Colorectal Cancer Screening (PDQ®)–Health Professional Version

Go to Patient Version

Summary of Evidence

Note: The Summary of Evidence section summarizes the published evidence on this topic. The rest of the summary describes the evidence in more detail.

Other PDQ summaries on Colorectal Cancer Prevention; Colon Cancer Treatment; and Rectal Cancer Treatment are also available.

Evidence of Benefit Associated With Colorectal Cancer Screening

Based on solid evidence, screening for colorectal cancer (CRC) reduces CRC mortality. In addition, there is solid evidence that some CRC screening modalities also reduce CRC incidence. A meta-analysis of randomized controlled trials of flexible sigmoidoscopy found that screening with sigmoidoscopy reduces all-cause mortality.

Table 1. Effect of Screening Intervention on Reducing Incidence and Mortality from Colorectal Cancer[a]

Screening Intervention	Study Design	Internal Validity	Consistency	Magnitude of Effect on CRC Incidence	Magnitude of Effect on CRC Mortality
Fecal Occult Blood Test (guaiac-based)	RCTs [7]	Good	Good	Likely small to none	15%–33%
Fecal Occult Blood Test (fecal immunochemical-based: FIT)	RCTs ongoing[b]	Fair	Fair	Fair	Fair
Sigmoidoscopy	RCTs	Good	Good	20%–25%	22%–31%; 13%–50% for distal colon

Screening Intervention	Study Design	Internal Validity	Consistency	Magnitude of Effect on CRC Incidence	Magnitude of Effect on CRC Mortality
Digital Rectal Exam	Case-control studies	Fair	Good	No effect	No effect
Colonoscopy	One RCT (RCTs in-progress)[c]; case-control studies; observational cohort studies that use historical/other controls	Poor	Poor	About 60%–70% for left colon; uncertain for right colon[c] [6]	About 60%–70% for distal colon; uncertain for right colon

CRC = colorectal cancer; FIT = fecal immunochemical testing; RCT = randomized controlled trial.

[a]There are no data from RCTs on the effect of other screening interventions (i.e., barium enema, computed tomographic colonography, and stool DNA mutation tests) on mortality from CRC. There are also no publish of RCTs of FIT with mortality as an end point.

[b]FIT is being compared with colonoscopy in two RCTs in Europe (NCT00906997 [Spain] and NCT02078804 [S one in the United States (NCT01239082), and one in China (ChiCTR1900025257).[1,2] The trial in Sweden comp colonoscopy with FIT and population controls. Mortality results are not available and may be limited for FIT b the absence of no-screening comparison groups in several trials. Current guideline recommendations have on FIT using the same mechanism as guaiac tests, the most sensitive of which had similar sensitivity to FIT [showed significant reductions in both mortality and incidence of CRC.[3-5]

[c]The NordICC trial compares a colonoscopy group with a usual-care control group [NCT00883792].[6]

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Significance

Background

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide [1] and the second leading cause of cancer deaths in the United States.[2] It is estimated that in 2025 there will be 154,270 new cases diagnosed in the United States and 52,900 deaths due to this disease. From 2012 to 2021, incidence rates for CRC declined by about 1% per year overall due to screening uptake and changing patterns in risk factors. However, this declining incidence is confined to individuals aged 65 years and older. Between 2012 and 2021, incidence rates increased by 2.4% per year in individuals younger than 55 years and by 0.4% per year in individuals aged 50 to 64 years. Over the last decade, the mortality rate from CRC declined by 1.7% per year in both men and women.[2] Incidence is higher in men than in women. The incidence rates range from 34.5 per 100,000 per year in Asian or Pacific Islander men to 53.6 per 100,000 per year in American Indian or Alaska Native men. In women, the incidence rates range from 25.3 per 100,000 per year in Asian or Pacific Islander women to 45.5 per 100,000 per year in American Indian or Alaska Native women. The age-adjusted mortality rates are 15.4 per 100,000 per year in men and 10.8 per 100,000 per year in women. About 4.0% of Americans are expected to develop the disease within their lifetime, and the lifetime risk of dying from CRC is 1.4%.[3] Age-specific incidence and mortality rates show that most cases are diagnosed after age 54 years and 77% of cases occur in individuals aged 55 years and older; about 15% of CRC cases occur in individuals aged 45 to 54 years.[3-5]

An analysis of national data for 1975 to 2010 addressed long-term trends in CRC.[6] Incidence increased for men from 1975 to 1985, but there were marked declines from 1985 to 1995 for both men and women, followed by a nonsignificant increase from 1995 to 1998, then marked declines from 1998 to 2010. Death rates from CRC have declined since 1984 in both men and women, with an accelerated rate of decline since 2002 for men and since 2001 for women. From 1997 to 2010, CRC incidence declined for all racial and ethnic groups. The fastest annual rate of decline occurred in men and women aged 65 years or older. There was a trend of increasing short-term incidence rates for individuals younger than 50 years in most population subgroups. Incidence rates of distal colon and rectal cancers decreased in men and women for all ages combined. Incidence rates of proximal colon cancer also decreased in men and women for all races and ethnicities combined.

Risk Factors

Age and family history

The main risk factor for CRC is increasing age; 90% of all CRCs are diagnosed after age 50 years. History of CRC in a first-degree relative, especially when diagnosed before age 55 years, approximately doubles the risk.

Adenomas

The presence of adenomas (lesions considered to be the histological [neoplastic but nonmalignant] precursors of CRC) is another major risk factor. Adenomas are extremely common. For example, in individuals older than 50 years, the prevalence of adenomas is approximately 30% but can be as high as 50% with the use of high-definition endoscopes, which can detect 1-mm to 2-mm adenomas.[7,8] Adenomas confer risk as they may themselves evolve into CRC. Additionally, even after removal, an adenoma (particularly if it is **high risk** based on size and histology) may indicate future risk of CRC. Managing adenomas and risk is challenging because adenomas are prevalent as people age, but most will never become CRC.

Understanding risk and risk management has been complicated by the intense focus on **adenoma-detection rates** in the last 15 years, which has led to increased detection of adenomas, especially very small ones (<0.5 cm). Risk factors for developing CRC are not completely understood, but generally include the following:

- Personal history of CRC or high-risk adenomas.
- Large adenomas (>1 cm).
- Multiple adenomas (>3).
- Adenomas with an advanced or worrisome histology (severe dysplasia; serrated, especially in the proximal colon).
- Flat or difficult-to-detect lesions (including serrated polyps, which may be more common in the right colon than in the left colon.)

Increased future risk of CRC is indicated by a personal history of CRC or high-risk adenomas (i.e., large [>1 cm] tubular adenomas, sessile-serrated adenomas, or multiple adenomas). Follow-up of individuals with these adenomas after they have undergone screening is considered **surveillance** and not screening.[9]

The term **serrated polyp** includes hyperplastic polyps, sessile-serrated adenomas, traditional-serrated adenomas, and mixed-serrated polyps.[10,11] The clinical significance of these lesions is uncertain because the natural history of any polypoid lesion is difficult to learn. However, the histological and molecular characteristics of some serrated lesions suggest possibly important malignant potential (e.g., mutations in the *BRAF* gene may be an early step toward carcinogenesis in serrated polyps).[12]

Prevalence of adenomas and CRC in asymptomatic populations

In a colonoscopy study of 3,121 predominantly male U.S. veterans (mean age, 63 years), advanced neoplasia (defined as an adenoma ≥10 mm in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer) was identified in 10.5% of the individuals.[8] Among patients with no adenomas distal to the splenic flexure, 2.7% had advanced proximal neoplasia. Patients with large adenomas (≥10 mm) or small adenomas (<10 mm) in the distal colon were more likely to have advanced proximal neoplasia (odds ratio [OR], 3.4; 90% confidence interval [CI], 1.8–6.5) than were patients with no distal adenomas (OR, 2.6; 90% CI, 1.7–4.1). One-half of those with advanced proximal neoplasia had no distal adenomas. In a study of 1,994 adults aged 50 years or older who underwent colonoscopy screening as part of a program sponsored by an employer, 5.6% of adults had advanced neoplasms.[7] Forty-six percent of those with advanced proximal neoplasms had no distal polyps (hyperplastic or adenomatous). If colonoscopy screening had been performed only in patients with

distal polyps, about one-half of the cases of advanced proximal neoplasia would not have been detected.

Analysis of data from a colonoscopy-based screening program in Warsaw, Poland, demonstrated higher rates of advanced neoplasia in men than in women. Of the 43,042 participants aged 50 to 66 years, advanced neoplasia was detected in 5.9% of participants (5.7% in women with a family history of CRC, 4.3% in women without a family history of CRC, 12.2% in men with a family history of CRC, and 8.0% in men without a family history of CRC).

