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Screening for Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force in updating its recommendation on screening for colorectal cancer (CRC). Our review addresses the effectiveness of CRC screening, the test accuracy of CRC screening modalities, and the harms of CRC screening.

Data Sources: We updated our prior systematic review and searched MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials to locate relevant studies for all key questions, from the end of our prior review through December 4, 2019.

Study Selection: We reviewed 11,306 newly identified abstracts and 502 articles against the specified inclusion criteria. We carried an additional 126 studies forward from our prior review. Eligible studies included English-language studies conducted in asymptomatic screening populations age 40 years and older at average risk or unselected for risk factors. We evaluated direct visualization screening tests and currently available stool-, serum-, and urine-based screening tests. For effectiveness, we included trials or prospective cohort studies with contemporaneous controls; for test accuracy, we included diagnostic accuracy studies using a colonoscopy or cancer registry reference standard; and for harms, we included trials or observational studies reporting serious adverse events.

Data Analysis: We conducted dual independent critical appraisal of all included studies and extracted all important study details and outcomes from fair- or good-quality studies. We narratively synthesized results by key question and type of screening test. When appropriate, we used random-effects meta-analyses. We graded the overall strength of evidence as high, moderate, low or insufficient based on criteria adapted from the EPC Program.

Results:
Effectiveness. We included 33 unique fair- to good-quality studies that assessed the effectiveness or comparative effectiveness of screening on CRC incidence and mortality. Based on four RCTs (n=458,002), a one- or two-time FS was consistently associated with a decrease in CRC incidence (IRR 0.78 (95% CI, 0.74 to 0.83) and CRC-specific mortality (IRR 0.74 (95% CI, 0.68 to 0.80) compared with no screening at 11 to 17 years of followup. Based on five RCTs (n=419,966), biennial screening with Hemoccult II was associated with a reduction of CRC-specific mortality compared with no screening after two to nine rounds of screening at 11 to 30 years of followup (RR 0.91 [95% CI, 0.84 to 0.98] at 19.5 years; RR 0.78 [95% CI, 0.65 to 0.93] at 30 years). Two prospective observational studies evaluated screening colonoscopy on CRC incidence or mortality. In one study (n=88,902), after 24 years of followup, the CRC-specific mortality rate was lower in people who self-reported at least one screening colonoscopy compared with those who had never had a screening colonoscopy (adjusted HR, 0.32 [95% CI, 0.24 to 0.45]). Results were no longer statistically significant after 5 years in people with a first-degree relative with CRC, as opposed to a sustained association beyond 5 years in people without a family history. Another study (n=348,025) with much shorter followup found that people ages 70 to 74 years who underwent a screening colonoscopy had a lower 8-year standardized risk for CRC (-0.42 percent; 95% CI, -0.24 to -0.63) than those who did not undergo the test. The magnitude of benefit was lower and no longer statistically significant for

people ages 75 to 79 years, and this study did not report any mortality outcomes. One prospective study (n=5,417,699) evaluating a national FIT screening program found that one to three rounds of screening with a biennial FIT were associated with lower CRC mortality than no screening (adj RR 0.90, 95% CI, 0.84, 0.95). While 3 Hemoccult II studies include adults under age 50 years, none of these studies conducted subgroup analyses in adults who initiated screening before age 50.

Although we included 21 studies comparing different screening tests in average-risk populations, most of the studies were not true comparative effectiveness studies. Because most of these studies are limited to the evaluation of a single round of screening, report a low CRC yield (number of cancers detected), and do not report interval cancers, they do not provide robust direct evidence of comparative benefit on CRC incidence or mortality outcomes. Several ongoing comparative effectiveness trials that are powered to detect a difference in CRC incidence and/or mortality have not yet reported outcomes.

Test accuracy. We included 59 fair- to good-quality studies evaluating the one-time test accuracy of various screening tests compared to an adequate reference standard.

Direct visualization tests. Only 4 studies (n=4,821) reported the test accuracy of colonoscopy generalizable to community practice. The sensitivity to detect CRC was imprecise because of the limited number of cancers in these studies; the per-person sensitivity ranged from 0.18 to 1.0 (95% CI range 0.01, 1.0). For the detection of adenomas ≥10mm, the sensitivity ranged from 0.89 to 0.95 (95% CI range, 0.70 to 0.99) and the specificity from one study was 0.89 (95% CI, 0.86 to 0.91). For the detection of adenomas ≥6mm, the sensitivity ranged from 0.75 to 0.93 (95% CI range, 0.63 to 0.96) and the specificity was 0.94 (95% CI, 0.92 to 0.96) from one study. Based on 7 studies (n=5,328) of computed tomographic colonography (CTC) with bowel preparation, the per-person sensitivity to detect CRC was again imprecise and the per-person sensitivity ranged from 0.86 to 1.0 (95% CI range, 0.21 to 1.0). For the detection of adenomas ≥10mm, the sensitivity was 0.89 (95% CI, 0.83 to 0.96) and the specificity was 0.94 (95% CI, 0.89 to 1.0). For the detection of adenomas ≥6mm, the sensitivity was 0.86 (95% CI, 0.78 to 0.95) and the specificity was 0.88 (95% CI, 0.83 to 0.95). Based on two studies (n=920) evaluating screening capsule endoscopy, the sensitivity to detect adenomas 10 mm or larger ranged from 0.92 to 1.0 (95% CI range, 0.70 to 1.0) and specificity ranged from 0.95 to 0.98 (95% CI range, 0.93 to 0.99). For adenomas 6 mm or larger, one study reported sensitivity of 0.91 (95% CI, 0.85 to 0.95) and specificity of 0.83 (95% CI, 0.80 to 0.86). Both studies had a high proportion of incomplete exams.

Stool tests. Based on two studies (n=3,503) of Hemoccult Sensa using colonoscopy as a reference standard, sensitivity to detect CRC ranged from 0.50 to 0.75 (95% CI range, 0.09 to 1.0) and specificity ranged from 0.96 to 0.98 (95% CI range, 0.95 to 0.99). Hemoccult Sensa was not sensitive to detect AA. Based on 13 studies (n=44,597) of OC-Sensor family of FITs using colonoscopy as a reference standard, the sensitivity to detect CRC was 0.74 (95% CI, 0.64 to 0.83; I^2=31.6%) and the specificity was 0.94 (95% CI, 0.93 to 0.96; I^2=96.6%). For the detection of AA, the sensitivity was 0.23 (95% CI, 0.20 to 0.25; I^2=47.4%) and the specificity was specificity = 0.96 (95% CI, 0.95 to 0.97; I^2=94.8%). OC-Light (k=4, n=32,424) performed similarly to the OC-Sensor family of FITs. Other FITs were not evaluated for CRC detection in

more than a single study using a colonoscopy reference standard. Four studies evaluating FIT test performance found no differences in test performance for persons age <50 years compared with older aged adults. Based on 4 studies (n=12,424) of Cologuard (sDNA-FIT) using colonoscopy as a reference standard, the pooled sensitivity to detect CRC was 0.93 (95% CI, 0.87 to 1.0; I^2=0%) and the pooled specificity was 0.85 (95% CI, 0.84 to 0.86; I^2=37.7%). For the detection of AA, the pooled sensitivity was 0.43 (95% CI, 0.40 to 0.46; I^2=0%) and the pooled specificity was 0.89 (95% CI, 0.86 to 0.92; I^2=87.8%).

Serum test. Based on one nested case-control study (n=6845), the sensitivity of Epi proColon to detect CRC was 0.68 (95% CI, 0.53 to 0.80), and the specificity was 0.79 (95% CI, 0.77 to 0.81). For the detection of AA, the sensitivity was 0.22 (95% CI, 0.18 to 0.24), and the specificity was 0.79 (95% CI, 0.76 to 0.82).

Urine test. Based on one small study (n=228) in average and high-risk persons, the sensitivity of PolypDx to detect AA was 0.22 (95% CI, 0.18 to 0.24), and the specificity was 0.79 (95% CI, 0.76 to 0.82).

Harms. We included 131 fair- to good-quality studies for the harms of CRC screening. Serious adverse events from a single screening colonoscopy or colonoscopy in asymptomatic persons are relatively uncommon, with a pooled estimate of 3.1 perforations (k=23) (95% CI, 2.3 to 4.0) and 14.6 major bleeds (k=22) (95% CI, 9.4 to 19.9) per 10,000 procedures. Serious adverse events from a single screening FS are even less common, with a pooled estimate of 0.2 perforations (k=11) (95% CI, 0.1 to 0.4) and 0.5 major bleeds (k=10) (95% CI, 0 to 1.3) per 10,000 procedures. Complication rates are higher in colonoscopy following abnormal stool tests or FS. Nineteen studies found increasing rates of serious adverse events with increasing age, including perforation and bleeding. The pooled estimate of perforations for a single screening CTC (k=7) was 1.3 per 10,000 (95% CI, 0 to 2.9). CTC may also have harms resultant from exposure to low-dose ionizing radiation (range, 0.8 to 5.3 mSv per examination). Approximately 1.3 to 11.4 percent of examinations have extracolonic findings that are potentially important requiring diagnostic followup.

