be considered for patients who are at increased risk because they have been treated for colorectal cancer, have an adenomatous polyp diagnosed, or have a disease that predisposes them to colorectal cancer, such as inflammatory bowel disease.

Health care providers who perform the tests should have appropriate proficiency, and the tests should be performed correctly. To achieve these aims, care systems should establish standards and operating procedures.

Screening should be accompanied by efforts to optimize the participation of patients and health care providers—both with screening tests and appropriate diagnostic evaluation of abnormal screening test results—and to remind patients and providers about the need for rescreening at recommended intervals.

Risk Stratification

Clinicians should determine an individual patient's risk status well before the earliest potential initiation of screening (typically around age 20 years, but earlier if there is a family history of familial adenomatous polyposis) (Figure 1). The individual's risk status determines when screening should be initiated and what tests and frequency are appropriate.

Risk stratification can be accomplished by asking several questions aimed at uncovering the risk factors for colorectal cancer:

1. Has the patient had colorectal cancer or an adenomatous polyp?

2. Does the patient have an illness (e.g., inflammatory bowel disease) that predisposes him or her to colorectal cancer?
3. Has a family member had colorectal cancer or an adenomatous polyp? If so, how many, was it a first-degree relative (parent, sibling, or child), and at what age was the cancer or polyp first diagnosed?

A positive response to any of these questions should prompt further efforts to identify and define the specific condition associated with increased risk.

Recommendations for Screening People at Average Risk

Men and women at average risk should be offered screening with one of the following options beginning at age 50 years. The rationale for presenting multiple options is that no single test is of unequivocal superiority and that giving patients a choice allows them to apply personal preferences and may increase the likelihood that screening will occur. The strategies are not equal with regard to evidence of effectiveness, magnitude of effectiveness, risk, or up-front costs. Reviewing the rationale section for each screening test (below) will provide clinicians with information that they can use in presenting the relative effectiveness of each test to patients.

Fecal Occult Blood Testing

Recommendation. Offer yearly screening with fecal occult blood test (FOBT) using a guaiac-based test

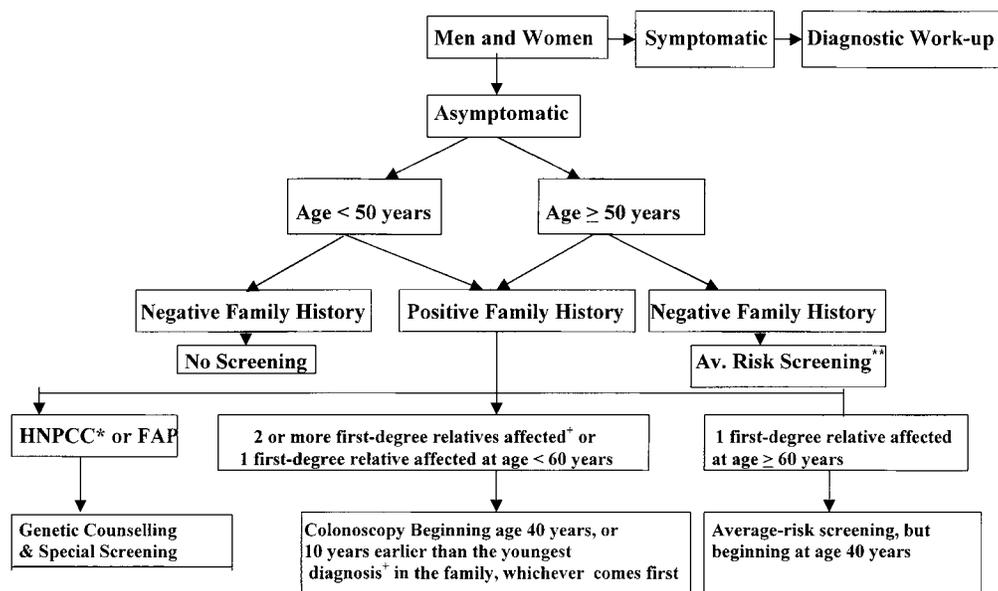


Figure 1. Algorithm for colorectal cancer screening. +, Either colorectal cancer or adenomatous polyp; *, HNPCC = hereditary nonpolyposis colorectal cancer and FAP = familial adenomatous polyposis. **See text.

with dietary restriction or an immunochemical test without dietary restriction. Two samples from each of 3 consecutive stools should be examined without rehydration. Patients with a positive test on any specimen should be followed up with colonoscopy.

Rationale. Testing of 2 samples from each of 3 consecutive stools for the presence of occult blood using a guaiac-impregnated slide test has been shown in 3 randomized controlled trials to reduce the risk of death from colorectal cancer.⁷⁻¹⁰ Although the sensitivity of a single FOBT is low, in the 30%–50% range, a program of repeated annual testing can detect as many as 92% of cancers.⁷ Offering yearly FOBT with rehydration reduced colorectal cancer deaths by 33% after 13 years; biennial testing reduced colorectal cancer deaths by 15% and 18% after 7.8 and 10 years, respectively, without rehydration^{8,9} and 21% at 18 years with rehydration.¹⁰ People who actually follow through with screening have a greater benefit; a substantial proportion of patients in these trials did not complete the recommended screening. We recommend yearly testing because it is more effective than screening every 2 years. Rehydration is not recommended: although rehydration of the guaiac-based slides increases sensitivity, the readability of the test is unpredictable, and rehydration substantially increases the false positive rate. Newer guaiac-based and immunochemical tests are available that have improved sensitivity and appear to maintain acceptable specificity.^{11,12} Dietary restrictions during testing are commonly recommended to reduce the false positive rate for the more sensitive guaiac-based tests but are not necessary for the immunochemical and less sensitive guaiac-based tests.