In a cohort study within the Polish Colonoscopy Screening Program, nearly 166,000 participants were followed for up to 17 years after a single negative colonoscopy. Standardized incidence ratios that compared the participants to the general population were 0.32 (95% CI, 0.29–0.35) for low-quality colonoscopy (LQC) and 0.16 (95% CI, 0.13–0.20) for high-quality colonoscopy (HQC). Standardized mortality ratios were 0.22 (95% CI, 0.18–0.25) for LQC and 0.10 (95% CI, 0.06–0.14) for HQC. Colonoscopy, especially HQC, was predictive of low CRC incidence and mortality for at least 10 years after a negative exam, suggesting that the currently recommended 10-year interval for screening is safe and could potentially be extended.[13]

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Evidence of Benefit

Fecal Occult Blood Test (FOBT)

In FOBT testing, stool samples are collected and analyzed for the presence of small amounts of blood. The first generation of FOBTs used guaiac-based assays to detect blood, which are less sensitive and less specific than immunochemical-based testing. The now-classic randomized controlled trials (RCTs) that assessed colorectal cancer (CRC) mortality reduction all used guaiac-based testing. The finding of decreased CRC mortality provided a major foundation to draft CRC screening recommendations. The first-generation guaiac-based tests are being replaced with more sensitive and more specific immunochemical tests, which have not yet been assessed in RCTs with a no-screening control group.

In this setting, the RCT evidence about guaiac-based testing is reviewed briefly here, with further discussion of how immunochemical FOBT (iFOBT or FIT) may provide improved sensitivity and specificity. Generally, if guaiac FOBT (gFOBT) is acceptable as a screening test (as shown in RCTs), then a strong case can be made for using a more sensitive and more specific test like FIT.

gFOBT collection details vary somewhat for different tests, but they typically involve collection of as many as three different specimens on 3 different days, with small amounts from one specimen smeared by a wooden stick on a card with two windows or otherwise placed in a specimen container.

The guaiac test identifies peroxidase-like activity that is characteristic of human and nonhuman hemoglobin. Thus, the test records blood from ingested meat, upper airway bleeding such as epistaxis, upper gastrointestinal (GI) bleeding, and colonic lesions.

A systematic review regarding evidence of benefit was conducted through the Cochrane Collaboration. It examined all CRC screening randomized trials that involved gFOBT testing done on more than one occasion. The combined results showed that trial participants allocated to screening had a 16% lower CRC mortality (relative risk [RR], 0.84; 95% confidence interval [CI], 0.78–0.90). There was no difference in all-cause mortality between the screened groups and the control groups (RR, 1.00; 95% CI, 0.99–1.02). The trials reported a low positive predictive value (PPV) for the FOBT test, suggesting that most positive tests were false positives. The PPV was 5.0% to 18.7% in the trials using nonrehydrated slides (Funen and Nottingham studies), and it was 0.9% to 6.1% in the trials using rehydrated slides

(Goteborg and Minnesota studies). The report contained no discussion about contamination in the control arms of the trials and no information about treatment by disease stage.[1,2]

On initial (prevalence) examinations, 1% to 5% of unselected individuals tested with gFOBT had positive test results. Of those who tested positive, approximately 2% to 10% had cancer and approximately 20% to 30% had adenomas,[3,4] depending on how the test was done. Data from RCTs of gFOBT testing are summarized in Table 2.

Four controlled clinical trials to evaluate the efficacy of screening with gFOBT have been completed or are in progress. While more sensitive stool blood tests based on measuring human hemoglobin have been developed (and are discussed later in this summary), results of their performance in RCTs have not yet been reported. For gFOBT, the Swedish trial was a targeted study for individuals aged 60 to 64 years.[5] The English trial selected candidates from lists of family practitioners.[6] The Danish trial offered screening to a population aged 45 to 75 years who were randomly assigned to a control or study group.[7,8]

The Minnesota trial randomly assigned 46,551 men and women aged 50 to 80 years to one of three arms: (1) CRC screening with gFOBT, (2) rehydrated (with some small percentage of unrehydrated) FOBT every year (n = 15,570) or (3) every 2 years (n = 15,587), or a control group (n = 15,394). This trial demonstrated that annual FOBT screening decreased mortality from CRC by 33% after 18 years of follow-up (RR, 0.67; 95% CI, 0.51–0.83, compared with the control group) and that biennial testing resulted in a 21% relative mortality reduction (RR, 0.79; 95% CI, 0.62–0.97).[9] Some part of the reduction may have been attributed to chance detection of cancer by colonoscopies; rehydration of guaiac test slides greatly increased positivity and consequently increased the number of colonoscopies performed.[10] Subsequent analyses by the Minnesota investigators using mathematical modeling suggested that for 75% to 84% of the patients, mortality reduction was achieved because of sensitive detection of CRCs by the test; chance detection played a modest role (16%–25% of the reduction).[11] Nearly 85% of patients with a positive test underwent diagnostic procedures that included colonoscopy or double-contrast barium enema plus flexible sigmoidoscopy (FS). After 18 years of follow-up, the incidence of CRC was reduced by 20% in the annually screened arm and 17% in the biennially screened arm. With follow-up through 30 years, there was a sustained reduction in CRC mortality of 32% in the annually screened arm (RR, 0.68; 95% CI, 0.56–0.82) and 22% in the biennially screened arm (RR, 0.78; 95% CI, 0.65–0.93). There was no reduction in all-cause mortality in either screened arm (RR, 1.00; 95% CI, 0.99–1.01 for the annually screened arm and RR, 0.99; 95% CI, 0.98–1.01 for the biennially screened arm).[12] Important information that was not reported includes the treatment of CRC cases by stage by arm and the extent of CRC screening in each arm by FOBT, sigmoidoscopy, or colonoscopy after the completion of the trial protocol.[12,13]

The English trial allocated approximately 76,000 individuals to each arm. Those in the screened arm were offered nonrehydrated gFOBT testing every 2 years for three to six rounds from 1985 to 1995. At a median follow-up of 7.8 years, 60% completed at least one test, and 38% completed all tests. Cumulative incidence of CRC was similar in both arms, and the trial reported an RR reduction of 15% in CRC mortality (odds ratio [OR], 0.85; 95% CI, 0.74–0.98).[14] The serious complication rate of colonoscopy was 0.5%. There were five deaths within 30 days of surgery for screen-detected CRC or adenoma in a total of 75,253 individuals screened.[15] After a median follow-up of 11.8 years, no difference in CRC incidence between the intervention and control groups was observed. The disease-specific mortality rate ratio associated with screening was 0.87 (0.78–0.97; P = .01). The rate ratio for

death from all causes was 1.00 (0.98–1.02; *P* = .79).[16] When the median follow-up was extended to 19.5 years, there was a 9% reduction in CRC mortality (RR, 0.91; 95% CI, 0.84–0.98) but no reduction in CRC incidence (RR, 0.97; 95% CI, 0.91–1.03), or death from all causes (RR, 1.00; 95% CI, 0.99–1.02).[17]

The Danish trial in Funen, Denmark, entered approximately 31,000 individuals into two arms, in which individuals in the screened arm were offered nonrehydrated gFOBT testing every 2 years for nine rounds over a 17-year period. Sixty-seven percent of participants completed the first screen, and more than 90% of individuals invited to each subsequent screen underwent FOBT testing. This trial demonstrated an 18% reduction in CRC mortality at 10 years of follow-up,[18] 15% at 13 years of follow-up (RR, 0.85; 95% CI, 0.73–1.00),[19] and 11% at 17 years of follow-up (RR, 0.89; 95% CI, 0.78–1.01).[20] CRC incidence and overall mortality were virtually identical in both arms.