Limitations: Studies comparing different screening modalities to date do not provide evidence of the relative benefit of different screening programs on CRC incidence or mortality. FIT test accuracy is specific to each FIT or family of FITs. Serum testing is promising but to date has only one prospective study evaluating its screening test accuracy. Overall, we have limited data of effectiveness, test accuracy, and harms by age under 50 years, race/ethnicity, or family history. Few studies of endoscopy harms report rates of adverse events in nonendoscopy comparator arms. It is unclear if detecting extracolonic findings represents a true overall benefit or harm.

Conclusions: Since the 2016 USPSTF recommendation, there is more evidence on effectiveness and test accuracy of newer stool tests (FIT and sDNA-FIT), and the test accuracy of a serum test FDA approved for use in persons declining colonoscopy, FS, gFOBT, or FIT. We also identified a new metabolomic urine test with only one small study with test accuracy data, thus far limited to detection of adenomas. We also have more data on colonoscopy harms demonstrating higher estimates of major bleeding than previously described in 2016. Currently used screening

modalities, including colonoscopy, FS, CTC, and various high-sensitivity stool-based tests, and a serum-based test each have different levels of evidence to support their use, different test performance to detect cancer and precursor lesions, and different risks of harms. Recommendations regarding which screening tests to use, or if there is a hierarchy of preferred screening tests, will depend on the decisionmaker's criteria for sufficiency of evidence and weighing the net benefit.

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Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update the 2016 screening for colorectal cancer recommendation.[1]

Condition Definition

Colorectal cancer (CRC), also called colorectal adenocarcinoma, is a malignant tumor that develops within the walls of the large intestine, which comprises the following segments: the cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum. CRC does not include tumors in the tissues of the anus or the small intestine. Adenomas are benign epithelial polyps that can progress to adenocarcinomas (**Table 1**). Adenomas can be flat, sessile, or pedunculated. Adenomas can have different degrees of dysplasia or different histologic characteristics (e.g., tubular, tubulovillous, villous). Advanced adenomas (AAs) are benign tumors with an increased likelihood to progress to CRC. Sessile serrated lesions (SSLs)—also referred to as sessile serrated adenomas or polyps—also have an increased risk of progression to CRC.[2] However, SSL are not usually included in the definition of an advanced adenoma (AA). Although there is some variation in the exact definition of AAs, they generally refer to adenomas 1 cm or larger, with villous components (tubulovillous or villous), or with high-grade or severe dysplasia. The term advanced neoplasia (AN), on the other hand, refers to a composite outcome of AAs and all stages of CRC.

Prevalence and Burden

CRC causes significant morbidity and mortality in the United States: Among all cancers, it is third in incidence and cause of cancer death for both men and women.[3] However, incidence rates have been declining for the past 20 years. According to data from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program, the age-adjusted incidence of CRC has fallen from 53.2 new cases per 100,000 people in 1995 to 36.5 new cases per 100,000 people in 2015.[4] Approximately 94 percent of CRC diagnoses occur in adults older than age 45 years.[4] However, cohort trends indicate that CRC incidence is decreasing only for those age 55 years and older, and increasing among those younger than 55 years.[5] The incidence of CRC has increased by 1 to 2 percent annually since the mid-1980s in adults ages 20–39, and by 0.5 to 1.3 percent annually since the mid-1990s in adults ages 40–54.[6] As a result, the incidence of CRC in persons age 45 years in 2011 was comparable to the incidence in persons age 50 years in 1992 prior to widespread screening (24.0 and 25.6 cases per 100,000 persons respectively), although the incidence of CRC in persons age 45 have declined somewhat since 2011 (20.8 cases per 100,000 persons in 2016).[7]

The lifetime risk of acquiring CRC in the United States is about 4.2 percent, with an age-adjusted death rate of 14.5 deaths per 100,000 people. Survival largely depends on the stage of cancer at the time of diagnosis. Patients with localized disease at diagnosis have a 5-year survival rate of 90 percent. Five-year survival rates drop to 71 percent, however, for those diagnosed with regionalized disease (cancer spread to regional lymph nodes). These rates decrease dramatically—to 14 percent—for those with distantly metastasized disease.[4]

Increasing age, male sex, and Black race are all associated with an increased incidence of CRC (**Figure 1**). The median age at diagnosis is 67 years, and nearly half of all new cases are diagnosed in people ages 65–84 years.[4] Based on data from the National Cancer Database (NCDB), the trend of increasing CRC diagnoses in adults under 50 years from 2004–2015 appeared to be similar for men and women; increases in CRC diagnoses in adults under 50 years were observed in white and Latino but not Black or Asian people.[8] Black and Latino people have higher proportions of CRC diagnosed before age 50 years (14.0 and 18.3 percent respectively) compared to white people (11.0 percent). Overall Black men and women have the highest incidence of CRC compared with other racial/ethnic subgroups. This is troubling given that Black men and women also have a disproportionately high mortality from CRC.[3, 9, 10] This health disparity has increased in the past 20 years, illustrated by the fact that CRC incidence and mortality rates have decreased more among white people than Black people.[3, 11, 12] The overall 5-year age-adjusted CRC-related death rate (2014-2018) is notably higher in Black, as well as American Indian and Alaskan Native, people as compared to Latino and Asian Pacific Islanders people: 22.5 deaths per 100,000 Black men and 14.8 deaths per 100,000 Black women, 18.4 deaths per 100,000 American Indian and Alaskan Native men and 12.4 deaths per 100,000 American Indian and Alaskan native women, 14.0 deaths per 100,000 Latino men and 8.6 deaths per 100,000 Latina women, and 11.2 per 100,000 Asian or Pacific Islander men and 7.9 per 100,000 Asian or Pacific Islander women.[4]

Proximal vs. Distal Cancers

The distal large intestine can be defined as distal to the splenic flexure (including the descending colon, sigmoid colon, and rectum). The proximal large intestine or colon is generally defined as proximal to the splenic flexure (including the cecum, ascending and transverse colon).

CRC incidence differs by tumor location in the colon.[12-14] Based on data from the NCI's SEER Program and the North American Association of Central Cancer Registries (NAACCR) from 2009–2013, the age-adjusted incidence of cancer is 20.5 cases per 100,000 people in the distal colon/rectum and 16.9 cases per 100,000 people in the proximal colon.[15] CRC prognosis and mortality also varies by anatomic location. Analyses of SEER data have shown a higher late- to early-stage incidence for proximal compared to distal colon/rectum cancer.[16] Proximal cancers have lower 5-year survival (65% vs. 69%) and greater mortality compared with distal cancers.[15] Colonoscopy may also be less effective in reducing proximal compared to distal CRC incidence and mortality.[17-21] The reason for this finding remains unclear and we do not know if this discrepancy is due to inadequate quality/implementation of colonoscopy (e.g., failure to reach the cecum, poor bowel preparation) and/or to biologic differences in the types of lesions and natural history of lesions in the proximal versus distal large intestine. It is well-established that there are physiological differences between the proximal and distal large intestine as well as differences in proximal and distal CRC.[22] Cancers in the proximal and distal colon appear to arise from different molecular pathways, and these molecular differences may explain differences in both morphology and natural history.[22, 23 16, 24, 25]

The distribution of CRC differs by age, sex, and race/ethnicity. The incidence of proximal cancers is higher with advancing age.[3] A 2019 systematic review of the anatomic distribution of CRC in younger adults found that approximately 75 percent of CRC diagnosed before age 50 are in the distal colon and rectum.[26] Based on data from the NAACCR from 2012-2016, proximal cancers are also more common in women than in men.[3] Despite this difference, men have higher rates of CRC (distal and proximal) incidence and mortality.[3] Based on SEER data, the overall decrease in incidence of distal cancers between 1980–1984 and 2000–2013 was greater among white people than Black people.[27] In addition, Black men and women appear to have a higher proportion of proximal cancers and lower 5-year survival rates for proximal cancers than other racial/ethnic groups.[28] Although poverty is a confounder for CRC incidence and survival, recent data suggest that socioeconomic status plays a more prominent role for distal colon and rectal cancers than proximal cancers in white, Black, and Asian and Pacific Islander people.[16, 29, 30]

Etiology and Natural History

CRC usually develops over a period of several years, with the cancer beginning as a precancerous lesion. Experts estimate that at least 95 percent of cases of CRC arise from preexisting adenomas.[31, 32] This hypothesis that CRC arises from an adenoma-carcinoma sequence initially came from observations of a greatly elevated CRC risk status in patients with hereditary polyposis syndromes[33-35] and from observational studies showing a reduction in CRC incidence after polypectomy.[36-43]

Colorectal adenomas are very common; a 2009 meta-analysis found that the pooled prevalence of adenomas was 30.2 percent (95% CI, 27 to 33) among people undergoing routine screening.[44] While adenomas can develop into cancers, most do not. Each adenoma's tendency toward net growth or regression, however, may vary by polyp size and histology, as well as by other characteristics such as patient age, tumor location, and number of lesions.[45, 46] In general, larger adenomas and those with greater dysplasia are more likely to progress to cancer.[47] SSLs, as opposed to other adenomas, may not initially have dysplasia but do have malignant potential.[48] These lesions are the major precursor lesion of serrated pathway cancers and are thought to represent 20 to 35 percent of CRC cases.[48] Overall, the rate of progression of adenoma to cancer is unknown, such that some lesions grow quickly and others very slowly.