Disadvantages of FOBT are that currently available tests for fecal occult blood fail to detect many polyps and some cancers. Also, most people who test positive will not have colorectal neoplasia (have a false positive test result) and thus will undergo the discomfort, cost, and risk of colonoscopy without benefit. Colonoscopy is recommended for all those with a positive FOBT because it was the diagnostic procedure used throughout most of the trials, and because it is substantially more accurate than double contrast barium enemas for the detection of both small cancers and adenomas.¹³

New evidence. With longer (18 years) follow-up in the Minnesota trial, FOBT screening every other year was found to reduce colorectal cancer mortality by 21%,¹⁰ a rate consistent with the results of the biennial screening in the 2 European trials.^{8,9} The incidence of colorectal cancer was also reduced in the screened group.¹⁴ A systematic review of 3 clinical trials has shown that a restricted diet does not reduce the positivity

rate for the older, less sensitive guaiac-based tests and that very restricted diets may reduce compliance rates.¹⁵ However, dietary restriction does affect the performance of the more sensitive guaiac-based tests more recently introduced into clinical practice.¹⁶⁻¹⁸ Dietary restriction can be confined to red meat alone by waiting 3 days before developing the test.¹⁷ One study showed that testing for FOBT at the time of digital rectal examination (office FOBT) has a high positive predictive value for neoplasia, but its sensitivity and specificity are not known.¹⁹ A study of screening colonoscopy in people 40–49 years old confirmed that colorectal cancers are uncommon in this age group, supporting the recommendation that screening in average risk people begin at age 50 years.²⁰ One national study showed that only 1 in 3 people with a positive FOBT currently undergoes colonoscopy and therefore is in a position to benefit fully from screening.²¹

Sigmoidoscopy

Recommendation. Offer flexible sigmoidoscopy every 5 years.

Rationale. Four case-control studies have reported that sigmoidoscopy was associated with reduced mortality for colorectal cancer.²²⁻²⁵ The strongest of these reported that screening sigmoidoscopy reduced colorectal cancer mortality by two thirds for lesions within reach of the sigmoidoscope.²² Colon cancer risk in the area beyond the reach of the sigmoidoscope was not reduced, affirming the validity of this study. A 5-year interval between screening examinations is a conservative choice. It is supported by the observation that a reduction in colorectal cancer deaths related to screening sigmoidoscopy was present up to 10 years from the last screening examination,²² that repeat colonoscopy 5 years after a negative colonoscopy found few instances of advanced neoplasia,²⁶ and follow-up of a cohort of patients after polyp excision showed that development of advanced neoplasia was rare up to 5 years after a negative colonoscopy.²⁷ The interval is shorter than for colonoscopy because flexible sigmoidoscopy is less sensitive than colonoscopy even in the area examined because of the technique and quality of bowel preparation, the varied experience of the examiners performing the procedure, and the effect patient discomfort and spasm may have on depth of sigmoidoscope insertion and adequacy of mucosal inspection. A 10-year interval seems adequate when the examination is performed by a well-trained examiner, either a physician or a nonphysician-endoscopist, in a patient who is well prepared and has been examined up to or near the splenic flexure.

The decision to perform colonoscopy after the detection of a neoplasm on flexible sigmoidoscopy is controversial and should be individualized. Factors associated with an increased risk of advanced proximal neoplasia include age >65 years, villous histology in distal adenomas and adenomas ≥ 1 cm, multiple distal adenomas, and a positive family history of colorectal cancer.^{28–30} Whether persons with only a single distal tubular adenoma <1 cm in size are at increased risk for advanced proximal neoplasia remains uncertain. Polyps ≥ 1 cm in size detected at flexible sigmoidoscopy should generally be assumed to be adenomas because a very large proportion of these polyps are adenomatous. For polyps <1 cm in size, biopsy will distinguish hyperplastic from adenomatous polyps. Identification of villous elements or high-grade dysplasia, information that may be useful in deciding whether to proceed with colonoscopy, may not be obtainable when the polyp is adenomatous and approaches 1 cm in size. For these patients, whether to proceed with colonoscopy is an individual clinical decision. Current evidence suggests that the risk of advanced proximal neoplasia in persons with only hyperplastic polyps in the distal colon is comparable to the risk in persons with no distal polyps.

New evidence. Several studies have shown that the prevalence of proximal advanced adenomas in patients without distal adenomas is in the 2–5% range.^{28–31} Analysis of findings from colonoscopies on 2885 veterans suggested that a flexible sigmoidoscopy followed by colonoscopy if a polyp were found would have identified 70%–80% of patients with advanced proximal neoplasia.²⁹ In one randomized control trial, screening sigmoidoscopy followed by colonoscopy when polyps were detected was associated with an 80% reduction in colorectal cancer incidence.³² The preliminary findings of a randomized controlled trial of screening flexible sigmoidoscopy have been reported.³³ The effectiveness results will not be available for several years. The relationship between hyperplastic polyps and adenomas and colorectal cancer in some patients is undergoing reevaluation.^{34–36}

Combined FOBT and Flexible Sigmoidoscopy

Recommendation. Offer screening with FOBT every year combined with flexible sigmoidoscopy every 5 years. When both tests are performed, the FOBT should be done first.

Rationale. The effectiveness of this combined screening strategy in reducing mortality has never been studied directly in a randomized trial. It is likely that the combination of both screening methods is more effective

than either method of screening alone for several reasons: FOBT may be less sensitive for distal colon lesions,³⁷ case-control studies report screening FOBT and sigmoidoscopy each are associated with reduced colorectal cancer mortality after controlling for the other,^{22,38} and a non-randomized controlled trial reported a 43% reduction (which was not statistically significant) in colorectal cancer deaths in people screened with FOBT and sigmoidoscopy relative to sigmoidoscopy alone.³⁹ When both tests are to be done at any given time, the FOBT should be performed first because a positive result is an indication for colonoscopy, obviating the need for the sigmoidoscopy examination. The disadvantage of the FOBT/sigmoidoscopy strategy is that people incur the inconvenience, cost, and complications of both tests with an uncertain gain in effectiveness.

New evidence. A recent study showed that while sigmoidoscopy identified 70% of patients with advanced neoplasia, the addition of a one-time FOBT increased the detection rate to 76%.⁴⁰ Two randomized controlled trials have reported that a one-time FOBT detected substantially fewer clinically important neoplasms than FOBT plus sigmoidoscopy.^{41,42} In one of these studies, 3 times as many cancers and 5 times as many large adenomatous polyps were detected in the combined group.⁴² These studies did not include sufficient numbers of patients, over a long enough period of time, to assess the effects on colorectal cancer mortality. Also, there is good evidence that a program of annual FOBT testing is more sensitive than a one-time test.