The Swedish trial in Goteborg enrolled all 68,308 citizens in the city who were born between 1918 and 1931 and were aged 60 to 64 years, and randomly assigned them to screening and control groups of nearly equal size. Participants in the control group were not contacted and were unaware they were part of the trial. Screening was offered at different frequencies to three different cohorts according to year of birth. Screening was done using the gFOBT Hemoccult-II test after dietary restriction. Nearly 92% of tests were rehydrated. Individuals with a positive test result were invited to an examination consisting of a case history, FS, and double-contrast barium enema. Follow-up ranged from 6 years 7 months to 19 years 5 months, depending on the date of enrollment. The primary end point was CRC-specific mortality. The overall screening compliance rate was 70%, and 47.2% of participants completed all screenings. Of the 2,180 participants with a positive test, 1,890 (86.7%) underwent a complete diagnostic evaluation with 104 cancers and 305 adenomas of at least 10 mm detected. In total, there were 721 CRCs (152 Dukes D, 184 Dukes C) in the screening group and 754 CRCs (161 Dukes D, 221 Dukes C) in the control group, with an incidence ratio of 0.96 (95% CI, 0.86–1.06). Deaths from CRC were 252 in the screening group and 300 in the control group, with a mortality ratio of 0.84 (95% CI, 0.71–0.99). This CRC mortality difference emerged after 9 years of follow-up. Deaths from all causes were very similar in the two groups, with a mortality ratio of 1.02 (95% CI, 0.99–1.06).[5]

Stage distribution

All trials have shown a more favorable stage distribution in the screened population than in controls (see Table 2). Data from the Danish trial indicated that while the cumulative incidence of CRC was similar in the screened and control groups, a higher percentage of CRCs and adenomas were Dukes A and Dukes B lesions in the screened group.[18] A meta-analysis of all previously reported randomized trials using biennial FOBT showed no overall mortality reduction by gFOBT screening (RR, 1.002; 95% CI, 0.989–1.085). The RR of CRC death in the gFOBT arm was 0.87 (95% CI, 0.8–0.95), and the RR of non–CRC death in the gFOBT group was 1.02 (95% CI, 1.00–1.04; *P* = .015).[21]

Mathematical modeling

Mathematical models have been constructed to extrapolate the results of screening trials and screening programs for benefit of the general population in community health care delivery settings. These models project that using currently available screening methodology can reduce CRC mortality or increase life expectancy.[22]

Table 2. Randomized Controlled Screening Trials to Assess Outcome: Guaiac-Based Fecal Occult Blood Testing

Site	Population Size	Positivity Rate (%)	% Cancers Localized[a]		Testing Interval	CRC Mortality Relative Risk (95% CI)
			Screened	Control		
Minnesota [9,23]	48,000	Unrehydrated: 2.4%	59	53	Annual	0.67 (0.51–0.83)
		Rehydrated: 9.8%			Biennial	0.79 (0.62–0.97)
United Kingdom [14]	150,000	Unrehydrated: 2.1%	52	44	Biennial	0.85 (0.74–0.98)
Denmark [18]	62,000	Unrehydrated: 1.0%	56	48	Biennial	0.82 (0.68–0.99)
Sweden [24]	68,308	Unrehydrated: 1.9%	52	50	Varied	0.84 (0.71–0.99)
		Rehydrated: 5.8%				

CI = confidence interval; CRC = colorectal cancer; RR = risk ratio.

[a]% Localized = T1–3 N0 M0.

Immunochemical FOBTs (iFOBT or FIT): Nonrandomized Controlled Trial Evidence to Assess Lesion Detection

The immunochemical FOBT (iFOBT or FIT) was developed to detect intact human hemoglobin. The advantage of FIT over gFOBT is that it does not detect hemoglobin from nonhuman dietary sources. Also, FIT does not detect partly digested human hemoglobin that comes from the upper respiratory or GI tract. Preliminary studies of several commercially developed FIT tests define their sensitivity and specificity compared with concurrently performed colonoscopy. The studies also examine these outcomes for different cutpoints, and the benefit of multiple versus single stool samples.[25,26]

Overall, FIT testing is much more sensitive than gFOBT, and it is more sensitive for cancers than for benign neoplasias. As expected, higher cutpoints decrease sensitivity and increase specificity. Fecal immunochemical tests may vary with regard to numbers of stools tested and cutoff values for a positive result.[26]

A systematic review of FIT studies in 2019 found 31 studies, with 120,255 participants and 18 types of FIT tests, that used screening colonoscopy as the reference standard, thus allowing calculation of test sensitivity and specificity.[27] Performance depended on the threshold for a positive result, so that a threshold of 10 μg/g (micrograms of hemoglobin per gram of feces) resulted in a CRC sensitivity of 0.91 (95% CI, 0.84–0.95) and a specificity of 0.90 (95% CI, 0.86–0.93), while a threshold greater than 20 μg/g resulted in a sensitivity of 0.71 (95% CI, 0.56–0.83) with specificity of 0.95 (95% CI, 0.94–0.96). For advanced adenomas, at a threshold of 10 μg/g, sensitivity was 0.40 (95% CI, 0.33–0.47) with a specificity of 0.90 (95% CI, 0.87–0.93). Comparison of three FITs at three thresholds was inconclusive because CIs overlapped, and the comparisons were across rather than within studies. Overall, FIT appears to provide a substantially improved sensitivity compared with gFOBT, although with some compromise in specificity.

The diagnostic sensitivity of FIT testing may vary depending on lesion location in the colon. Proximal lesions may be harder to detect for several reasons, including that they may arise from **serrated lesions** that are flat and, because they are less vascular than traditional adenomas, tend to bleed less frequently. In a population-based screening program of every-other-year FIT (set to detect 100 ng of hemoglobin per mL of buffer) testing, individuals who had six FITs over time were assessed to learn the frequency with which proximal and distal lesions were discovered.[28] Over 12 years (2002–2014), 123,000 participants had 441,000 FITs. The detection rate for proximal colon cancer declined only from the first to the second screening round (0.63–0.36 per 1,000 screened participants), while the rate for both distal colon and rectal cancer decreased across all six rounds (distal cancer, 1.65 in the first round to 0.17 in the sixth round). (Similar trends occurred for advanced adenomas.) The proportional interval cancer rate—the number of cancers observed versus expected—was higher in the proximal colon than in the distal colon (25.2% vs. 6.0%), suggesting that many proximal cancers (or their immediate precursors) may have been missed by FIT. These results suggest that FIT is less sensitive for proximal CRC and certainly for advanced adenomas, although it is possible that the miss rate may have been inflated if colonoscopy done in response to a positive FIT had missed a precursor lesion. Overall, these results raise questions about the degree of efficacy of FIT in preventing proximal CRC mortality.

The performance and acceptability of FIT over time was assessed by Kaiser-Permanente of Northern and Southern California in a screening program. A retrospective cohort of 323,349 persons aged 50 to 70 years was followed for up to four screening rounds over 4 years. Of patients invited, participation in round one was 48.2%, and of those remaining eligible, 75.3% to 86.1% participated in subsequent rounds. The authors reported that “programmatic FIT screening detected 80.4% of patients with CRC diagnosed within 1 year of testing, including 84.5% in round one and 73.4% to 78.0% in subsequent rounds.” An important observation was the degree of participation found. One limitation of the study is that it was not clear how work-up bias was addressed; e.g., when individuals with a positive test result are preferentially worked up to ascertain the presence or absence of CRC, while individuals with a negative test, but who might have CRC, are not. Although a **look-back** method was used to ascertain whether an individual had cancer, it is not clear that the duration of follow-up was long enough to discover everyone who should have been included in the denominator of the sensitivity calculation.

Nevertheless, the results suggested that subsequent FIT results were at least partially independent of previous results. Longer follow-up may help clarify this issue. Mortality reduction could not be assessed in this study.[29]

Potential false-positive test results because of an increased risk of upper GI bleeding are of concern with FOBT testing and pretest protocols, therefore; low-dose aspirin regimens are discontinued for a week or more before FOBT. The performance of FIT was tested in an ongoing diagnostic study (2005–2009) at 20 internal medicine GI practices in southern Germany. Nineteen hundred seventy-nine patients (233 regular low-dose aspirin users and 1,746 never users) were identified in the records for inclusion in the analysis. All patients provided one stool sample taken within a week before colonoscopy preparation, which was collected according to instructions in a container that was kept refrigerated or frozen until rendered to the clinic on the day of colonoscopy, and the patients agreed to complete a standard questionnaire regarding the use of analgesics and low-dose aspirin (for prevention of cardiovascular disease). Stool samples were thawed within a median of 4 days after arrival at the central laboratory (shipped frozen from the recipient clinics). Fecal occult blood levels were measured by two automated FIT tests according to the manufacturer's instructions (RIDASCREEN Haemoglobin and RIDASCREEN Haemo-/Haptoglobin Complex, r-biopharm, Bensheim, Germany) following clinical procedures and blinded to colonoscopy results. Advanced neoplasms were found in 24 aspirin users (10.3%) and in 181 nonusers (10.4%). At the cut point recommended by the manufacturer, sensitivities for the two tests were as follows: 70.8% (95% CI, 48.9%–87.4%) for users compared with 35.9% (95% CI, 28.9%–43.4%) for nonusers for the Haemoglobin test (P = .001) and 58.3% (95% CI, 36.6%–77.9%) for users compared with 32% (95% CI, 25.3%–39.4%) for nonusers for the Haemo-/Haptoglobin test (P = .01). Specificities were as follows: 85.7% (95% CI, 80.2%–90.1%) for users compared with 89.2% (95% CI, 87.6%–90.7%) for nonusers for the Haemoglobin test (P = .13) and 85.7% (95% CI, 80.2%–90.1%) for users compared with 91.1% (95% CI, 89.5%–92.4%) for nonusers for the Haemo-/Haptoglobin test (P = .01). For these FITs, sensitivity for advanced neoplasms was notably higher with the use of low-dose aspirin while specificity was only slightly reduced, suggesting that there might be an advantage of aspirin use to increase sensitivity without much decrease in specificity.[30]