While there is general agreement that the risk of in situ cancer, or progression to cancer, for polyps 10 mm or larger is sufficiently high as to require immediate removal, the necessity and benefit of removing smaller polyps is not clear.[49, 50] A recent review found that those with low-risk adenomas (small tubular adenomas with no high-grade dysplasia) had an increased risk of developing AAs compared to those with a normal colonoscopy, but a lower risk of developing CRC and of CRC mortality when compared to the general population.[51] Greater understanding of the natural history of small adenomas will influence choice and implementation of screening test as well as definitions of test positivity (e.g., referral, polypectomy, or surveillance criteria for endoscopy and computed tomographic colonography [CTC]). In addition, unnecessarily removing smaller polyps can increase the risk of harms, including bleeding and perforation. A systematic review by Hassan and colleagues assessed the distribution of AAs in average-risk screening populations according to polyp size and reported that the overall prevalence of AAs was 5.6 percent (95% CI, 5.3 to 5.9) in four studies (n=20,562). The prevalence of diminutive polyps (≤5 mm) was 27 percent, prevalence of small polyps (6–9 mm) was 9 percent, and prevalence of large polyps (≥10 mm) was 6 percent. Diminutive polyps (≤5 mm) accounted for 4.6 percent (95% confidence interval [CI], 3.4 to 5.8) of patients with AAs. Small polyps (6–9 mm) accounted for 7.9 percent (95% CI, 6.3 to 9.4) of patients with AAs. In contrast, large polyps (≥10 mm) accounted for 87.5 percent (95% CI, 86.0 to 89.4) of AAs.[52]

One large cohort study (n=22,006) of asymptomatic adults undergoing routine CRC screening with CTC demonstrated that 9 percent (1,982/22,006) of adults had small polyps (6–9 mm) at baseline. Of the 306 small polyps in 243 adults who were followed with CTC surveillance (mean surveillance interval 2.3 years), 22 percent (68/306) progressed (≥20% growth), 50 percent (153/306) were stable, and 28 percent (85/306) regressed (≥20% reduction). Histology was established in 43 percent of polyps (131/306) after final CTC. Ninety-one percent (21/23) of proven AAs compared to 37 percent (31/84) of proven nonadvanced adenomas progressed.

The prevalence of adenomas, as well as their tendency toward net growth, increases with aging and male sex.[45, 46, 53, 54] However, it is yet uncertain the role that race/ethnicity plays in the natural history of adenomas. A large cohort study among screening colonoscopy recipients through Kaiser Permanente Northern California (n=20,792) evaluated the prevalence of adenomas by age, sex, and race/ethnicity. It found that the prevalence of adenomas substantially increased with age and male sex, and also that proximal adenomas were more common in Black than white people, although the total prevalence of adenomas was similar.[53] A cross-sectional study[55] assessing data from the Clinical Outcomes Research Initiative (CORI) compared the prevalence of large polyps (<9 mm) in people undergoing screening colonoscopy (n=177,666). It found that men had a greater prevalence of large polyps compared with women, and Black women had a greater prevalence of large polyps than non-Black women and similarly aged men. However, a 2018 systematic review[56] found that among average-risk individuals undergoing colonoscopy (n=302,128), the prevalence of AAs did not differ significantly between Black (6.57%) and white (6.20%) participants, although a subgroup analysis of five studies that evaluated advanced proximal lesions demonstrated a higher prevalence of AAs in Black compared with white participants. In addition, CRC screening trials have generally found similar prevalence of adenomas and AAs in Black participants compared with white participants.[57, 58]

Risk Factors

Most cases of CRC are sporadic, with 75 percent developing in average-risk people, versus about 20 percent developing in people with some type of family history. The remainder of cases develop in people who have predisposing inflammatory bowel disease or a known inherited familial syndrome (defined by mutations in known high-risk cancer susceptibility genes), including familial adenomatous polyposis and Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer).[59-62] Family history of CRC that is not attributable to any known inherited syndromes is a well-established risk factor (**Appendix H**).[63] People with a family history of CRC are commonly cited as having an average 2- to 4-fold increase in risk of CRC compared with those who do not have a family history, but there is great heterogeneity in the published literature in how family history is defined (age of relative[s] with CRC, the number of relative[s] with CRC, and relationship to relative[s] with CRC).[64-66] As a result, the risk of developing CRC varies approximately 20-fold between people in the lowest quartile (average lifetime risk, 1.25%) and the highest quartile (average lifetime risk, 25% in people with an inherited familial syndrome).[67, 68]

Some modifiable risk factors, with varying levels of evidence, have also been linked to an increased or decreased risk of developing CRC. Most notably long-term smoking, unhealthy alcohol use, being overweight or having obesity, and having type 2 diabetes appear to increase the risk of developing CRC.[69-71]

Rationale and Current Clinical Practice

Because CRC has precursor lesions and survival largely depends on the stage at the time of diagnosis, screening can find and remove precancerous lesions that could later become malignant, and/or detect early cancers that can be more effectively treated than later stage cancers. Screening for CRC generally implies a screening program in which there is a method for identifying those eligible for (and interested in) screening and to administer repeated screening and followup testing as indicated over time. Adherence to both screening and followup testing is a critical factor in the effectiveness of a screening program.

Large, well-conducted randomized, controlled trials (RCTs) have demonstrated that screening for CRC can reduce disease incidence and disease-specific mortality. The decrease in CRC incidence and mortality in the past two decades in the United States corresponds to an increase in self-reported screening rates. In 2018, 69 percent of adults age 50 to 75 years reported they were up to date with their CRC screening.[72] However, there is evidence of racial/ethnic and socioeconomic disparities in CRC screening, with lower rates of CRC screening in nonwhite and Hispanic populations and less-educated adults.[73, 74] Multiple patient, clinician, and healthcare delivery factors have been found to negatively influence CRC screening, including low socioeconomic or educational status, lack of physician recommendation, and lack of insurance or limited access to healthcare.[73, 75]

In contrast to many other cancers, there are multiple tests that screen for CRC, including direct visualization, stool-based, serum-based, and urine-based testing (**Table 2**). Except for screening colonoscopy, an abnormal result on any of these screening tests necessitates a followup colonoscopy. Many of these tests have been evaluated as screening tests, but each modality has differing levels of evidence to support their use, as well as different considerations about their tradeoffs (including harms), feasibility, acceptability, and availability. Colonoscopy remains the most commonly used screening modality in the United States.[76-78] In 2015, for example, 58.3 percent of U.S. residents had up to date screening with colonoscopy compared with 7.1 percent with a stool test (fecal occult blood test [FOBT]) and 0.7 percent with flexible sigmoidoscopy (FS) in combination with a stool test (FOBT).[76] Biomarkers in stool, blood, and urine samples are of continued interest, and a field of active research. To date, however, only two tests incorporating biomarkers are currently FDA approved to screen for CRC (Cologuard and Epi proColon)[79]; the urine test (PolypDx) is available as a test for Clinical Laboratory Improvement Amendments (CLIA) certified laboratories.

Current Screening Recommendations

Most organizations strongly endorse CRC screening but there are some difference on preferred screening strategies as well as on recommendations around ages to start and stop screening. The optimal age to start screening may vary by sex or race/ethnicity based on differences in onset and incidence of CRC. When screening should stop for average-risk adults is uncertain; thus, screening from ages 76 to 85 years should be individualized based on the patients' comorbid conditions and prior screening results.