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.^{1–5} However, several lines of evidence support the effectiveness of screening colonoscopy. Colonoscopy was an integral part of the clinical trials of FOBT screening that showed that screening reduced colorectal cancer mortality.^{7–10} Visualization of neoplasms by colonoscopy is at least as good as by sigmoidoscopy. There is direct evidence that screening sigmoidoscopy reduces colorectal cancer mortality^{22,23} and colonoscopy allows more of the large bowel to be examined. Colonoscopy has been shown to reduce the incidence of colorectal cancer in 2 cohort studies of people with adenomatous polyps.^{27,43} Colonoscopy permits detection and removal of polyps and biopsy of cancer throughout the colon. However, colonoscopy involves greater cost, risk, and inconvenience to the patient than other screening tests,

and not all examinations visualize the entire colon. The added value of colonoscopy over sigmoidoscopy screening therefore involves a tradeoff of incremental benefits and harms.

Choice of a 10-year interval between screening examinations for average-risk people (if the preceding examination is negative) is based on estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop. The dwell time from the development of adenomatous polyps to transformation into cancer is estimated to be at least 10 years on average.^{27,44} Few clinically important adenomas are missed by colonoscopy (6% or less of advanced adenomas).⁴⁵ A case-control study of screening rigid sigmoidoscopy found a protective effect from death due to distal cancer lasting up to 10 years from the last screening examination.²²

New evidence. In 2 large prospective studies of screening colonoscopy, about half of patients with advanced proximal neoplasms had no distal colonic neoplasms.^{29,30} Similarly, a prospective study of distal colon findings in a cohort of average-risk persons with cancer proximal to the splenic flexure found that 65% had no neoplasm distal to the splenic flexure.⁴⁶ A randomized controlled trial of sigmoidoscopy with follow-up colonoscopy for all patients with polyps compared with no screening demonstrated a significant reduction in colorectal cancer incidence in the screened patients.³² A cohort of 154 asymptomatic average-risk persons with negative screening colonoscopies had a <1% incidence of advanced neoplasms at a second colonoscopy 5 years later,²⁶ lending support to the recommended interval of 10 years. Two colonoscopy studies suggested that flat and depressed adenomas account for 22% and 30% of adenomas,^{47,48} and one report suggests that dye spraying is necessary to not miss these lesions.⁴⁷ However, the precise prevalence and clinical significance of flat adenomas is uncertain.

Double-Contrast Barium Enema

Recommendation. Offer double-contrast barium enema (DCBE) every 5 years.

Rationale. There are no randomized trials evaluating whether screening DCBE reduces the incidence or mortality from colorectal cancer in people at average risk of the disease. The sensitivity of DCBE for large polyps and cancers is substantially less than with colonoscopy, the procedure does not permit removal of polyps or biopsy of cancers, and DCBE is more likely than colonoscopy to identify artifacts and other findings (such as stool) as polyps. Patients with an abnormal barium enema need a subsequent colonoscopy.

DCBE is included as an option because it offers an alternative (albeit less sensitive) means to examine the entire colon, it is widely available, and it detects about half of large polyps, which are most likely to be clinically important. Adding flexible sigmoidoscopy to DCBE is not recommended in the screening setting. The incremental detection rate achieved by adding flexible sigmoidoscopy is uncertain and probably small, and there is increased cost and patient inconvenience associated with the combination. A 5-year interval between DCBE examinations is recommended because DCBE is less sensitive than colonoscopy in detecting colonic neoplasms.

New evidence. In a case-control study, screening barium enema was associated with a 33% reduction in colorectal cancer deaths but the confidence intervals on this estimate were wide.⁴⁹ In a prospective study of DCBE in a surveillance population with a spectrum and prevalence of disease similar to a screened population, DCBE detected 53% of adenomatous polyps 6–10 mm in size, and 48% of those >1 cm in size compared with colonoscopy.¹³ In a nonrandomized study of 2193 consecutive colorectal cancer cases in community practice, the sensitivity for cancer was 85% with DCBE and 95% with colonoscopy.⁵⁰

Recommendations for Screening People at Increased Risk

People With a Family History of Colorectal Cancer or Adenomatous Polyps

Recommendations. People with a first-degree relative (parent, sibling, or child) with colon cancer or adenomatous polyps diagnosed at age <60 years or 2 first degree relatives diagnosed with colorectal cancer at any age should be advised to have screening colonoscopy starting at age 40 years or 10 years younger than the earliest diagnosis in their family, whichever comes first, and repeated every 5 years (Table 3).

People with a first-degree relative with colon cancer or adenomatous polyp diagnosed at age \geq 60 years or 2 second degree relatives with colorectal cancer should be advised to be screened as average risk persons, but beginning at age 40 years.

People with 1 second-degree relative (grandparent, aunt, or uncle) or third-degree relative (great-grandparent or cousin) with colorectal cancer should be advised to be screened as average risk persons.

Rationale. Colon cancer screening recommendations based on familial risk are derived from the known effectiveness of available screening procedures and the observed colon cancer risk in relatives of patients with large bowel malignancy (Table 4) and relatives of pa-

Table 3. Colon Cancer Screening Recommendations for People With Familial or Inherited Risk

| Familial risk category | Screening recommendation |
|--|--|
| First-degree relative affected with colorectal cancer or an adenomatous polyp at age ≥ 60 years, or 2 second-degree relatives affected with colorectal cancer | Same as average risk but starting at age 40 years |
| Two or more first-degree relatives ^a with colon cancer, or a single first-degree relative with colon cancer or adenomatous polyps diagnosed at an age <60 years | Colonoscopy every 5 years, beginning at age 40 years or 10 years younger than the earliest diagnosis in the family, whichever comes first |
| One second-degree or any third-degree relative ^{b,c} with colorectal cancer | Same as average risk |
| Gene carrier or at risk for familial adenomatous polyposis ^d | Sigmoidoscopy annually, beginning at age 10-12 years ^e |
| Gene carrier or at risk for HNPCC. | Colonoscopy, every 1-2 years, beginning at age 20-25 years or 10 years younger than the earliest case in the family, whichever comes first |

^aFirst-degree relatives include patients, siblings, and children.