Sigmoidoscopy

The flexible fiberoptic sigmoidoscope was introduced in 1969. The 60 cm flexible sigmoidoscope became available in 1976.[31] The flexible sigmoidoscope permits a more complete examination of the distal colon with more acceptable patient tolerance than the older rigid sigmoidoscope. The rigid instrument can discover 25% of polyps, while the 60-cm scope can find as many as 65% of them. The finding of an adenoma by FS may warrant a colonoscopy to evaluate the more proximal portion of the colon.[32,33] The prevalence of advanced proximal neoplasia is increased in patients with a villous or tubulovillous adenoma distally and is also increased in those aged 65 years or older with a positive family history of CRC and with multiple distal adenomas.[34] Most of these adenomas are polypoid, flat, and depressed lesions, which may be somewhat more prevalent than previously recognized.[35]

Four major sigmoidoscopy screening RCTs have reported incidence and mortality results (a fifth, the Telemark trial in Norway, was very small, with 800 total participants). These are the Norwegian Colorectal Cancer Prevention (NORCCAP) trial; the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST); the Screening for COlon REctum (SCORE) trial in Italy; and the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (see Table 3). Participants were aged 55 to 74

years in PLCO and aged 55 to 64 years in the other three trials. Together, the trials enrolled 166,000 participants in the screened groups and 250,000 participants in the control groups. Median follow-up was approximately 11 years for each group. Results were summarized in three systematic reviews. There was an 18% relative reduction in CRC incidence (RR, 0.82; 95% CI, 0.75–0.89), an overall 28% relative reduction in CRC mortality (RR, 0.72; 95% CI, 0.65–0.80), a 31% relative reduction in the incidence of distal CRC (RR, 0.69; 95% CI, 0.63–0.74), and a 46% relative reduction in the mortality of distal CRC (RR, 0.54; 95% CI, 0.43–0.67).[36] A meta-analysis showed a statistically significant, although clinically small, effect on all-cause mortality (RR, 0.97; 95% CI, 0.96–0.99).[37]

Three of the four trials above published long-term follow-up analyses of trial results. For UKFSST, median follow-up was 17.1 years. The RRs for CRC incidence and mortality were similar to those originally reported: an RR of 0.70 (95% CI, 0.62–0.79) for CRC mortality and an RR of 0.74 (95% CI, 0.70–0.80) for CRC incidence. For the PLCO trial, median follow-up was 15.8 years for incidence and 16.8 years for mortality; RRs were 0.75 (95% CI, 0.66–0.85) for CRC mortality and 0.82 (95% CI, 0.76–0.88) for CRC incidence. Median follow-up in the NORCCAP trial was approximately 15 years; HRs were 0.79 (95% CI, 0.65–0.96) for CRC mortality and 0.78 (95% CI, 0.70–0.87) for CRC incidence.[38,39] A pooled analysis of the four trials, using data through 15 years of follow-up and restricted to those aged 55 to 64 years at randomization, showed a rate ratio of 0.79 (95% CI, 0.75–0.83) for CRC incidence and 0.80 (95% CI, 0.72–0.88) for CRC mortality.[40]

There are no strong direct data from studies of sigmoidoscopy to determine the optimal frequency of screening tests in programs of screening.

Table 3. Randomized Controlled Screening Trials to Assess Outcome: Sigmoidoscopy[a]

Site	Population Size (Intervention)	FS Rate[b] (%)	Colonoscopy Rate[c] (%)	Cumulative CRC Incidence (%)	CRC Deaths per 100,000 Person-Years	CRC Mortality Relative Risk (95% CI
United Kingdom 2010	Intervention: 57,099	71.1	5.0	1.5	Intervention: 30	0.69 (0.59–0.80)
	Control: 112,939				Control: 44	
Italy 2011	Intervention: 17,136	57.8	7.8	1.6	Intervention: 35	0.78 (0.56–1.08)
	Control: 17,136				Control: 44	

Site	Population Size (Intervention)	FS Rate[b] (%)	Colonoscopy Rate[c] (%)	Cumulative CRC Incidence (%)	CRC Deaths per 100,000 Person-Years	CRC Mortalit Relative Risk (95% CI
United States 2012	Intervention: 77,445	86.6	25.3	1.5	Intervention: 29	0.74 (0.63–0.87)
	Control: 77,455				Control: 39	
Norway 2014	Intervention: 20,572[d]	63.0	19.5	1.4	Intervention: 31	0.73 (0.56–0.94)
	Control: 78,220				Control: 43	

CI = confidence interval; CRC = colorectal cancer; FS = flexible sigmoidoscopy.

[a]Adapted from Lin *et al.*[26]

[b]The FS rate refers to the % of individuals who received FSG in the screened group.

[c]The colonoscopy rate refers to the % of individuals who received a colonoscopy as a follow-up to a positive who received a sigmoidoscopy. In the U.S. study, individuals with a polyp found at the time of a sigmoidosco follow-up, which was generally done with a colonoscopy. In the other studies, the referral criteria for a colon histology of lesion(s) found at the time of the sigmoidoscopy.

[d] Half of the intervention group was also offered FOBT.

[e]These data are from Lin *et al.*[26], eFigure 1. Forest plot of randomized controlled trials of FS screening on dis

Combination of FOBT and Flexible Sigmoidoscopy: Impact on Neoplasm Detection

A combination of FOBT and sigmoidoscopy might increase the detection of lesions in the left colon (compared with sigmoidoscopy alone) while also increasing the detection of lesions in the right colon. Sigmoidoscopy detects lesions in the left colon directly but detects lesions in the right colon only indirectly when a positive sigmoidoscopy (that may variously be defined as a finding of advanced adenoma, any adenoma, or any polyp) is used to trigger a colonoscopic examination of the whole colon.

In 2,885 veterans (97% male; mean age, 63 years), the prevalence of advanced adenoma at colonoscopy was 10.6%. It was estimated that combined screening with one-time FOBT and sigmoidoscopy would detect 75.8% (95% CI, 71.0%–80.6%) of advanced neoplasms. Examination of the rectum and sigmoid colon during colonoscopy was defined as a surrogate for sigmoidoscopy. This represented a small but statistically insignificant increase in the rate of detection of advanced neoplasia when compared with FS alone (70.3%; 95% CI, 65.2%–75.4%). The latter result could be

achieved assuming that all patients with an adenoma in the distal colon undergo complete colonoscopy. Advanced neoplasia was defined as a lesion measuring at least 10 mm in diameter, containing 25% or more villous histology, high-grade dysplasia, or invasive cancer.[41] One-time use of FOBT differs from the annual or biennial application reported in those studies summarized in Table 2.

A study of 21,794 asymptomatic individuals (72% were men) who had both colonoscopy and FIT for occult blood compared the detection of proximal cancers as triggered by different test results. FIT alone resulted in a sensitivity of 58.3% and a specificity of 94.5% for proximal cancer diagnosis. FIT plus the finding of advanced neoplasia in the rectosigmoid colon yielded a sensitivity of 62.5% and a specificity of 93%. In this study, the addition of sigmoidoscopy to FIT did not substantially improve the detection of proximal colon cancers, compared with FIT alone.[42]

Colonoscopy

Randomized controlled trial evidence about colorectal cancer incidence or mortality reduction

Five RCTs exploring the impact of colonoscopy on CRC mortality or incidence have been initiated (NCT01239082, NCT00883792, NCT00906997, NCT02078804, and ChiCTR1900025257). Results of one RCT have been reported.

The NordICC trial (NCT00883792) was a pragmatic randomized trial of colonoscopy screening, begun in 2009 in Poland, Norway, Sweden, and the Netherlands. Men and women aged 55 to 64 years were identified from population registries and randomly assigned in a 1:2 ratio to receive either an invitation to undergo a single colonoscopy screening (invited group) or no invitation to screening (usual care group). Individuals were randomly assigned before they were asked whether they wanted to participate in the trial. Except for the 6,900 participants from Norway, participants in the usual-care group were not informed of their enrollment in the trial. The primary end points were risk of developing CRC and CRC-related death. The secondary end point was death from any cause.