Currently, most U.S. guideline organizations, including the USPSTF, agree that the recommended options in screening for CRC include colonoscopy every 10 years, annual high-sensitivity guaiac FOBT (gFOBT) or fecal immunochemical test (FIT), and FS every 5 to 10 years with stool blood testing (FOBT or FIT). Among professional societies in the United States and internationally, a number of important areas of disagreement remain (e.g., age to start/stop screening, risk tailored screening, interval of screening, preferred screening modalities) (**Table 3**). Some notable differences exist between the 2016 USPSTF recommendation and the 2018 American Cancer Society (ACS) and 2017 U.S. Multi-Society Task Force (USMSTF) recommendations. The ACS recommends CRC screening for all adults beginning at age 45 (qualified recommendation), the USMSTF recommends that African Americans begin screening at 45 years and others at age 50 years, and the USPSTF recommends that screening begin at age 50 for all people. The USPSTF and USMSTF both recommend colonoscopy, FIT, FS with or without FIT, stool DNA with FIT (sDNA-FIT), and CTC, but the USMSTF prioritizes certain strategies over others (colonoscopy and FIT as the first tier) and recommends capsule endoscopy (third tier). ACS states that clinicians should be prepared to offer both stool based or visual exam options when recommending screening. There is also variation in the recommended age to stop screening, with recommended ages to stop spanning from 74 to 85 years. Notably, two groups (CTFPHC, Council of the European Union) do not recommend colonoscopy to screen for CRC, and the American Academy of Family Physicians does not recommend CTC. One guideline panel, as part of the BMJ Rapid Recommendations series, issued a weak recommendation against screening in asymptomatic adults ages 50 to 79 with an estimated 15-year CRC risk below 3 percent using a risk calculator including a number of variables in addition to age, sex, race/ethnicity, and family history.[80]

Previous USPSTF Recommendation

In 2016, the USPSTF recommended screening for CRC starting at age 50 years and continuing until age 75 years (A recommendation). The decision to screen for CRC in adults ages 76 to 85 years should be based on the individual, taking into account the patient's overall health and prior screening history (C recommendation). Adults in this age group who have never been screened for CRC are more likely to benefit. Screening would be most appropriate among adults who (1) are healthy enough to undergo treatment if CRC is detected and (2) do not have comorbid conditions that would significantly limit their life expectancy. The A recommendation was based on high certainty that the net benefit of screening for CRC in adults ages 50 to 75 years was substantial (i.e., reduced CRC mortality and few harms of screening). The C recommendation was based on moderate certainty that the net benefit of screening for colorectal cancer in adults ages 76 to 85 years who have been previously screened is small, and adults who have never been screened for colorectal cancer are more likely to benefit.

The 2016 recommendation differed from the 2008[81] recommendation in two important ways. First, the 2016 recommendation offered an expanded number of strategies to screen for CRC, including high sensitivity guaiac-based fecal immunochemical test (HSgFOBT) or FIT annually, sDNA-FIT annually or every 3 years, colonoscopy every 10 years, CTC or FS every 5 years, and FS every 10 years with annual FIT. The recommendation noted that the different options had varying levels of evidence supporting their effectiveness, as well as different strengths and limitations. Second, the 2016 recommendation eliminated the D recommendation for adults older than 85 years; however, the 2016 recommendation still stated in the clinical considerations section that adults older than 85 years should not receive CRC screening.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review in conjunction with microsimulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET) to update its 2016 recommendation statement on screening for CRC.[1] This review is an update of our prior work[82, 83] and addresses the benefit and harms associated with CRC screening and the test accuracy of the individual screening tests currently available in U.S. clinical practice. The accompanying CISNET simulation models address how the benefits and harms of screening might vary by screening test, screening interval, age to start screening, age to stop screening, as well as by sex, race/ethnicity, and comorbidities.

Key Questions and Analytic Framework

The analytic framework is presented in **Figure 2**.

Key Questions

1. What is the effectiveness or comparative effectiveness of screening programs in reducing colorectal cancer, mortality, or both?
    a. Does the effectiveness of screening programs vary by subgroups (e.g., age, sex, race/ethnicity)?
2. What is the accuracy of direct visualization, stool-, serum-, or urine-based screening tests for detecting colorectal cancer, advanced adenomas, or adenomatous polyps based on size?
    a. Does the accuracy of the screening tests vary by subgroups (e.g., age, sex, race/ethnicity)?
3. What are the serious harms of the different screening tests?
    a. Do the serious harms of screening tests vary by subgroups (e.g., age, sex, race/ethnicity)?

Data Sources and Searches

We searched the following databases to identify English-language literature published between January 1, 2015 and December 4, 2019: MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**). We also reviewed all included studies from the prior review,[82, 83] which identified studies prior to 2015. We then supplemented our database searches with expert suggestions and by reviewing reference lists from other recent relevant systematic reviews.[84-98] We also searched ClinicalTrials.gov for ongoing screening trials. We imported the literature from these sources directly into EndNote X9 (Thomson Reuters, New York, NY).

Study Selection

Two investigators independently reviewed 11,306 newly identified titles and abstracts using an online platform (DistillerSR) and 502 articles (**Appendix A Figure 1**) with specified inclusion criteria (**Appendix A Table 1**). We resolved discrepancies through consensus and consultation with a third investigator. We carried forward 126 studies (159 articles) from our prior review. Four studies from the previous review were not included in this review due to study design (screening effectiveness studies comparing multiple screening tests among the same group of participants[99, 100]), screening modality (early versions of sDNA tests[101]), or outcomes (no description of colonoscopy complications[102]). Additionally, we excluded articles that did not meet inclusion criteria or those we rated as poor quality (i.e., at high risk of bias). **Appendix D** contains a list of all excluded trials.

Eligible studies included asymptomatic screening populations of individuals age 40 years and older at average risk for CRC. We excluded symptomatic populations and populations selected for: personal history of CRC, high risk for CRC due to known genetic susceptibility syndromes (e.g., Lynch syndrome, familial adenomatous polyposis), first-degree relative younger than age 60 years with CRC, personal history of inflammatory bowel disease, previous abnormal screening test, iron deficiency anemia, or under surveillance for a previous colorectal lesion. In studies with mixed populations, we limited our inclusion to those with less than 50 percent surveillance and/or less than 10 percent with symptoms, abnormal gFOBT or FIT, or anemia. For studies of harms of screening, we allowed mixed populations (e.g., indications for colonoscopy or CTC not reported or detailed) if the sample was larger than 10,000 participants. This allowed us to include studies that might detect rare or uncommon harms. We arrived at the number 10,000 based on estimates derived from our 2008 systematic review.[103, 104] Because many studies reporting extracolonic findings on CTC limited population descriptions to asymptomatic or symptomatic, we included any studies in asymptomatic people that could include people at high risk for CRC (e.g., anemia, abnormal FOBT result, personal history of CRC or colorectal lesions).

For the greatest applicability to U.S. practice, we focused on studies conducted in developed countries, as defined by “very high” development according to the United Nations Human Development Index.[105] We included only studies that published their results in English because of resource constraints.

We included studies that evaluated direct visualization screening tests (i.e., colonoscopy, FS, CTC, capsule endoscopy) and currently available stool-, serum-, or urine-based screening tests. Although we reviewed the evidence for benefit of older-generation gFOBT (i.e., Hemoccult II) on cancer incidence and mortality (Key Question 1), we did not update the evidence of its test accuracy (Key Question 2) because it has been replaced with high-sensitivity gFOBT (HSgFOBT) and FIT in U.S. practice. We excluded stool testing based on in-office digital rectal examination, double-contrast barium enema, and magnetic resonance colonography, as none of these modalities are used or recommended for use in screening for CRC. We also excluded studies that primarily focused on evaluating technological improvements to colonoscopy or CTC. We excluded endoscopy studies conducted in primarily single-center research settings or those with a limited number of endoscopists (e.g., <5 to 10) in order to approximate test performance and harms of screening tests in community practice.

Key Question 1

We included randomized or controlled trials of CRC screening versus no screening or another screening test. For screening tests without trial-level evidence, we examined well-conducted prospective cohort studies. We included trials and prospective observational studies that reported outcomes of cancer incidence and/or CRC-specific or all-cause mortality. Included studies could report either intention to screen or ‘as screened’ results. We excluded retrospective cohort studies and population-based case control studies. We also excluded decision analyses because this review is paired with CISNET microsimulation models designed to compare the effectiveness and harms of different screening strategies.

Key Question 2

We included test accuracy studies that used colonoscopy as a reference standard. We generally excluded studies whose design was subject to a high risk of bias, including those that did not apply colonoscopy to at least a random subset of screen-negative people (verification bias),[106] although we made an exception for otherwise well-conducted diagnostic accuracy studies of FITs in which screen-negative people received registry followup (instead of colonoscopy) to determine cancer outcomes. We excluded studies without an adequate representation of a full spectrum of patients (spectrum bias), such as case-control studies.[106-110] Test accuracy studies had to include outcomes of test performance (i.e., sensitivity, specificity, and positive and negative predictive value) for the detection of CRC, AA, SSL, and/or adenomatous polyp by size (≥6 mm or ≥10 mm). We also captured test performance by location in the colon (i.e., proximal vs. distal), when reported.