^bSecond-degree relatives include grandparents, aunts, and uncles.

^cThird-degree relatives include great-grandparents and cousins.

^dIncludes the subcategories of familial adenomatous polyposis, Gardner syndrome, some Turcot syndrome families, and AAPC.

^eIn AAPC, colonoscopy should be used instead of sigmoidoscopy because of the preponderance of proximal colonic adenomas. Colonoscopy screening in AAPC should probably begin in the late teens or early 20s.

tients diagnosed with adenomas at a young age (≤ 60 years). Estimates of risk of colorectal cancer in close relatives of individuals with adenomatous polyps are still evolving. Future evidence may better delineate this risk. The rationale for beginning screening at age 40 years in persons with an affected first-degree relative is that the incidence of colon cancer in such persons parallels the risk in persons with no family history but precedes it by about 10 years.⁵¹ Mortality reduction studies directed at screening persons with a family history of colorectal cancer or adenomatous polyps are not yet available. The screening recommendations given for this group must therefore be considered provisional.

New evidence. A very large twin study estimated that 35% of all colon cancer cases arose from heritable factors, 5% from shared environmental factors, and 60% from nonshared environmental factors.⁵² A meta-analysis examined all studies that assessed familial risk of colon cancers and adenomatous polyps (27 studies in total) since 1966.⁵³ The relative risk of colon cancer when a first-degree relative was affected with large bowel malig-

nancy was 2.4. Increased risk was found when the relative was affected with either colon or rectal cancers but was greater for colon. If more than 1 relative was affected, the risk was 4.2. The risk was 3.8 for relatives if colon cancer was diagnosed before age 45 years, 2.2 if it was diagnosed between ages 45 and 59 years, and 1.8 if the cancer was diagnosed at >59 years old. The relative risk for colon cancer if the first-degree relative had an adenomatous polyp was 1.9, with age effects similar to those observed for cancer. Another study found that second-degree relatives (grandparent, aunt, or uncle) with colon cancer increased a person's relative risk by about 1.5.⁵⁴

In addition to the genes associated with the rare syndromes of colon cancer, a number of genes have now been identified that seem to play a role in this more common but less penetrant category of inherited colon cancer. Among these are the I1307K APC mutation in Jewish persons of Ashkenazi descent, the HRAS1-VNTR polymorphism in the general population, the methyl-entetrahydrofolate reductase val/val polymorphism (protective),⁵³⁻⁵⁵ and the TGF β R-1(6A) polymorphism.⁵⁶

Table 4. Familial Risk

| Familial setting | Approximate lifetime risk of colon cancer |
|---|---|
| General population risk in the U.S. | 6% |
| One first-degree relative with colon cancer ^a | 2-3-fold increased |
| Two first-degree relatives with colon cancer ^a | 3-4-fold increased |
| First-degree relative with colon cancer diagnosed at ≤ 50 years | 3-4-fold increased |
| One second- or third-degree relative with colon cancer ^{b,c} | About 1.5-fold increased |
| Two second-degree relatives with colon cancer ^b | About 2-3-fold increased |
| One first-degree relative with an adenomatous polyp ^a | About 2-fold increased |

^aFirst-degree relatives include parents, siblings, and children.

^bSecond-degree relatives include grandparents, aunts, and uncles.

^cThird-degree relatives include great-grandparents and cousins.

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These and other genes may well soon become part of the clinical armamentarium of colon cancer susceptibility testing but have not yet undergone sufficient evaluation to be recommended for routine use.

Familial Adenomatous Polyposis

Recommendations. People who have a genetic diagnosis of familial adenomatous polyposis (FAP), or are at risk of having FAP but genetic testing has not been performed or is not feasible, should have annual sigmoidoscopy, beginning at age 10–12 years, to determine if they are expressing the genetic abnormality. Genetic testing should be considered in patients with FAP who have relatives at risk. Genetic counseling should guide genetic testing and considerations of colectomy.

Rationale. FAP is an autosomal dominant syndrome caused by mutations in the adenomatous polyposis coli (APC) gene. Affected persons have a risk of colorectal cancer approaching 100%. The average age of adenoma appearance in FAP is 16 years, and the average age of colon cancer is 39 years. Most affected patients develop >100 colorectal adenomas, and persons with more than 100 adenomas have FAP by definition. A variant of FAP called attenuated APC (AAPC) is associated with variable number of adenomas, usually 20–100, a tendency toward right-sided colonic adenomas, an age onset of colorectal cancer that is approximately 10 years later than for FAP, and mutations near the 5-prime or 3-prime end of the APC gene.^{57–60} Although sigmoidoscopy is adequate screening for most FAP kindreds, colonoscopy should be used in those with AAPC, beginning in the late teens or early 20s, depending on the age of polyp expression in the family.

Genetic testing should be considered in a person with an FAP phenotype (>100 adenomas) if there are unaffected first-degree relatives <40 years old. Persons >40 years old without the FAP phenotype can be assumed to not be gene mutation carriers, with the exception of families with AAPC. Genetic testing in children can be delayed until age 10 years. Genetic testing can have psychological effects and subject persons with positive tests to the risks of discrimination. Therefore, it should only be performed after genetic counseling of patients and parents of children. Genetic testing is performed on DNA from peripheral white blood cells. The first person tested in any kindred should have the FAP phenotype. The disease producing mutation can be identified in approximately 80% of kindreds. Once the mutation is found in a person known to have FAP, other family members can be tested for the presence or absence of the same mutation with nearly 100% accuracy. When other family members test negative, they can be assumed to be

at average risk. If they test positive, they should be followed by sigmoidoscopy until they develop polyps, at which point the timing of colectomy is considered. The benefit of genetic testing in FAP is presumed but has not been proven.