Data were reported for 84,585 participants in Poland, Norway, and Sweden: 28,220 in the invited group, of whom 42% underwent screening, and 56,365 in the usual-care group. Opportunistic colonoscopy screening activity was monitored in the trial regions, and no additional colonoscopy procedures were identified beyond what would have been expected for clinical indications, indicating minimal, if any, contamination in the usual-care group. Hence, this trial compared colonoscopy screening with no screening. After a median follow-up of 10 years, in intention-to-screen analyses, the risk of developing CRC was 0.98% in the invited group and 1.20% in the usual-care group (risk ratio, 0.82; 95% CI, 0.70–0.93). The risk of death from CRC was 0.28% in the invited group and 0.31% in the usual-care group (risk ratio, 0.90; 95% CI, 0.64–1.16). The risk of death from any cause was 11.03% in the invited group and 11.04% in the usual-care group (risk ratio, 0.99; 95% CI, 0.96–1.04). Since only 42% of invited participants underwent screening, adjusted analyses were performed to estimate the effect of screening if all participants randomly assigned to screening actually had been screened. The risk ratio for CRC was 0.69 (95% CI, 0.55–0.83), and the risk ratio for CRC-related death was 0.50 (95% CI, 0.27–0.77). Fifteen participants had major bleeding after polyp removal, and there were no perforations or screening-related deaths within 30 days after colonoscopy.[43]

Caveats for this trial include the following:

1. Data from the Netherlands, roughly 10% of the participants, were not included.
2. Only 42% of invited participants underwent screening.
3. Follow-up duration may not be long enough to realize the full effect of the screening; additional analyses after 15 years are anticipated.
4. Colonoscopy is operator dependent, and 29% of the trial endoscopists had an adenoma detection rate (ADR) below the recommended minimum threshold.
5. There is a suggestion that high-risk individuals in Poland chose to undergo colonoscopy, which could have led to an underestimation of the screening effect.[44]

Indirect evidence of benefit comes from the detection rate of lesions that may be clinically important (like early CRC or advanced adenomas). Some case-control results are available. The **sensitivity** of a CRC screening test for adenomas (and for CRC) may be helpful in considering its possible clinical usefulness, given that there are no completed RCTs of the impact of colonoscopy on CRC mortality or incidence. Colonoscopy is commonly considered the **gold standard** because it directly assesses the physical presence of lesions in the colon. However, colonoscopy can miss roughly 10% of cancers and advanced adenomas because of suboptimal bowel cleansing, lesions being hidden behind **folds** (or haustra) in the colon, or suboptimal examination by the endoscopist. Recent data suggest that the magnitude of an endoscopist's **adenoma-detection rate** (commonly measured as the proportion of colonoscopies in which an adenoma is found) is related to reduced incidence of CRC.

Adenoma detection rate (ADR)

Detection rates in colonoscopy screening vary with the rate at which the endoscopist examines the colon while withdrawing the scope. In one study, there were differences among gastroenterologists in the rates of detection of adenomas (range of the mean number of lesions per patient screened, 0.10–1.05; range of the percentage of patients with adenomas, 9.4%–23.7%) and the times of withdrawal of the scope (3.1–16.8 minutes for procedures not including polyp removal). Examiners whose mean withdrawal time was 6 minutes or more had higher detection rates than those with mean withdrawal times of less than 6 minutes (28.3% vs. 11.8%; $P < .001$ for any neoplasia and 6.4% vs. 2.6%; $P < .005$ for advanced neoplasia).[45]

In the first 10 years of the German CRC screening program, detection of nonadvanced adenomas increased in men from 13.3% to 22.3% and in women from 8.4% to 14.9%. Most of the nonadvanced adenomas, however, were small (<0.5 cm) and had uncertain clinical significance. The detection of advanced adenomas and CRC increased by a much smaller amount.[46]

Overall detection rates of adenomas and cancer may be affected by how thoroughly endoscopists search for flat adenomas and flat cancer. While the phenomenon of flat neoplasms has been appreciated for years in Japan, it has more recently been described in the United States. In a study in which endoscopists used high-resolution white-light endoscopes, flat or nonpolypoid lesions accounted for only 11% of all superficial colon lesions, but these flat or nonpolypoid lesions were about 9.8 times as likely as polypoid lesions to contain cancer (*in situ* neoplasia or invasive cancer).[35] However, because the definition of **flat** or **nonpolypoid** was height less than one-half of the diameter, it is likely that many lesions classified as nonpolypoid in this study would be routinely found and described by U.S. endoscopists as **sessile**. The existence of very flat or depressed lesions—depressed

lesions are very uncommon but highly likely to contain cancer—requires that endoscopists pay more attention to this problem.[47] Flat lesions may play a role in the phenomenon of missed cancers.[48]

A health maintenance organization assessed the impact of ADRs in follow-up after 314,872 colonoscopies performed from 1998 to 2010 by 136 gastroenterologists, each of whom had done at least 300 colonoscopies during that period. The goal was to determine rates of interval CRC, interval advanced CRC, and CRC death and to relate those rates to a gastroenterologist's ADR. There were 712 interval cancers (155 advanced) and 147 CRC deaths. The risk of interval cancer from lowest-to-highest quintile of ADR was 9.8, 8.6, 8.0, 7.0, and 4.8 per 10,000 person-years of follow-up. The adjusted hazard ratio (HR) for physicians in the highest quintile compared with those in the lowest quintile was 0.52 for any interval CRC, 0.43 for advanced CRC, and 0.38 for fatal CRC. Each 1.0% increase in ADR was associated with a 3% decrease in risk of cancer, although the CI for each quintile was broad. Limitations of the study include the inability to determine which specific feature of ADR led to reduced interval cancer. For example, it is unclear whether it was due to the following:

- Removal of small adenomas that may grow rapidly to become CRC.
- ADR being a surrogate outcome for an endoscopist's ability to remove adenomas more completely.
- ADR being a surrogate outcome for an endoscopist's ability to better detect large, flat, serrated lesions.
- Higher ADR leading to recommendations for more frequent postpolypectomy surveillance colonoscopy.

Another limitation is that the harms of a colonoscopy associated with ADR could not be measured.[49]

Nonrandomized controlled trial evidence about colorectal cancer incidence or mortality reduction

Although there is little RCT evidence to assess reduction of CRC incidence or mortality by colonoscopy, some case-control evidence is available.[50] Based on case-control data about sigmoidoscopy, noted above, there was speculation that protection for the right colon might be similar to that for the left colon. A 2009 case-control study of colonoscopy raised questions about whether the impact of colonoscopy on proximal lesions might be different than the impact on distal lesions.[51] Using a province-wide administrative database in Ontario, Canada, investigators compared cases of individuals who were diagnosed with CRC from 1996 to 2001 and had died by 2003. Controls were selected from persons who did not die of CRC. Billing claims were used to assess exposure to previous colonoscopy. The OR for the association between complete colonoscopy and distal lesions was 0.33, suggesting a substantial mortality reduction. For proximal lesions, however, the OR of 0.99 indicated virtually no mortality reduction. However, this study had limited data about whether examinations were complete to the cecum and about bowel prep. Further, many endoscopists were not gastroenterologists.

A case-control study assessed CRC reduction (but not CRC mortality reduction) in the right side versus the left side of the colon. In a population-based study from Germany using data from administrative and medical records, 1,688 patients with CRC were compared with 1,932 participants without CRC, aged 50 years or older.[52] Data were collected about demographics, risk factors, and previous screening examinations. According to colonoscopy records, the cecum was reached 91% of the time.

Colonoscopy in the previous 10 years was associated with an OR for any CRC of 0.23, for proximal CRC of 0.44, and for distal CRC of 0.16. While this study did not assess CRC mortality, the results suggested that the magnitude of the right-side versus the left-side difference may be smaller than previously found.[51] It would be extremely useful to assess right-side versus left-side differences in a RCT.

Other case-control data suggest a reduction of CRC incidence on the right side of about 64% compared with about 74% on the left side.[53]

Because there is little RCT evidence and case-control evidence is limited, it is important to consider the degree of mortality reduction from colonoscopy. While a figure of 90% is sometimes cited as the degree of mortality reduction,[54] the question will not be properly answered until the completion of European RCT that has a control group of **routine care** that involves minimal screening of any kind.[55] Reliable results from colonoscopy RCTs are needed to confirm the studies of FS that suggest a mortality reduction of approximately 50% might occur in the right colon, similar to the demonstrated impact of FS in the left colon. This generalization is limited by a number of factors, including that proximal lesions may have a different pathology (e.g., a serrated appearance and different molecular pathway).