Key Question 3

We included all trials or observational studies that reported serious adverse events requiring unexpected or unwanted medical attention and/or resulting in death. These events included, but were not limited to, perforation, major bleeding, severe abdominal symptoms, and cardiovascular events. We excluded studies whose reported harms were limited to minor adverse events that did not necessarily result in medical attention (e.g., patient dissatisfaction, worry, minor gastrointestinal complaints), physiologic outcomes only (e.g., hypoxia, renal or electrolyte disturbances), or harms of health certificate effect (i.e., people with negative screening results engaging in risky health behaviors or not pursuing future screening). Studies of harms did not have to include a comparator (i.e., people who did not receive any screening test). We also included studies designed to assess for extracolonic findings (incidental findings on CTC) and resultant diagnostic workup and harms of workup. We extracted extracolonic findings and radiation exposure per CTC examination from relevant diagnostic accuracy (Key Question 2) studies, when reported.

Quality Assessment and Data Abstraction

At least two reviewers critically appraised all articles that met inclusion criteria using the USPSTF's design-specific quality criteria (**Appendix A Table 2**).[111] We supplemented this criteria with the Newcastle Ottawa Scales for cohort and case-control studies,[112] and the Quality Assessment of Diagnostic Accuracy Studies for studies of test accuracy.[113] We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear whether it met, at least one criterion, but also had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. We excluded all poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, consultation with a third independent reviewer.

Only one RCT examining screening effectiveness was excluded for poor quality.[114] This study had several limitations: it was a small pilot study not powered to detect a difference in CRC, it had variable adherence to each arm, and there was crossover between arms. The most common fatal flaw for test accuracy studies was application of the reference standard to only those with an abnormal screening result (screen positive), because verification of only screen-positive patients will generally lead to an overestimation of both sensitivity and specificity.[106, 109, 110, 115] We also excluded test studies that did not provide a description of followup of screen-negative people for poor quality because of limitations in reporting. For cohorts examining harms of screening, the most common limitation was poor reporting (so uncertain risk of bias).

One reviewer extracted key elements of included studies into standardized evidence tables in DistillerSR. A second reviewer checked the data for accuracy. Evidence tables were tailored for each key question and to specific study designs and/or specific screening tests. Tables generally included details on: study design/quality, setting and population (e.g., country, inclusion criteria, age, sex, race/ethnicity, family history), screening test/protocol (e.g., who administered, how administered, definition of test positive/diagnostic threshold[s], frequency/interval), reference standard or comparator (if applicable), adherence to testing, length of followup, outcomes (e.g., CRC incidence, mortality, sensitivity/specificity, harms) and outcomes for *a priori* specified subgroups.

Data Synthesis and Analysis

We synthesized results by key question and type of screening test, incorporating those studies from our previous review that met our updated inclusion criteria.

Key Question 1

We organized the syntheses primarily by study design and separated them into three main categories: 1) trials designed to assess the effectiveness (intention to screen) of screening tests (either as a one-time application or in a screening program) compared with no screening on CRC-specific and/or all-cause mortality; 2) well-conducted observational studies designed to assess the effectiveness of receipt of a screening test (either as a one-time application or in a screening program) compared with no screening on CRC incidence and mortality; and 3) comparative effectiveness trials of one screening test (e.g., FIT) versus another screening test (e.g., colonoscopy). Many of the trials comparing screening tests that met our inclusion criteria, however, were designed to determine the differential uptake of tests and/or to determine the comparative yield between tests and were not powered to detect differences in CRC outcomes or mortality (i.e., comparative effectiveness). Primary outcomes of interest were: CRC incidence (by stage if reported), CRC mortality, and all-cause mortality, as well as CRC incidence and mortality by location of CRC (distal vs. proximal).

Because of the limited number of studies and/or clinical heterogeneity of studies, we primarily synthesized results qualitatively using summary tables and figures to allow for comparisons across different studies. We conducted quantitative analyses of incidence rate ratios for four large FS trials for the above stated outcomes. We conducted random-effects meta-analyses using the restricted maximum likelihood (REML) method to estimate the pooled IRR in Stata version 16 (StataCorp LP, College Station, TX). We assessed the presence of statistical heterogeneity among the studies using the I^2 statistic.

Key Question 2

We organized our synthesis by type of screening test. Most commonly, these results are limited to a single application of a screening test. Our analyses primarily focused on per-person test sensitivity to detect CRC, AAs (as defined by the study), advanced neoplasia (a composite outcome of AA plus CRC), and adenomas by size (≥6 or ≥10 mm). SSLs were sometimes included in the definition of AA, and when possible, we report test sensitivity for SSL alone. If the per-person sensitivity was not reported and could not be calculated, we substituted per-lesion test performance. If per-person test accuracy was not reported for adenomas by size, we allowed for any lesion (i.e., polyp) regardless of histology. We calculated sensitivity and specificity for adenomas by size and AAs excluding CRC lesions (i.e., people who had CRC were removed from the contingency table for AA). Analyses were conducted in Stata version 16. Data from contingency tables was analyzed in Stata using a bivariate model, which modeled sensitivity and specificity simultaneously. If there were not enough studies to use the bivariate model, sensitivity and specificity were pooled separately. We did not quantitatively pool results when data were limited to fewer than three studies. When quantitative analyses were not possible, we used summary tables and forest plots, prepared using Stata, to provide a graphical summary of results. We assessed the presence of statistical heterogeneity among the studies using the I^2 statistic. When analyses found large statistical heterogeneity, we suggest using the 95% CI or range of estimates across the individual studies as opposed to point estimates. However, the high statistical heterogeneity for specificity is in part due to the high degree of precision around estimates from individual studies.

For test performance of CTC, we synthesized results for examinations with bowel preparation separately from those without bowel preparation. For studies of stool-based tests, we focused on designs that provided a colonoscopy to all patients (the reference standard) regardless of the screening test result. In this way we avoided potential test referral bias, which increases apparent test sensitivity and decreases specificity. We separately evaluated studies that employed differential followup (i.e., registry followup for screen-negative people and direct visualization for screen-positive people). For the FITs, we conducted random-effects meta-analyses by "family" (**Appendix D Table 1**). For example, tests produced by the same manufacturer, utilizing the same components and method, and compatible with different automated analyzers (and often reported by analyzer name) were placed in the same FIT family. We attempted to report test cutoff values expressed in µg Hb/g feces because values expressed in µg Hb/g feces are more comparable between tests.[116]

In support of accompanying microsimulation models, we conducted additional pooled analyses. These pooled analyses are located in **Appendix F** and include studies identified at an interim phase of the review (literature identified through January 2019).

Key Question 3

We organized our synthesis into four main categories, all for direct visualization tests: 1) harms from screening FS and colonoscopy; 2) harms from colonoscopy following an abnormal screening test; 3) harms from CTC, including radiation exposure and extracolonic findings; and 4) harms from capsule endoscopy. We did not hypothesize any serious harms for stool- or blood/serum-based screening tests beyond those from followup testing (i.e., colonoscopy following an abnormal screening test).

We primarily synthesized results qualitatively using summary tables to allow for comparisons of studies. When possible, we conducted quantitative analyses for serious harms, including major bleeding and perforation, for colonoscopy or FS. We defined major bleeding as any bleeding that required medical attention or intervention (e.g., emergency visit, hospitalization, transfusion, endoscopic management, surgery), or defined/reported as "major" or "serious" by the individual study. Using Stata version 16, we conducted random-effects meta-analyses using the DerSimonian and Laird method to estimate rates of serious adverse events. We assessed the presence of statistical heterogeneity among the studies using the I^2 statistic. Quantitative analyses were not performed for other serious adverse events, as they were not routinely or consistently reported or defined.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center (EPC) approach,[117] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group.[118] Our method explicitly addresses four of the five EPC-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). The body-of-evidence limitations reflect potential reporting bias, study quality, and other important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimation of an effect. We developed our overall strength-of-evidence grade based on consensus discussion involving at least two reviewers.

Expert Review and Public Comment

The draft Research Plan was posted on the USPSTF Web site for public comment from January 3 to January 30, 2019. In response to public comment, the USPSTF modified the analytic framework to be more consistent with USPSTF methodology and to indicate which screening tests have conditional approval from the U.S. Food and Drug Administration. The USPSTF also added urine-based tests as a screening method. Additionally, in the inclusion and exclusion criteria, the USPSTF revised the language to distinguish between the cancer location (proximal or distal colon or rectum) and added SSL as an outcome of interest for test accuracy studies. The USPSTF made no other substantive changes that altered the scope of the review.

A draft version of this report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report. Additionally, a draft of the full report was posted on the USPSTF Web site from October 27 through November 24, 2020. All comments and suggested citations were considered; minor editorial changes were made to the report based on these comments (e.g., inclusion of more detail on differences by race/ethnicity, provision of absolute numbers in addition to relative findings when possible, updated citations to the background and discussion sections) but no substantive changes were made to the included evidence, our interpretation of the evidence, or to our conclusions.