New evidence. The colorectal cancer mortality rate is lower in FAP patients who choose to be screened compared with those who present with symptoms.⁶¹ The clinical and genetic description of AAPC (attenuated FAP) continues to emerge since its original description.^{57,58–60}

Mutations in the far 5' end, the far 3' end, and occasional specific mutations in other areas of the APC gene result in an attenuated form of FAP characterized by fewer but variable number of adenomas, a proximal colonic distribution of polyps (thus requiring colonoscopy for screening), a somewhat delayed adenoma and cancer occurrence, and a somewhat decreased colon cancer risk.⁶⁰ Age of presentation in typical FAP also correlates with location of the mutation in the APC gene. The density of colonic polyposis and highest cancer risk also correlates with the mutation location, with the most dense polyposis arising from mutations of the mid portion of the gene, less dense polyposis from mutations proximal and distal to this region, and the most sparse polyposis from mutations at the far proximal and distal ends of the gene.⁶² Despite the detailed genetic knowledge now available for FAP, genetic testing is frequently poorly applied and poorly interpreted, underscoring the importance of skilled genetic counseling as part of the testing process.^{63,64}

Hereditary Nonpolyposis Colorectal Cancer

Recommendations. People with a genetic or clinical diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC) or who are at increased risk for HNPCC should have colonoscopy every 1–2 years beginning at age 20–25 years, or 10 years earlier than the youngest age of colon cancer diagnosis in the family—whichever comes first. Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited mismatch repair (MMR) gene mutation. It should also be offered when the family mutation is not already known, but 1 of the first 3 of the modified Bethesda Criteria is met (Table 5).

Rationale. Colonoscopy screening guidelines are based on the clinical characteristics of HNPCC, together with a study that has shown decreased colon cancer incidence and mortality with every 3-year colonoscopy.⁶⁵ One to 2-year intervals are usually recommended, however, because advanced cancers, although rare, have been reported with 3-year follow-up. The age to begin screen-

Table 5. Clinical Criteria for HNPCC

Amsterdam Criteria⁶⁷ (for Clinical Identification of HNPCC)

- At least 3 relatives with colorectal cancer plus all of the following:
 - One affected patient is a first-degree relative of the other two
 - Two or more successive generations affected
 - One or more affected relative received colorectal cancer diagnosis at age < 50 years
 - FAP excluded
 - Tumors verified by pathologic examination

Amsterdam II⁶⁶ (Criteria for Clinical Identification of HNPCC, modified to take into account the increased occurrence of cancer other than of the colon and rectum)

- At least 3 relatives with an **HNPCC-associated cancer (colorectal cancer and cancer of the endometrium, small bowel, ureter, or renal pelvis)**^a plus all of the following:
 - One affected patient is a first-degree relative of the other two
 - Two or more successive generations affected
 - One or more affected relative received colorectal cancer diagnosis at age <50 years
 - FAP excluded **in any case of colorectal cancer**^a
 - Tumors verified by pathologic examination

Bethesda Guidelines⁶⁸ (For identification of patients with colorectal tumors who should undergo testing for microsatellite instability)

- B1 - Individuals with cancer in families that meet the Amsterdam Criteria
- B2 - Individuals with 2 HNPCC-related tumors, including synchronous and metachronous colorectal cancer or associated extracolonic cancer (endometrium, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional-cell carcinoma of the renal pelvis or ureter)
- B3 - Individuals with colorectal cancer and a first-degree relative with colorectal cancer or HNPCC-related extracolonic cancer or a colorectal adenoma; one of the cancers diagnosed at age <45 years,^c and the adenoma diagnosed <40 years
- B4 - Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 years^b
- B5 - Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid, cribriform) on histopathology diagnosed at age <45 years^b (solid or cribriform), defined as poorly differentiated for undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces
- B6 - Individuals with signet-ring-cell type colorectal cancer diagnosed at age <45 years^b (composed of >50% signet-ring cells)
- B7 - Individuals with adenomas diagnosed at age <40 years

^aDifferences between Amsterdam and Amsterdam II in **bold**.

^bModified Bethesda criteria replace the age of “<45” for colorectal cancer diagnosis in B3, B4, B5, and B6 to “<50”; see reference ⁷³.

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ing in HNPCC is based on the observation that the average age of colon cancer diagnosis is 44 years, and cancers before the age of 25 years are very unusual. Similar to average risk screening, colorectal cancer screening in HNPCC is directed at finding and removing adenomatous polyps as well as detecting early-stage cancer.

The benefit of genetic testing for HNPCC is presumed but has not been verified by strong research. Testing is successful in identifying the disease causing mutation in 50%–70% of families that meet the Amsterdam criteria. Once a mutation has been found in an index case, relatives can be tested for the presence or absence of that specific mutation with near 100% accuracy. Amsterdam-positive families in which a mutation is not found should still be treated as having HNPCC because they may have as yet unknown mutations.

Five percent or more of high-risk colon cancer families who do not meet the strict Amsterdam criteria nonetheless may have HNPCC. This group likely represents a large fraction of those with HNPCC.

Two approaches have been developed to direct when genetic testing should be done to find HNPCC among high-risk families. One approach is based on family

history using the modified Amsterdam criteria, the Amsterdam II criteria⁶⁶ (which were developed because of concern that the Amsterdam criteria⁶⁷ are too exclusionary) or using the modified Bethesda criteria (Table 5)⁶⁸ for the same reason. An alternative approach to finding those who should have genetic testing is to perform microsatellite instability (MSI) testing on the colon cancer tissue of patients meeting any of the Bethesda modified criteria (Table 5).⁶⁸ If MSI is positive, one should then proceed to genetic testing.

New evidence. A prospective 15-year screening study reported a 62% decreased risk of colon cancer and an elimination of colon cancer deaths with every 3-year colonoscopy in children of patients with HNPCC.⁶⁹ The most recent studies suggest that HNPCC accounts for between 0.86% and 2.0% of colon cancer cases.^{70,71} The cumulative incidence of HNPCC-related cancers was determined in HNPCC gene carriers up to age 70 years in the Finnish Cancer Registry.⁷² By age 70 years, the percent developing these cancers were: colorectal, 82%; endometrium, 60%; stomach, 13%; ovary, 12%; bladder, urethra, and ureter, 4.0%; brain, 3.7%; kidney, 3.3%; and biliary tract and gallbladder, 2.0%.