The benefit of continued CRC screening after age 75 years is uncertain. An observational cohort study with the Harvard Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) sought to determine whether CRC mortality or morbidity was affected by lower endoscopy (colonoscopy or sigmoidoscopy) screening in individuals older than 75 years, based on a person's age, comorbidity, family history of CRC, and screening history. Individuals were followed from 1988 to 2016 and had follow-up questionnaires every 2 years, with a 90% response rate. Among over 50,000 individuals, there were 661 CRCs and 323 CRC-related deaths. Screening after age 75 years was associated with reduced CRC incidence (HR, 0.61; 95% CI, 0.51–0.74) and CRC-related mortality (HR, 0.60; 95% CI, 0.46–0.78), regardless of screening history. It is not clear exactly what **past screening history** meant, however—i.e., the number and results of exams before age 75 years (no polyps; or some polyps indicating increased future risk). The study also assessed the relation of comorbidity to benefit and found that individuals with serious comorbidity—defined as myocardial infarction, stroke, or three comorbidities (high blood pressure, diabetes, and hypercholesterolemia)—did not benefit from screening. Although observational and not an RCT, this study likely provides the best-available data for a scenario in which a formal RCT is unlikely to be performed. It suggests that healthy people older than 75 years may benefit from continued CRC screening and reduction in mortality and morbidity.[56]

Virtual Colonoscopy (Computed Tomographic Colonography [CTC])

Virtual colonoscopy (also known as CTC or CT pneumocolon) refers to the examination of computer-generated images of the colon constructed from data obtained from an abdominal CT scan. These images simulate the effect of a conventional colonoscopy. Patients must take laxatives to clean the colon before the procedure, and the colon is insufflated with air (sometimes carbon dioxide) by insertion of a rectal tube just before radiographic examination.[57]

The American College of Radiology Imaging Network group conducted a large, paired-design study, with 2,531 participants at average risk (prevalence of polyps or cancer ≥10 mm, 4%; mean age, about 58 years) screened with both CTC and optical colonoscopy (OC). The gold standard was the OC, including repeat OC exams for people with lesions found by CTC but not by OC. Of 109 people with at

least one adenoma or cancer 10 mm or larger, 98 (90%) were detected by CTC (referring everyone with a CTC lesion of ≥5 mm). Specificity was 86%, and PPV was 23%. This study raises several concerns, including the following:

- Most, but not all, lesions found by CTC and not by OC were followed up with repeat OC.
- The design did not allow for following patients, thus potentially missing lesions that grow rapidly and would only be seen after follow-up.
- Because the centers conducting the screening were primarily academic centers and the radiologists and endoscopists were carefully trained, the generalizability of the findings is not clear.
- Sixteen percent of participants had an extracolonic finding that required further evaluation.

Unknowns from the study include the following for either OC or CTC:[58]

- The number of detected polyps that would have progressed to invasive cancer.
- The number of people harmed by the screening process.

Another study reported similar sensitivity and specificity in individuals with an increased risk of CRC.[59] In this study, the sensitivity of OC could not be determined because it was done in an unblinded manner. This cross-sectional study suggested that virtual colonoscopy might be an acceptable screening or surveillance test for individuals at high risk of CRC, but it did not address outcome or frequency of testing in those at high risk.

Some studies have assessed how well virtual colonoscopy can detect colorectal polyps without a laxative prep. The question is of great importance for implementation because the laxative prep required by both conventional colonoscopy and virtual colonoscopy is considered a great disadvantage by patients. By tagging feces with iodinated contrast material ingested for several days before the procedure, investigators in one study were able to detect lesions larger than 8 mm with 95% sensitivity and 92% specificity.[60] The particular tagging material used in this study caused about 10% of patients to become nauseated; however, other materials are being assessed.

Another study [61] used a low-fiber diet, orally ingested contrast, and "electronic cleansing," a process that subtracts tagged feces. CTC identified 91% of adenomas 10 mm or larger, but it detected fewer (70%) lesions of at least 8 mm. Patients who received both CTC and OC preferred CTC to OC (290 vs. 175). This study shows that CTC without a laxative prep detects small 1-cm lesions with high sensitivity and is acceptable to patients. Long-term utilization of CTC will depend on several issues, including the frequency of follow-up exams that would be needed to detect smaller lesions that were undetected and may grow over time.

Extracolonic abnormalities are commonly detected with CTC. Fifteen percent of patients in an Australian series of 100 patients, referred for colonography because of symptoms or family history, were found to have extracolonic findings, and 11% of the patients needed further medical workups for renal, splenic, uterine, liver, and gallbladder abnormalities.[62] In another study, 59% of 111 symptomatic patients referred for clinical colonoscopy in a Swedish hospital between June 1998 and September 1999 were found to have moderate or major extracolonic conditions on CTC. CTC was

performed immediately before a colonoscopy, and these findings required further evaluation. The extent to which follow-up of these incidental findings benefited patients is unknown.[63]

Sixty-nine percent of 681 asymptomatic patients in Minnesota had extracolonic findings, 10% of which were deemed highly important by the investigators; these patients required further medical workup. Suspected abnormalities involved kidney (34), chest (22), liver (8), ovary (6), renal or splenic arteries (4), retroperitoneum (3), and pancreas (1);[64] however, the extent to which these findings contribute to benefits or harms is uncertain. Two other studies, one large (N = 2,195) and one small (n = 136) examined the moderate or high importance of extracolonic findings from CTC. The larger study [65] found that 8.6% of patients had an extracolonic finding of at least moderate importance, while 24% of patients in the smaller study [66] required some evaluation for an extracolonic finding. The larger study found nine cancers from these evaluations, at a partial cost (they did not include all costs) of $98.56 per patient initially screened. The smaller study found no important lesions from evaluation, at a cost of $248 per person screened. Both of these estimates of cost are higher than previous studies have found. The extent to which any patients benefited from the detection of extracolonic findings is not clear. Because both studies were conducted in academic medical centers, the generalizability to other settings is also not clear. Neither of these studies examined the effect of extracolonic findings on patient anxiety and psychological function.

Technical improvements involving both the interpretation methodology, such as three-dimensional (3-D) imaging, and bowel preparation are under study in many centers. While specificity for detection of polyps is homogeneously high in many studies, sensitivity can vary widely. These variations are attributable to a number of factors including characteristics of the CT scanner and detector, width of collimation, mode of imaging (two dimensional [2-D] vs. 3-D and/or **fly-through**), and variability in the expertise of radiologists.[67]

Digital Rectal Examination

A case-control study reported that routine digital rectal examination was not associated with any statistically significant reduction in mortality from distal rectal cancer.[68]

Detection of DNA Mutations in the Stool

The molecular genetic changes that are associated with the development of colorectal adenomas and carcinoma have been well characterized.[69] Advanced techniques have been developed to detect several of these gene mutations that shed into the stool.[70-73] Stool DNA testing was recently assessed in a prospective study of asymptomatic individuals who received colonoscopy, three-card FOBT (Hemoccult II), and stool DNA testing based on a panel of markers assessing 21 mutations. Conducted in a blinded way with prestated hypotheses and analyses, the study found that among 4,404 patients, the DNA panel had a sensitivity for CRC of 51.6% (for all stages of CRC) versus 12.9% for Hemoccult II, while the false-positive rates were 5.6% and 4.8%, respectively.[74,75]

A next-generation multitargeted stool test combined methylation markers for *NDRG4* and *BMP3*, several *KRAS* mutations, and a human hemoglobin immunoassay. The markers, each quantitated separately, were combined using an algorithm in a prespecified multivariable analysis. In the DeeP-C trial, the assay's sensitivity and specificity were compared with a commercial FIT test (OC FIT-CHEK Polymedco), using colonoscopy as the gold standard. Among 12,776 participants aged 50 to 84 years (weighted toward >65 years) who underwent colonoscopy screening and were enrolled at 90 sites

across the United States and Canada between 2011 and 2012, 9,989 had fully evaluable results. There were 65 CRC and 757 advanced adenomas or sessile serrated polyps 1 cm or greater. The sensitivity for CRC was 92.3% (60 of 65 CRC) for the multitargeted test and 73.8% for FIT. Sensitivity for advanced lesions was 42.4% for the multitargeted test and 23.8% for FIT. Sensitivity for high-grade dysplasia was 69.2% for the multitarget test and 46.2% for FIT. Sensitivity for serrated sessile polyps 1 cm or greater was 42.4% for the multitargeted test and 5.1% for FIT. Specificities were 86.6% for the multitargeted test and 94.9% for FIT, using nonadvanced or negative colonoscopy results, and were 89.8% and 96.4% for totally negative colonoscopy results. A receiver operating characteristic (ROC) analysis showed that the multitargeted test has higher sensitivity than FIT alone, even when the FIT **cutoff** is reduced to try to increase sensitivity. A limitation is that there were no data about performance of repeated testing over time and what may be an appropriate testing interval.[76]

A newer version of the multitargeted stool DNA (mt-sDNA) test was recently developed. This test incorporates a novel molecular marker panel that includes methylated DNA markers of four genes—*LASS4*, *LRRC4*, *PPP2R5C*, and *ZDHHC1*—while retaining the fecal hemoglobin marker. In the BLUE-C trial, which was structured similarly to the DeeP-C trial, the investigators compared the sensitivity and specificity of the newer version of the mt-sDNA test with FIT (OC FIT-CHEK Polymedco), using colonoscopy as the gold standard for detecting stage I, II, and III CRC and advanced precancerous lesions in average-risk individuals older than 40 years.[77]