USPSTF Involvement

The authors worked with five USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis.

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project, coordinated systematic review work with decision models, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Description of Included Studies

This systematic review updates our prior review, which supported the 2016 USPSTF recommendation on screening for colorectal cancer. We found 33 studies[21, 119-150] on the effectiveness or comparative effectiveness of screening on colorectal cancer incidence or mortality (13 of which are new since the prior review[119, 122, 125, 127, 130-132, 135-137, 139, 149, 150]), 59 studies[151-209] on the diagnostic accuracy of various screening tests (28 new[154, 155, 158, 159, 161, 162, 164, 166, 168, 170, 171, 173, 179, 180, 187, 189, 196-200, 202-204, 206-209]), and 131 studies[119, 121, 124, 125, 127, 129, 130, 133-136, 138, 140-144, 147, 150, 169, 172, 177, 178, 181, 184, 188, 195, 198, 205, 210-313] on harms of screening (37 new[119, 125, 127, 130, 135, 136, 150, 198, 217, 218, 221, 226, 231, 237, 240, 244, 248, 250, 260-262, 270, 271, 281, 282, 287, 290, 298, 302, 303, 307-313]) (**Table 4**). A full list of included studies and their ancillary publications is available in **Appendix B**. This review includes evidence for direct visualization screening tests (i.e., flexible sigmoidoscopy, colonoscopy, CTC, capsule endoscopy), stool-based screening tests (i.e., gFOBT, HSgFOBT, FIT, sDNA), serum-based screening tests, and urine-based screening tests. Urine tests and capsule endoscopy as screening modalities were not included in the prior review.

KQ1. What Is the Effectiveness or Comparative Effectiveness of Screening Programs in Reducing Colorectal Cancer, Mortality, or Both? Does the Effectiveness of Screening Programs Vary by Subgroups (e.g., Age, Sex, Race/Ethnicity)?

Summary of Results

We included 33 unique fair- to good-quality studies (published in 66 articles[21, 119-150, 314-346]) to assess the effectiveness or comparative effectiveness of screening tests on CRC incidence and mortality (**Table 4**). We found two prospective cohort studies[21, 125] that examined the effectiveness of screening colonoscopy, four RCTs[119, 127, 130, 140] that examined the effectiveness of FS with or without a FIT, no studies that examined the effectiveness of CTC, six trials[124, 128, 129, 132, 138, 143] that examined the effectiveness of a gFOBT, one prospective cohort study[122] that examined the effectiveness of a FIT, and no studies that examined the effectiveness of HSgFOBT, sDNA, serum-based, or urine-based tests versus no screening. In addition to one screening FS RCT[127] evaluating FS plus FIT versus FS alone, we found 20 studies[120, 121, 123, 126, 131, 133-137, 139, 141, 142, 144-150] that compared screening modalities, however, the majority were designed to assess the relative uptake and CRC yield between different screening modalities, rather than to assess the reduction in CRC incidence and mortality.

Effectiveness of Screening

We found well-conducted trials for one- or two-time FS and annual or biennial gFOBT screening programs demonstrating a reduction in CRC incidence and mortality (**Table 5**). Since our previous review, three previously included FS trials have published longer followup[119, 127, 130]; these data are consistent with our prior understanding of benefit. Based on four RCTs[119, 127, 130, 140] (n=458,002) that used intention-to-treat analyses, a one- or two-time FS was consistently associated with a decrease in CRC incidence (IRR 0.78 (95% CI, 0.74 to 0.83) and CRC-specific mortality (IRR 0.74 (95% CI, 0.68 to 0.80) compared with no screening at 11 to 17 years of followup. Reductions in CRC incidence and mortality were greater for men than women. Based on five RCTs (n=419,966) that used intention-to-treat analyses, biennial screening with Hemoccult or Hemoccult II was associated with a reduction of CRC-specific mortality compared with no screening after two to nine rounds of screening at 11 to 30 years of followup (RR 0.91 [95% CI, 0.84 to 0.98] at 19.5 years; RR 0.78 [95% CI, 0.65 to 0.93] at 30 years). One additional trial of screening with gFOBT in Finland (n=360,492) had only interim findings, with a followup of 4.5 years. While neither FS nor Hemoccult II is commonly used in the United States to screen for CRC, these trials provide foundational evidence for newer, yet similar, screening tests.

We found two large, prospective observational studies evaluating the association of receipt of screening colonoscopy and one evaluating receipt of FIT on CRC incidence and/or mortality.[21, 125] For colonoscopy, after 24 years of followup, one study (n=88,902) among health professionals found the CRC-specific mortality rate was lower in people who self-reported at least one screening colonoscopy compared with those who had never had a screening colonoscopy (adjusted HR, 0.32 [95% CI, 0.24 to 0.45]).[21] This study found that screening colonoscopies were associated with lower CRC mortality from both distal and proximal cancers. It also found that results were no longer statistically significant after 5 years in people with a first-degree relative with CRC, as opposed to a sustained association beyond 5 years in people without a family history. Another study among Medicare beneficiaries (n=348,025) with much shorter followup found that people ages 70 to 74 years who underwent a screening colonoscopy had a lower 8-year standardized risk for CRC (-0.42 percent [95% CI, -0.24 to 0.63]) than those who did not undergo the test.[125] The magnitude of benefit was lower and no longer statistically significant for people ages 75 to 79 years, and this study did not report any mortality outcomes. Although many observational studies have evaluated national FIT screening programs, we found only one prospective observational study meeting our inclusion and quality criteria. This study (n=5,417,699) found that one to three rounds of screening with a biennial FIT (OC-Sensor or HM JACK) were associated with lower CRC mortality than no screening (adjusted RR, 0.90 [95% CI, 0.84 to 0.95]).[122]

While three gFOBT studies include adults under age 50 years, none of them provided age-stratified analyses for this age group. We could not directly compare the magnitude of benefit in CRC mortality and cancer incidence among screening tests because of major differences in the design of included studies for each test type (e.g., trial versus observational study, intention to screen versus as screened, outcome metric reported). We found no studies evaluating the effectiveness of CTC, capsule endoscopy, HSgFOBT, sDNA, serum, or urine tests on CRC incidence and/or mortality.

Comparative Effectiveness of Screening

In one FS screening RCT, persons in the FS plus FIT arm had lower CRC-specific mortality than those in the FS-only arm, age-adjusted HR 0.62 (95% CI, 0.42 to 0.90) versus 0.84 (95% CI, 0.61 to 1.17), although this difference was not statistically significant. Additional included trials were primarily designed to evaluate the comparative uptake/adherence, test positivity, and initial cancer detection of one screening test versus another. Only a handful of studies were adequately powered to detect a reduction in cancer incidence or mortality. In general the number of cancers detected in these studies was low, and only one study reported mortality outcomes. Most studies only reported cancer yield after one round of screening, and only three studies reported interval cancers. As a result, we cannot draw any robust conclusions about the comparative effectiveness of various screening tests on reducing cancer incidence or mortality from empiric studies. Based on one study, one-time FS or colonoscopy does not appear to detect more cancers than 4 rounds of FIT. Based on 4 studies, FIT can detect more cancers than Hemoccult II, and a two-sample FIT does not appear to be superior to a one-sample FIT. In addition, 4 studies comparing different FITs did not find statistically significant differences in cancers after one or two rounds of screening, despite differences in test positivity. However, the overall number of cancers was low and none of these studies reported interval cancers. Several adequately powered studies are currently underway that will evaluate the comparative effectiveness of direct visualization versus stool-based screening programs (**Appendix I**). We found no active comparative effectiveness trials evaluating sDNA, serum tests, or urine tests.

Detailed Results for the Effectiveness of Direct Visualization Tests

Flexible Sigmoidoscopy

We found four fair-quality trials (n=458,002) assessing the effectiveness of FS screening on CRC incidence and/or mortality; all four of these trials were included in our previous review. However, since our prior synthesis of these trials, three trials[119, 127, 130] have published results with longer followup. Because all of these trials were included in our previous review, we provide only a brief discussion of these trials below. Additional details can be found in our prior review.[82, 83]

Study and Population Characteristics

Only one of the four trials was conducted in the United States (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCO]); the other three were conducted in western Europe (**Table 6**). All trials recruited average-risk adults between age 50 and 74 years, with a mean age ranging from 56 to 60 years. Colorectal cancer prevalence among participants screened at baseline ranged from 0.3 to 0.5 percent. The cumulative incidence of CRC identified in screened and unscreened participants over a median of 10 to 17 years of followup ranged from 1.6 to 2.6 percent. All trials recruited an even mix of men and women. Two trials reported that approximately 10 percent of the participants had a family history of CRC. One trial, the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST), explicitly excluded participants with two or more close relatives with CRC. Only the PLCO trial reported the race/ethnicity of participants, approximately 14 percent of whom were nonwhite.