A large number of recent studies have addressed MSI testing and MMR gene testing for HNPCC. These have been extensively reviewed.⁷³ In brief, MSI is found in >95% of colorectal cancers from HNPCC patients, but only about 15% of colorectal cancers from those with sporadic colorectal cancer. Germline MMR mutations are found in 45%–64% of families meeting the Amsterdam criteria, and finding MSI in patients with colorectal cancer increases the likelihood of finding a MMR disease mutation in most settings.

In an effort to exclude fewer families and persons who may have HNPCC from genetic testing, expanded Amsterdam criteria have been agreed upon, called Amsterdam II criteria (Table 5). Consensus criteria were also developed for when to perform MSI testing, which are called the Bethesda criteria. Finally, consensus was reached on which markers should be used for determining MSI tumor status; MSI results should be reported as MSI-high (>1 marker affected by mutation), MSI-low (only 1 affected marker), and MS-stable (no markers affected).⁷⁴ BAT 26 seems to be the most revealing marker and is almost as useful as the recommended panel together.⁷⁵

Surveillance of People at Increased Risk

People with a History of Adenomatous Polyps

Recommendation. Patients who have had 1 or more adenomatous polyps removed at colonoscopy should be managed according to the findings on that colonoscopy. Patients who have had numerous adenomas, a malignant adenoma (with invasive cancer), a large sessile adenoma, or an incomplete colonoscopy should have a short interval follow-up colonoscopy based on clinical judgment. Patients who have advanced or multiple adenomas (≥ 3) should have their first follow-up colonoscopy in 3 years. Patients who have 1 or 2 small (<1 cm) tubular adenomas should have their first follow-up colonoscopy at 5 years. It is not unreasonable, given available evidence, to choose even longer intervals. However, the evidence is still evolving. Future evidence may clarify the intervals more precisely.

The timing of the subsequent colonoscopy should depend on the pathology and number of adenomas detected at follow-up colonoscopy. For example, if the first follow-up colonoscopy is normal or only 1 or 2 small (<1 cm) tubular adenomas are found, the next colonoscopy can be in 5 years.

Rationale. Colonoscopic polypectomy and surveillance has been shown to reduce subsequent colorectal

cancer incidence.^{27,43} The rate of developing adenomas with advanced pathology after adenomas are found and removed is low after several years of follow-up,⁶⁵ and there is randomized trial evidence of no better detection of advanced lesions with follow-up examination 1 year after the initial colonoscopy than with follow-up examination at 3 years.⁶⁵ Because a reduction in incidence of advanced lesions has been shown for colonoscopic polypectomy and surveillance, colonoscopy is the recommended follow-up procedure.

The approach to surveillance following polypectomy is based on risk stratification to direct surveillance to those most likely to benefit and to reduce surveillance intensity in those who are less likely to benefit but would be placed at risk for complications from removal of small polyps. Patients at low risk for advanced adenomas at follow-up are those with only 1 or 2 small adenomas at baseline.⁷⁶ Patients at increased risk for advanced adenomas and colorectal cancer at follow-up are those with large (>1 cm) or villous adenomas or multiple adenomas (≥ 3).

Follow-up examinations are for 2 purposes. First, they detect and remove adenomas missed on the initial examination. Second, they establish whether the patient has a tendency to form new adenomas with advanced pathology. However, within recommended surveillance intervals, most metachronous neoplasms are small (<1 cm), and few of these have malignant change at this stage in their development. Studies have suggested that the initial colonoscopy is responsible for the major benefit of polypectomy and that follow-up surveillance may not add significant benefit except in people at high risk for future advanced adenomas.^{65,76}

New evidence. New evidence supports the concept that colonoscopic polypectomy reduces subsequent colorectal cancer incidence. A recent study of post-polypectomy surveillance demonstrated a 66% reduction in colorectal cancer incidence, similar to the previous report of the National Polyp Study.⁴³ A randomized trial of screening sigmoidoscopy followed by colonoscopic polypectomy demonstrated an 80% reduction in colorectal cancer incidence.³²

People With a History of Colorectal Cancer

Recommendation. Patients with a colon cancer that has been resected with curative intent should have a colonoscopy around the time of initial diagnosis to rule out synchronous neoplasms. If the colon is obstructed preoperatively, colonoscopy can be performed approximately 6 months after surgery. If this or a complete preoperative examination is normal, subsequent colonos-

copy should be offered after 3 years, and then, if normal, every 5 years.

Rationale. The incidence of colorectal cancer is increased after the first occurrence, apart from recurrence of the original cancer.⁷⁷ As with the original cancer, these subsequent cancers are preceded by adenomatous polyps. 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 colorectal cancer. Although colonoscopy can detect recurrent colon cancer, anastomotic recurrences occur in only about 2% of colon cancers and are generally accompanied by intra-abdominal disease that cannot be resected for cure.⁷⁸

New evidence. In a follow-up study, the incidence of secondary colorectal cancers was increased despite intensive surveillance (standardized incidence ratio, 6.8) in patients treated for localized colon cancer, relative to patients with adenomatous polyps who had undergone frequent colonoscopy.⁷⁹ A randomized controlled trial performed in 325 patients with curative resections of colorectal cancer compared the effects of annual colonoscopy, liver computerized tomography (CT), and chest radiography plus regular history, physical examination, and carcinoembryonic antigen measurement with the effects of history, examination, and carcinoembryonic antigen alone. Annual colonoscopy detected no surgically curable recurrences, and liver CT and chest radiography detected 1 each.⁸⁰ This study indicated that the value of colonoscopy is confined to detection of metachronous adenomas and not recurrent intraluminal cancer.

People With Inflammatory Bowel Disease

Recommendation. In patients with long-standing, extensive inflammatory bowel disease, surveillance colonoscopy with systematic biopsies (see below) should be considered. This applies to both ulcerative colitis and Crohn's colitis because the cancer risk is similar in both diseases.