- Between November 2019 and January 2023, 20,176 participants were enrolled at 186 sites and underwent both colonoscopy and stool tests. The mean age was 63 years; 53% of participants were female, 60% were White individuals, 5.2% had a family history of CRC in a first-degree relative, and 13.4% had a positive next-generation mt-sDNA test. Among those enrolled, 0.5% (98/20,176) had CRC, and 10.6% (2,144/20,176) had advanced precancerous lesions. Among individuals with CRC, 84% (82/98) had stage I, II, or III CRC.
- The sensitivity for CRC was 93.9% (92/98) for the mt-sDNA test and 67.3% for FIT. According to the study, sensitivity did not vary substantially based on disease stage or location in the colon. The sensitivity for advanced precancerous lesions (large adenomas, large sessile serrated polyps, villous adenomas, or adenomas with high-grade dysplasia or carcinoma *in situ*) was 43.4% (931/2,144) for the mt-sDNA test and 23.3% for FIT. However, sensitivity rose to 74.6% (85/114) for the mt-sDNA test and to 47.4% for FIT when limited to lesions with high-grade dysplasia. Approximately 7% of participants had a false-positive test, defined as a positive stool DNA test but no adenomas, advanced precancerous lesions, or CRC were found by colonoscopy. Specificities were 92.7% for the mt-sDNA test and 95.7% for FIT, using nonadvanced or negative colonoscopy results, and 93.4% for the mt-sDNA test and 96.0% for FIT using negative colonoscopy results. The area under the ROC curve analysis also showed that the sensitivity for CRC and advanced neoplasia was greater for the mt-sDNA test compared with FIT alone.
- The study was limited by the high proportion of enrolled participants (20,176) whose samples could not be evaluated according to the protocol. This was due in part to the conduct of the study during the coronavirus disease pandemic.

Overall, the multitargeted test was more sensitive than FIT for both CRC and advanced precancerous lesions, but the test was less specific.[76,77]

Cell-Free DNA (cfDNA) Blood Test

A cfDNA blood test was developed for the detection of CRC. This test analyzes plasma cfDNA to identify aberrant DNA-methylation status, abnormal DNA-fragmentation patterns, and the presence or absence of somatic pathogenic variants in the *APC* and *KRAS* genes. In the ECLIPSE trial, researchers conducted a prospective multicenter study at 265 primary care sites and endoscopy centers across the United States.[78] The trial aimed to evaluate the performance of the cfDNA blood-based test in detecting asymptomatic and early-stage CRC in a screening-relevant population.

- Between October 2019 and September 2022, 22,877 participants were enrolled in the study. Among those enrolled, 0.3% (65/22,877) had CRC, and 4.8% (1,116/22,877) had advanced precancerous lesions. The clinical validation cohort included 10,258 participants, 7,861 of whom met all inclusion and exclusion criteria, had complete colonoscopies, and had evaluable cfDNA blood-based tests. This final study cohort had a mean age of 60 years (range, 45–84 years); 54% were female, and 79% were White individuals. In this cohort, 11.4% had a positive cfDNA blood-based test.
- The sensitivity of the cfDNA blood-based test for CRC was 83.1% (54/65) for the participants with CRC detected by colonoscopy. This means that a total of 83.1% of these participants had a positive cfDNA test and 16.9% had a negative test. Sensitivity for stage I, II, or III CRC was 87.5% (42/48), and sensitivity for advanced precancerous lesions was 13.2% (147/1,116). The specificity was 89.6% using nonadvanced adenomas, non-neoplastic findings, and negative colonoscopy results.

Overall, the study team demonstrated the feasibility of using plasma cfDNA to screen for CRC. However, the relatively low sensitivity for detecting advanced precancerous lesions presents a limitation. Currently, the cfDNA blood-based test is still awaiting approval by the U.S. Food and Drug Administration and is not covered by Medicare.[78]

Adherence to Screening

Benefit from CRC screening can only occur if eligible people are screened. There have been problems with screening adherence, particularly for low-income and uninsured people. There are also concerns that some people may be less likely to adhere to screening with a colonoscopy than with fecal tests. One well-conducted RCT found that, among an uninsured population, mailed FIT-kit outreach and follow-up reminder phone calls resulted in an adherence rate of 40.7%. Mailed colonoscopy invitations and follow-up phone reminders resulted in a 24.6% adherence rate. The usual-care adherence rate in this trial was 12.1%.[79]

Tailoring Screening to Risk

Benefit of screening might be improved by tailoring the recommended screening test to a person's degree of CRC risk. For example, if a subgroup of young women were to have a substantially lower risk of proximal neoplasms, then recommending sigmoidoscopy instead of colonoscopy might lead to higher compliance (the U.S. Preventive Services Task Force recommends both procedures without preference, as part of a program of screening those at average risk).

In a study to identify an average-risk group who had a higher versus lower risk of advanced neoplasia (CRC and advanced adenomas) anywhere in the colon, 2,993 individuals having a screening colonoscopy were stratified by age, sex, waist circumference, smoking, and family history (those in high-risk family categories, e.g., Lynch syndrome or adenomatous polyposis coli, were excluded). In a classification system derived in a training set, the risks of advanced neoplasm in four groups were:

1.92%, 4.88%, 9.93%, and 24%. In the two lowest-risk groups, sigmoidoscopy would have detected 51 (73%) of 70 advanced neoplasms. In the independent validation set, results were similar. Whether this system increases overall compliance has yet to be determined.[80]

A similar stratification system based on age, sex, smoking, and family history—and combined with FIT—was tested in Asia to determine whether use of the stratification system plus FIT could detect which people needed colonoscopy. If either the stratification system or FIT was positive, a person was recommended for colonoscopy. Using this strategy, 95% of those with CRC were correctly told to have colonoscopy.[81]

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Evidence of Harms

Potential harms are associated with the modalities used to screen for colorectal cancer (CRC), some of which have sufficient evidence and some that do not.

Overview

The tables for each screening test below show the magnitude of burden for several categories of harms encountered along the screening cascade. The magnitude of harms is a combination of the frequency and severity of harm, as perceived by the patient.

Harms are defined broadly as any negative effect on individuals or populations resulting from being involved in the screening process (cascade) compared with not screening. Potential harms are organized according to the type of harm (e.g., physical, psychological, and hassle/opportunity costs) and when they occur in the screening cascade (e.g., screening test/workup; screening test/workup results; surveillance and surveillance results; and early treatment and overtreatment). For example, potential harms of screening colonoscopy include harms of the screening test itself (e.g., perforation and bleeding), results of the screening test (e.g., anxiety from an abnormal result), surveillance (e.g., harms of more frequent colonoscopies), and treatment (e.g., earlier treatment or overtreatment). Harms are also associated with the workup for other colorectal cancer screening tests (e.g., colonoscopy for positive fecal occult blood test [FOBT]). A recent study of three major hospitals found that 71% of endoscopes tested positive for bacteria after cleaning and high-level disinfection of the scopes. This raises concern for endoscopy-associated pathogen transmission and patient safety, although no patients were involved in the study and the implications for patients are unknown.[1] For all aspects of participating in the screening cascade, there are time/effort and opportunity costs (nonfinancial harms) for the patient. The following tables do not include any financial harms to the patient/family, nor any psychological harm from anticipation of future financial costs related to screening.

Table 4. Colonoscopy

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Screening Test/Workup	Average 0.3% complications requiring hospitalization or resulting in death, higher with polypectomy and in older patients (fair evidence)	Percentage of people who suffer psychological distress on consideration of having colonoscopy; severity and duration (insufficient evidence)	About 38 hours (median) required for preparation, procedure, sedation (one study, fair evidence) [2]
	Discomfort of preparation and procedure; adverse effects of preparation (insufficient evidence to determine magnitude and frequency)		
	Complications from sedation during procedure (insufficient evidence to determine magnitude and frequency)		
Screening Test/Workup Results	Increased risk of suicide and cardiovascular mortality soon after diagnosis (insufficient evidence)	Percentage of people who suffer psychological distress after receiving positive screening and/or pathological results; severity and duration (insufficient evidence)	Time and effort required to receive and understand screening test or workup results, including extra physician visits for positive tests (insufficient evidence)
Surveillance/Results	More frequent colonoscopy	Percentage of people who suffer psychological distress after receiving positive screening and/or pathological results; severity and duration (insufficient evidence)	Time and effort required to undergo colonoscopy (median, 38 hours, see above)
			Time and effort required to receive and understand surveillance results (insufficient evidence)

CRC = colorectal cancer.