The screening protocol for the four trials varied. The Norwegian Colorectal Cancer Prevention (NORCCAP) trial evaluated a one-time FS with or without a FIT (approximately half of the screening participants also received a FIT) versus no screening. The other three trials compared a FS alone with no screening. The PLCO trial evaluated screening with a followup FS at 3 to 5 years, while the Screening for COlon REctum (SCORE) trial and the UKFSST evaluated a one-time FS. Followup colonoscopy varied widely by trial: from 5.2 percent in UKFSST to 32.9 percent in PLCO. Variation in colonoscopy rates reflect the different referral criteria used in each of the trials.

The adherence to initial FS ranged from 58 to 83 percent, with the highest adherence observed in the PLCO trial. Only the PLCO trial reported whether the control group received screening—about 47 percent of the control group was found to have some type of lower endoscopy during the screening phase of the trial. In the other three trials control participants were not contacted and were unaware of their trial involvement.

Outcomes

Based on intention-to-screen analyses of the four trials, one- or two-time FS decreased CRC incidence and CRC-specific mortality, but not all-cause mortality over a median of 11 to 17 years (**Table 7**). The pooled IRR for CRC incidence for FS versus no screening was 0.78 (95% CI, 0.74 to 0.83; I^2=29%) with 28 to 47 fewer CRC cases per 100,000 person-years among those with FS screening (**Figure 3**). The pooled IRR for CRC mortality for FS versus no screening was 0.74 (95% CI, 0.68 to 0.80; I^2=0%) (**Figure 4**) with 10 to 17 fewer CRC deaths per 100,000 person-years among those with FS screening. The pooled IRR for all-cause mortality for FS versus no screening was 0.99 (95% CI, 0.98 to 1.00; I^2=0.15%) (**Figure 5**).

In the NORCCAP trial, the FS plus FIT arm had lower CRC-specific mortality than the FS-only arm—age-adjusted HR 0.62 (95% CI, 0.42 to 0.90) versus 0.84 (95% CI, 0.61 to 1.17)—although this difference was not statistically significant.

By Stage or Location

Reductions in CRC incidence and CRC-specific mortality were greater for distal than proximal cancers (**Table 8**). The pooled IRR for CRC incidence for distal cancers was 0.67 (95% CI, 0.60 to 0.75; I^2=67%) versus 0.93 for proximal cancers (95% CI, 0.88 to 0.99; I^2=88%) (**Figure 6**). Likewise, the pooled IRR for CRC-specific mortality for distal cancers was 0.61 (95% CI, 0.49 to 0.74; I^2=66%) versus 0.90 for proximal cancers (95% CI, 0.80 to 1.00; I^2=0%) (**Figure 7**).

By Age, Sex, Race/Ethnicity, or Family History

While individual trials reported age-stratified results, age strata were not consistent and none of the trials included participants under age 50 years (**Table 8**). Overall, there were no statistically significant differences among age groups reported in individual trials.

Reductions in CRC incidence and CRC-specific mortality were greater for men than women (**Table 8**). The pooled IRR for CRC incidence for men was 0.73 (95% CI, 0.68 to 0.79; I^2=31%) versus 0.85 for women (95% CI, 0.79 to 0.92; I^2=12%) (**Figure 8**). The pooled IRR for CRC mortality for men was 0.67 (95% CI, 0.60 to 0.74; I^2=0%) versus 0.85 for women (95% CI, 0.72 to 1.00; I^2=32%) (**Figure 9**).

Trials did not report results by race/ethnicity or family history.

Colonoscopy

We found no trials that evaluated the effectiveness of screening colonoscopy on CRC incidence or mortality. We found two fair-quality prospective cohort studies[21, 125] (n=436,927) that evaluated the impact of receipt of screening colonoscopy on CRC incidence and mortality, one of which is new since the previous review.[125] Based on a priori inclusion and exclusion criteria, we excluded nested case-control and retrospective studies.

Study and Population Characteristics

One fair-quality study[21] used data from two large prospective cohorts in 1988, the Nurses' Health Study (57,166 women) and the Health Professionals Follow-up Study (31,736 men). Participants were health professionals who were generally considered average risk; people with a history of cancer, ulcerative colitis, familial polyposis syndromes, previous colorectal polyps, or previous lower endoscopy were excluded. Those with a family history of CRC were included. Ages at the start of the study ranged from 42 to 67 years for women and 42 to 77 years for men. The study analyzed the association between screening colonoscopy and FS and the risk of CRC over 22 years and CRC mortality over 24 years. All analyses were stratified by age and sex, and additional analyses for numerous other risk factors (i.e., obesity, smoking, family history, physical activity, dietary patterns, alcohol use, aspirin and other medication/supplement use) were also evaluated. Investigators conducted additional analyses adjusting for propensity scores to address selection bias.

The other fair-quality study used data from a 20 percent random subsample of Medicare beneficiaries from 1999 to 2012.[125] Participants were average-risk older adults, ages 70 to 79 years, without a prior history of CRC, adenoma, inflammatory bowel disease, or colectomy, and had not received any prior colonoscopy, FS, or FOBT. The analysis also excluded people who had received an abdominal CT or barium enema; had a diagnosis of anemia, GI bleeding, irritable bowel disease, diverticular disease, or ischemic bowel disease; or had symptoms of diarrhea, constipation, change in bowel habit, or weight loss in the previous 6 months. The study emulated a trial design of screening colonoscopy versus no screening using sequential simulated trials that included 348,025 nonunique individuals (10,034 who had a screening colonoscopy and 337,991 randomly selected people with no screening). The median followup was 40 months. Approximately 25 percent of beneficiaries were followed for more than 5.5 years. Baseline prevalence of CRC was 0.89% (in ages 70–74 years) and 1.14% (in ages 75–79 years) in people who had a screening colonoscopy, and 0.03% (both age groups) in people with no screening. Analyses were adjusted for age, sex, race, utilization of preventive services, geographic location, comorbidities, and calendar month. Beneficiaries who had a screening colonoscopy had a lower proportion of chronic disease and higher proportion of utilization of other preventive services.

Outcomes

Both studies demonstrated an association between receipt of screening colonoscopy and lower CRC incidence and mortality compared with no colonoscopy.

In the cohort study of health professionals,[21] there were 1,815 incident cases of CRC after 22 years of followup. Cancer incidence was lower in people who self-reported a screening endoscopy with polypectomy (multivariate HR, 0.53 [95% CI, 0.40 to 0.71]), negative screening colonoscopy (multivariate HR, 0.47 [95% CI, 0.39 to 0.57]), and negative screening FS (multivariate HR, 0.56 [95% CI, 0.49 to 0.65]) compared with those who had never had a screening endoscopy. During 24 years of followup, there were 474 deaths due to CRC. The CRC-specific mortality rate was lower in people with a self-reported screening colonoscopy (multivariate HR, 0.32 [95% CI, 0.24, 0.45]) and screening FS (multivariate HR, 0.59 [95% CI, 0.45 to 0.76]) compared with those who had never had a screening endoscopy.

In the cohort study of Medicare beneficiaries,[125] after a median followup of 40 months, 1,282 individuals who had a colonoscopy were diagnosed with CRC, and 45,530 who had no screening were diagnosed with CRC. For people ages 70 to 74 years, the standardized 8-year risk for CRC was 2.19 percent (95% CI, 2.00 to 2.37) if they underwent a screening colonoscopy versus 2.62 percent (95% CI, 2.56 to 2.67) if they were not screened (difference -0.42 percent; 95% CI, -0.24 to -0.63). Likewise, for people ages 75 to 79 years, the standardized 8-year risk for CRC was 2.84 percent (95% CI, 2.54 to 3.13) in people who had a screening colonoscopy versus 2.97 percent (95% CI, 2.92 to 3.03) in people who were not screened (difference -0.14 percent; 95% CI, -0.41 to 0.16). This study did not report any mortality outcomes.

By Stage or Location

In the cohort study of health professionals,[21] the lower cancer incidence in those who had colonoscopies versus no screening was observed at all stages of CRC at presentation. Only a negative screening colonoscopy was associated with reduced incidence of proximal CRC (multivariate HR, 0.74 [95% CI, 0.57 to 0.96]). This study found that screening colonoscopies were associated with reduced CRC mortality from both distal CRC (multivariate HR, 0.18 [95% CI, 0.10 to 0.31]) and proximal CRC (multivariate HR, 0.47 [95% CI, 0.29 to 0.76]), but this was not true for FS.

In a subsample of the cohort study of Medicare beneficiaries who were linked to the SEER registry,[125] a higher proportion of stage 0 to II cancers and lower proportion of stage IV cancers were observed in people who had a screening colonoscopy compared with people who did not have screening. Outcomes by location were not reported.