Rationale. There are no randomized controlled trials of surveillance colonoscopy in patients with chronic ulcerative colitis or Crohn's colitis. A case-control study has found better survival in ulcerative colitis patients in surveillance programs.⁸¹ It is common practice to perform surveillance every 1–2 years after 8 years of disease in patients with pancolitis or after 15 years in those with left-sided colitis although direct supporting evidence is lacking. All patients should have surveillance colonoscopy beginning with 8–10 years of disease because the extent of disease cannot otherwise be accurately assessed. Effective surveillance may depend on adherence to an extensive biopsy protocol. The consensus of experts is that biopsy specimens should be taken every 10 cm in all

4 quadrants and that additional biopsies should be taken of strictures and mass lesions other than pseudopolyps. Polyps that appear potentially dysplastic can be removed by polypectomy with biopsy of adjacent flat mucosa to determine if dysplasia is present.

Also based on expert opinion, patients with high-grade dysplasia or multifocal low-grade dysplasia in flat mucosa should be advised to undergo colectomy if the pathologic finding is confirmed by a pathologist experienced with dysplasia in inflammatory bowel disease (IBD). The recommendation for colectomy in the presence of low-grade dysplasia, particularly if it is unifocal, does not share the same consensus as high-grade dysplasia. A dysplasia-associated lesion or mass is a dysplastic mass lesion believed to have arisen because of the cancer potential of the colitis and is an indication for colectomy. Differentiation of dysplasia-associated lesion or mass from sporadic adenoma is sometimes difficult and requires consideration of endoscopic appearance, polyp histology, the presence of dysplasia in flat mucosa adjacent to the polyp, patient age, and duration of disease.

In individual patients, a decision regarding colectomy may be affected by other factors that increase risk, including ongoing colitis-related symptoms, life expectancy, duration and extent of colitis, a personal history of primary sclerosing cholangitis, and a family history of colorectal cancer. The benefit, harms, and shortcomings of colonoscopy surveillance and the option for colectomy should be discussed with the patient around the time of each surveillance examination.

New evidence. A recent study indicated that British gastroenterologists are often poorly informed regarding expert opinion on optimal colonoscopic technique of colitis surveillance and recommendations for the finding of dysplasia.⁸² A previous study had shown similar results among U.S. gastroenterologists.⁸³ Observational studies suggest that tubular adenomas with only low-grade dysplasia arising in areas of colitis and with no dysplasia in flat mucosa are not markers of cancer risk over short intervals.^{84,85} Such lesions can be considered sporadic adenomas, and, if other indications for colectomy are absent, surveillance can be continued. Mathematical models suggest that longer intervals between surveillance examinations are more cost-effective until the disease duration reaches 20 years.⁸⁶

Emerging Screening Tests

Several newly developed methods of screening for colorectal cancer have substantial promise but are not yet well enough developed, nor is their effectiveness and cost

well enough established, to be offered as screening options at this time.

Virtual Colonoscopy

Thin-section, helical, CT followed by off-line processing ("virtual colonoscopy") can yield high-resolution, 3-dimensional images of the colon. This procedure is performed after standard bowel preparation and air insufflation, which is uncomfortable, and the patient is exposed to radiation. However, the procedure is noninvasive and does not cause major complications. In a study of selected, high-risk patients, virtual colonoscopy detected 3 of 3 cancers and 20 of 22 polyps ≥ 1 cm (91%), with 19 false positives in 87 patients.⁸⁷ Another study reported detection of 74 of 82 polyps ≥ 1 cm (90%); specificity in this study was 72%.⁸⁸ Thus, current techniques for virtual colonoscopy apparently perform at a clinically useful level in selected patients in some centers, and the technology is still improving. However, virtual colonoscopy is not yet ready for widespread screening outside the research setting pending improvements in the technology, clinical studies of performance in average-risk patients, and a better understanding of its costs.

Altered DNA in Stool

Colorectal carcinogenesis is accompanied by a series of several acquired genetic abnormalities that may be responsible for transitions from normal mucosa to incurable cancer. These genetic changes are characteristic of neoplasia and are not limited to colorectal cancer. It is now possible to recover analyzable human DNA from stool and to test for these genetic and other abnormalities of DNA. One study of the performance of a panel of selected DNA alterations in 33 patients with neoplasia and 28 without neoplasia reported a sensitivity of 91% for cancer and of 82% for adenomas ≥ 1 cm and a specificity of 93%.⁸⁹ Another study, of 71 patients, testing a different panel of 3 abnormalities, reported a sensitivity of 71% for colorectal cancer.⁹⁰ Two additional studies add to the evidence that this approach is promising.^{91,92} Additional trials measuring the performance of the test in large numbers of average-risk people are in progress.

Discussion

There is now a consensus among guidelines that colorectal cancer screening is effective in reducing mortality from this disease in men and women. However, although these guidelines sound a similar message, specific recommendations differ. All include options for screening average-risk people: FOBT, sigmoidoscopy, colonoscopy, or DCBE.

Despite the recommendations of expert groups that all Americans age 50 years and older should be screened, screening rates remain low. In a national survey of U.S. residents age >50 years in 1999, only 20.6% had a home FOBT within 1 year, and 33.6% had undergone sigmoidoscopy or colonoscopy within 5 years. Rates have increased in recent years, but only by 1%–3% between 1997 and 1999.⁶

There are many reasons for these low screening rates, ranging from low levels of public awareness about colorectal cancer, the relatively recent emergence of a consensus on the need for screening, public and professional attitudes about screening, and implementation barriers. A contributing factor is that colorectal cancer screening guidelines, including the present one, are relatively complex. They include several options for screening average-risk people, whereas screening guidelines for other cancers, such as breast and cervix, emphasize just 1 type of test (mammography and Pap smear, respectively). Moreover, colorectal cancer screening guidelines identify several risk groups for which different screening programs (according to age of onset, screening tests, and intervals) are recommended. Although this approach does make the message more complex, it is consistent with the evidence and with the current trend to provide information for both physicians and patients on the consequences of various ways of dealing with the same health problem. With this information, patients can exercise their own preferences during decision-making about their preventive care.⁹³

For screening programs to be successful, a cascade of events must be negotiated from beginning to end. Physicians must remember to offer screening, patients must accept this advice, insurers must pay for screening and follow-up testing, and patient care organizations must have systems to track whether screening has taken place and provide reminders if it has not. Screening examinations must be feasible for providers, which is a special problem for sigmoidoscopy, and the work force to do examinations well must be in place, which is a problem for colonoscopy. If any 1 stage in this sequence is faulty, the screening program will fail. Therefore, those who care about effective screening programs must be concerned with all of these elements of success.