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Treatment (Early Treatment and Overtreatment)	Overdiagnosis and overtreatment of precursor polyps or earlier treatment of CRC (may or may not receive benefit from earlier treatment) (insufficient evidence)	Percentage of people who suffer psychological distress after undergoing overtreatment or earlier treatment without benefit; severity and duration (insufficient evidence)	Time and effort required to receive overtreatment or earlier treatment without benefit (insufficient evidence)

CRC = colorectal cancer.

Table 5. FOBT/FIT, Other Stool-Based Tests (Including Fecal DNA)

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Screening Test	None (no evidence)	Percentage of people who suffer psychological distress on consideration of having CRC screening; severity and duration (insufficient evidence)	Time and effort required to change diet (if required), collect samples, and return to appropriate facility (insufficient evidence)
Screening Test Results	N/A	Percentage of people who suffer psychological distress after receiving positive screening results; severity and duration (insufficient evidence)	Time and effort required to receive and understand screening test results, including extra physician visits or communication for positive tests (insufficient evidence)
Workup[a]	See colonoscopy	See colonoscopy	See colonoscopy

CRC = colorectal cancer; FIT= immunochemical fecal occult blood test; FOBT= fecal occult blood test; N/A = not applicable.

[a]Workup test is colonoscopy. Descriptions of the associated harms can be found in the colonoscopy section (for more information, see the Colonoscopy section in Evidence of Harms).

[b]Treatment harms will be the same for all screening tests.

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Workup Results	N/A	See colonoscopy	See colonoscopy
Surveillance/Results	See colonoscopy	See colonoscopy	See colonoscopy
Treatment (Early Treatment and Overtreatment)[b]	See colonoscopy	See colonoscopy	See colonoscopy

CRC = colorectal cancer; FIT= immunochemical fecal occult blood test; FOBT= fecal occult blood test; N/A = not applicable.

[a]Workup test is colonoscopy. Descriptions of the associated harms can be found in the colonoscopy section (for more information, see the Colonoscopy section in Evidence of Harms).

[b]Treatment harms will be the same for all screening tests.

Table 6. Flexible Sigmoidoscopy

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Screening Test	Average serious complications for 0.03% of patients (fair evidence) [3]	Percentage of people who suffer psychological distress on consideration of having colonoscopy; severity and duration (insufficient evidence)	Time and effort required to perform preparation, travel to and attend screening, return to usual activities (insufficient evidence)
Screening Test Results	N/A	See colonoscopy	See colonoscopy
Workup[a]	See colonoscopy	See colonoscopy	See colonoscopy

N/A = not applicable.

[a]Workup test is colonoscopy. Descriptions of the associated harms can be found in the colonoscopy section (for more information, see the Colonoscopy section in Evidence of Harms).

[b]Treatment harms will be the same for all screening tests.

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Surveillance/Results	N/A	See colonoscopy	See colonoscopy
Treatment (Early Treatment and Overtreatment)[b]	See colonoscopy	See colonoscopy	See colonoscopy

N/A = not applicable.

[a]Workup test is colonoscopy. Descriptions of the associated harms can be found in the colonoscopy section (for more information, see the Colonoscopy section in Evidence of Harms).

[b]Treatment harms will be the same for all screening tests.

Table 7. Computed Tomography Colonography

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Screening Test/Workup	Discomfort of preparation and procedure; radiation exposure (insufficient evidence)	Percentage of people who suffer psychological distress on consideration of screening; severity and duration (insufficient evidence)	Time required for preparation, procedure (exact time and effort uncertain) (insufficient evidence)
Screening Test/Workup Results	Increased risk of suicide and cardiovascular mortality soon after diagnosis (insufficient evidence)	Percentage of people who suffer psychological distress after receiving positive screening and/or pathological results; severity and duration (insufficient evidence)	Time and effort required to receive and understand screening test or workup results, including extra physician visits for positive tests (insufficient evidence)
	Incidental extra-colonic findings [3]		

CRC = colorectal cancer.

Stage of Screening Cascade			
	Physical	**Psychological**	**Time/Effort, Opportunity**
Surveillance/Results	More frequent colonoscopy	Percentage of people who suffer psychological distress after receiving positive screening and/or pathological results; severity and duration (insufficient evidence)	Time and effort required to undergo colonoscopy (mean, 38 hours, see Table 4)
			Time and effort required to receive and understand surveillance results (insufficient evidence)
Treatment (Early Treatment and Overtreatment)	Overdiagnosis and overtreatment of precursor polyps or earlier treatment of CRC (may or may not receive benefit from earlier treatment) (insufficient evidence)	Percentage of people who suffer psychological distress undergoing overtreatment or earlier treatment without benefit; severity and duration (insufficient evidence)	Time and effort required to receive overtreatment or earlier treatment without benefit (insufficient evidence)

CRC = colorectal cancer.

Evidence Summary

Colonoscopy

The potential physical harms of colonoscopy include adverse effects from the preparation and adverse effects from the procedure (e.g., colonic perforation, bleeding, effects of sedation).[4-6] A systematic review of 60 studies that assessed complications of colonoscopy screening in asymptomatic patients found infrequent serious morbidity, which comprised major bleeding (0.8/1,000 procedures; 95% confidence interval [CI], 0.18–1.63) and perforation (0.07/1,000 procedures; 95% CI, 0.006–0.17), and only minor and short-lasting psychological harms.[7] These complications can be serious, requiring hospitalization. Colonic perforation and serious bleeding occur more often with biopsy or polypectomy, with an overall average of three to five serious complications per 1,000 procedures. The physical harm of discomfort during the procedure has been reduced by sedation, although sedation has its own potential for physical harm (magnitude and severity uncertain because of insufficient evidence).

Physical harms are also associated with further steps in the screening cascade. These harms include diagnosis of CRC (some large ecological studies have shown an increase in suicide soon after diagnosis) and overdiagnosis/overtreatment due to treating lesions that would never have caused the patient important problems (evidence insufficient to determine magnitude and severity).

The potential psychological harms of colonoscopy include anticipation of the procedure and anxiety while awaiting the results of biopsy reports. For people with polyps, there may be increased distress in considering oneself at increased risk of CRC (evidence insufficient). For people newly diagnosed with CRC, many will experience increased anxiety and depression for at least 6 months, as prognosis and treatment are discussed (evidence insufficient).

The harm of time/effort and opportunity costs involved in moving through the demands of the screening cascade are present throughout the process (evidence insufficient to determine frequency and severity).

FOBT/immunochemical FOBT (FIT)

The potential physical harms of fecal-based testing include the same harms as for colonoscopy for people with a positive test who have been referred for diagnostic colonoscopy.

The potential psychological harms, as well as time/effort and opportunity costs are also similar to the description above for colonoscopy (for more information, see the Colonoscopy section in Evidence of Harms).[8] These harms are associated with moving through the screening cascade, regardless of the initial screening test. Although it is highly likely that these psychological harms, plus time/effort and opportunity costs, do occur, the exact frequency and severity of these harms are uncertain because of insufficient evidence.

Sigmoidoscopy

The potential physical harms of sigmoidoscopy are considerably less than those of colonoscopy, with a less intensive preparation. Serious procedural complications occur in approximately three in 10,000 sigmoidoscopies, compared with in three in 1,000 colonoscopies.[3] There is usually no sedation with sigmoidoscopy, which lowers the potential for complications even further.

The potential psychological harms of sigmoidoscopy screening, as well as the time/effort and opportunity costs of screening, are the same as given above for other screening strategies.

Computed tomography colonography (CTC)

The potential physical harms due directly to CTC are less than either colonoscopy or sigmoidoscopy, with rare procedural complications.[3] However, CTC does involve repeated radiation exposure, with uncertain associated harms, and it also detects a number of extra-colonic incidental findings.[9-13] Incidental findings have been detected in 40% to 98% of CTCs, with a variable number of these considered significant enough to proceed with further diagnostic testing. As there is little evidence that early detection of any of these findings could improve health outcomes for patients, these findings may be considered as harms until proven otherwise.

The potential psychological harms or time/effort and opportunity costs for CTC are similar to the descriptions above for patients moving through the screening cascade (evidence insufficient to determine frequency and severity).

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Latest Updates to This Summary (04/10/2025)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Significance

Updated statistics with estimated new cases and deaths for 2025 (cited Bray et al. as reference 1 and American Cancer Society as reference 2). Also revised text to state that between 2012 and 2021, incidence rates increased by 2.4% per year in individuals younger than 55 years and by 0.4% per year in individuals aged 50 to 64 years.

This summary is written and maintained by the PDQ Screening and Prevention Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® Cancer Information for Health Professionals pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about colorectal cancer screening. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Screening and Prevention Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

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- be cited with text, or
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Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

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