The number of places where breakdowns can occur is large. Some patients may not understand or carry out bowel preparation instructions. Providers must be able to perform tests correctly. Office staff, aided by information systems, must remember when screening tests are due and patients must accept part of this responsibility because they commonly change providers (because their

health plan changes) or move out of the area, leaving new doctors unable to determine when 5–10 years have passed since their last endoscopy. Also, shared decision making can be difficult to implement. Not all patients want to share decisions, and many prefer doctors to make a recommendation. Physicians may lack time, skill, and resources to carry out shared decision making correctly, and patients may not be able to digest the information presented. Many forms of patient information about colorectal cancer are available.⁹⁴

Although the present guidelines are similar to the 1997 version in broad outline, several changes were prompted by new evidence: no rehydration of FOBT; use of colonoscopy alone rather than colonoscopy or DCBE for diagnostic evaluations; a greater stratification of patients following polypectomy based on risk for advanced adenomas; more detailed recommendations for genetic testing in FAP and HNPCC; reliance solely on colonoscopy for screening in HNPCC and for people with a close relative with colorectal cancer or an adenomatous polyp at an age <60 years; and a shortening of the interval for DCBE screening to 5 years. The risk stratification of postpolypectomy patients is especially important. In these guidelines, the first follow-up colonoscopy is recommended in 5 years rather than in 3 years for patients at low risk for adenomas at follow-up. If adopted nationally, this would shift resources from surveillance to screening since the majority of postpolypectomy patients are at low risk for new adenomas at follow-up.

These guidelines, like their predecessor, take into consideration the full range of issues that should go into a policy decision. The size of the effect and the strength of the research evidence on which it is based are major considerations. But so also are the complications and inconvenience of screening, patient acceptance, and cost. Individual patients and providers may value some of these elements over others.⁹⁵

Cost-effectiveness analyses^{96–99} have shown that the cost per year of life saved by screening with any of the tests we have recommended is reasonable by U.S. standards. Although the specific results vary among analyses, in general, the marginal cost-effectiveness of this screening is less than \$25,000 per year of life saved. Screening for colorectal cancer was among the highest ranked services in an analysis of the value of preventive services based on the burden of disease prevented and cost-effectiveness.¹⁰⁰ Although the up-front costs vary by screening modality, the long-term cost-effectiveness is apparently similar across screening programs, so that decisions about which options to include, in the long run and from the perspective of society, do not need to be

heavily affected by costs. Costs increase out of proportion to benefits with shorter intervals between screening examinations. One analysis suggested that screening sigmoidoscopy might be cost-saving over a long period of time.⁹⁸

Newer screening tests, or others yet to be developed, may with time replace the options we have included in this report. Nevertheless, we believe that screening should take place with the tests available now and not wait until something better comes along. In this way, needless suffering and loss of life can be avoided for this, the second leading cause of cancer death. Screening may become even more successful if the promise of new technologies is confirmed and they enter clinical practice.

Questions for Future Research

What are the performance characteristics (e.g., sensitivity/specificity or likelihood ratios) in average-risk people in the general population of emerging screening tests: new tests for fecal occult blood (new guaiac-based slide tests, immunochemical tests); virtual colonoscopy; and tests for cancer-related DNA changes in stool?

For screening programs combining FOBT and sigmoidoscopy, what are the respective contributions of the 2 tests to neoplasm detection and reduction in colorectal cancer incidence and death, and what is the overall effectiveness?

What are the effects of varying the interval between screening examinations for each of the currently accepted tests?

What is the incremental benefit, in terms of colorectal cancer incidence and mortality, between flexible sigmoidoscopy and colonoscopy, and at what cost in complications and resources?

How effective is screening colonoscopy in reducing colorectal cancer incidence and mortality in average-risk people?

What technical changes in polypectomy could lower polypectomy complication rates?

What is the complication rate of colonoscopy in community practice?

Among patients with long-standing, extensive inflammatory bowel disease, does surveillance achieve better outcomes than timing colectomy according to the extent and duration of disease?

How can clinical and genetic information be used to stratify patients according to their risk of developing colorectal cancer?

Among people with first- or second-degree relatives with colorectal cancer, at what age should screening begin, and at what interval should they be repeated?

What is the prevalence and clinical significance of flat and depressed adenomas?

What is the effectiveness of screening programs in patients at increased risk because of family history or HNPCC?

What genes, beyond those already described, account for the increased risk of colorectal cancer in patients with a family history of this disease?

What interventions aimed at providers, patients, health care systems, and the population at large increase colorectal cancer screening rates?

What explains the different findings of published cost-effectiveness analyses, and what is the best estimate of cost-effectiveness corresponding to real-world practices and charges?

What training and experience is necessary to achieve and maintain technical competence in sigmoidoscopy, colonoscopy, and DCBE?

What factors (such as number of doctors and endoscopy facilities, and cost) are limiting access to sigmoidoscopy and colonoscopy in the U.S.?

Can minimal prep or prep-less methods for colon cleansing be developed for virtual colonoscopy?

What real-time methods (such as light-induced fluorescence and photodynamic diagnosis) will detect dysplasia in flat or depressed mucosal lesions?

Which biomarkers will stratify risks for colorectal cancer development in IBD patients?

How can screening be more universally implemented in the population?

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In applying the recommendations in the guidelines to patients, the individual circumstances of the patient must be considered in addition to the guideline recommendations.

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The recommendations in this report are based on the clinical literature or reports accepted for publication and available to the Panel in complete form as of June 1, 2002. Evidence that appears after this date should be taken into account when applying these guidelines. Clinical judgment should be used to tailor recommendations to the individual patient's special circumstances.

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