By Age, Sex, Race/Ethnicity, or Family History

In the cohort study of health professionals,[21] results related to CRC incidence and mortality were similar for men and women. The inverse association of colonoscopy and CRC was similar among age groups. In people with a first degree relative (FDR) with CRC, the association for CRC mortality was no longer statistically significant after 5 years (multivariate HR 0.91, 95% CI

0.55, 1.52) compared with a sustained association beyond 5 years in people without a family history (multivariate HR 0.43, 95% CI 0.32, 0.58) (p=0.04 for interaction). No subgroup analyses by age were reported.

The cohort study of Medicare beneficiaries reported age-stratified results (as described above) but no other subgroup analyses.

CT Colonography

We found no prospective studies evaluating the effectiveness of screening CTC on cancer incidence or mortality.

Capsule Endoscopy

We found no prospective studies evaluating the effectiveness of screening capsule endoscopy on cancer incidence or mortality.

Detailed Results for Effectiveness of Stool Tests

gFOBT

We found no new screening trials of gFOBT and one new publication[132] reporting longer-term followup for a previously included trial. Six previously included, large population screening trials (n=780,458) evaluating the effectiveness of Hemoccult or Hemoccult II are described in **Table 9.** The Finland trial is ongoing; however, interim findings[132] with a median 4.5 years of followup did not find a reduction in CRC mortality using biennial gFOBT (**Table 10**). Based on five RCTs (n=419,966) that used intention-to-screen analyses, biennial screening with gFOBT resulted in a reduction of CRC-specific mortality compared with no screening, ranging from 9 to 22 percentage points after two to nine rounds of screening with 11 to 30 years of followup (RR 0.91 [95% CI, 0.84 to 0.98] at 19.5 years; RR 0.78 [95% CI, 0.65 to 0.93] at 30 years) (**Table 10**). Based on one of these trials, conducted in the United States, annual screening with gFOBT after 11 rounds of screening resulted in non-statistically significant greater reductions in CRC-specific mortality (RR 0.68 [95% CI, 0.56 to 0.82]) at 30 years than biennial screening (RR 0.78 [95% CI, 0.74, 0.96]). For the same five RCTs with 11 to 28 years of followup, screening did not consistently reduce CRC incidence (RR range from 0.81 to 1.02), with only the trial conducted in Minnesota reporting a statistically significant reduction in CRC incidence (**Table 10**). None of the trials reported an association of gFOBT screening with all-cause mortality (**Table 10**). Detailed results are provided in our previous review.[82, 83] We found no prospective studies evaluating the effectiveness of HSgFOBT on cancer incidence or mortality.

By Age, Sex, Race/Ethnicity, or Family History

In three trials—those set in Denmark, Finland, and the United Kingdom— CRC-specific mortality reductions were similar for both males and females.[128, 132, 138] However, the difference between males and females in the Finland trial[132] was of borderline significance (p=0.06 for interaction), with a relative risk favoring the screening group for men and a relative risk favoring the unscreened group for women. Similarly, in the Minnesota trial,[143] men in the biennial screening group had greater CRC-specific mortality reductions compared to women in the biennial screening group at 30 years of followup (p=0.04 for interaction), but this result was not found for the annual screening group (p=0.30 for interaction).

While three trials[124, 128, 138] recruited adults aged less than 50 years (with 4 to16 percent of the recruited participants aged 45-49 years at the initial screen), none stratified their results by that age group. Two trials[138, 143] found no statistically significant difference in CRC-specific mortality for those younger than 60 years compared with those older than 60 years.

No subgroup analyses by race/ethnicity or family history were reported.

FIT

We found no trials that evaluated the effectiveness of FIT on CRC incidence or mortality. We found one fair-quality prospective cohort study (n=5,417,699) that evaluated a national screening program in Taiwan using biennial FIT in residents ages 50 to 69 years.[122] This screening program was implemented in a gradual manner due to financial resources and capacity for public health and colonoscopy. The study evaluated the initial 20 percent coverage rate over the first 5 years in which 1,160,895 participants underwent one to three rounds of FIT (OC-Sensor or HM-JACK) and followed for up to 6 years (mean followup time 3.09 years). Outcomes of CRC incidence and CRC deaths were ascertained from the screening database linked to national cancer and death registries. Although the cancer registry has very good coverage and accuracy, there is a delay in reporting (typically 2–3 years). People with an abnormal FIT result were referred to colonoscopy or FS with barium enema; approximately 85 percent of confirmatory exams were colonoscopy. The test positivity rate for the initial round was 4.0 percent and 3.8 percent for those who attended subsequent screening. The CRC detection rate per 1,000 people was 2.5 cancers in the first round and 1.7 cancers in subsequent screening rounds. The unadjusted RR for CRC mortality for screened versus unscreened subjects was 0.38 (95% CI, 0.35 to 0.42) at a mean followup time of 3 years; the adjusted RR for self-selection bias and increasing CRC incidence over time was 0.90 (95% CI, 0.84 to 0.95).

Several other countries have conducted opportunistic evaluations of their regional and national screening programs using FITs. Only a few countries have published studies on the impact of FIT screening using contemporaneous control groups. Three of these studies, which evaluated invited participants versus those not yet invited to screening, were excluded for poor quality because study reporting and followup were very limited, and the only outcome evaluated was stage of CRC at diagnosis.[347-349] These three studies demonstrated that an invitation to FIT screening resulted in a greater number of cancers detected than no invitation to screening, and/or a higher proportion of early-stage CRC with an invitation to FIT screening compared with no invitation to screening. Many other retrospective studies using historical controls or unscreened controls (without further details or adjustment for confounders) were excluded due to study design.

sDNA

We found no prospective studies evaluating the effectiveness of sDNA tests on CRC or mortality.

Detailed Results for Effectiveness of Serum or Urine Tests

Serum Tests

We found no prospective studies evaluating the effectiveness of serum-based screening on CRC incidence or mortality.

Urine Tests

We found no prospective studies evaluating the effectiveness of urine-based screening on CRC incidence or mortality.

Detailed Results for Comparative Effectiveness Trials

In addition to NORCCAP[127] (as described under Flexible Sigmoidoscopy), we included 20 fair-quality trials (published in 29 articles) that compared different screening tests in average-risk screening populations[120, 121, 123, 126, 127, 131, 133-136, 139, 141, 142, 144-150] (**Table 11**). Six of these trials are new since our prior review,[131, 135-137, 149, 150] although one study[149] utilized participants from other previously included trials. We also included one fair-quality, large prospective cohort study that was in our previous review which compared gFOBT versus FIT in average-risk screening populations.[123]

Trials and prospective cohort studies included asymptomatic men and women ages 50 to 74 years. The mean age, when reported, ranged from 58 to 62 years. Studies generally excluded people at high risk for CRC due to their symptoms, a personal history of CRC, or a strong family history of CRC. All studies were conducted in western European countries. Most included trials were primarily designed to assess the differential uptake (adherence) of testing and relative detection of colorectal lesions. Although these trials included CRC outcomes, they were not powered to detect differences in CRC incidence and/or mortality. To illustrate, approximately 6,000 participants per arm would be needed to detect a 0.3 percent difference in CRC incidence with 80 percent power, assuming 100 percent adherence. The trials that have been conducted generally had fewer than 6,000 participants per arm with less than 60 percent adherence to testing.

In total, nine studies had explicit primary outcomes of CRC mortality and/or CRC incidence; these include three pragmatic RCTs that were part of FIT-based national screening programs evaluating different FITs or numbers of stool samples,[131, 137, 139] one RCT[150] assessing FS as an adjunct to gFOBT within a national screening program, one trial[149] that utilized colonoscopy, FS, and FIT screening arms from three studies in the Netherlands, one randomized controlled trial[127] that also compared FS alone to FS with a FIT (NORCCAP, as described under Flexible Sigmoidoscopy), one prospective observational study evaluating Hemoccult II versus FIT,[123] one active trial[133] (COLONPREV) comparing FIT with colonoscopy; and one recently completed trial[136] (SAVE) that looked at FIT versus CTC versus colonoscopy. Several ongoing comparative effectiveness trials that are powered to detect a difference in CRC incidence and/or CRC-specific mortality have not yet reported outcomes; these trials are detailed in **Appendix I**.

Because most of these studies are limited to the evaluation of a single round of screening, report a low CRC yield (number of cancers detected), and do not report interval cancers, they do not provide robust direct evidence of comparative benefit on CRC incidence or mortality outcomes (**Figure 10**).

Direct Visualization vs. Direct Visualization

Only five trials evaluated the comparative effectiveness between different direct visualization screening tests: COCOS[144] (CTC vs. colonoscopy), SCORE III[142] (FIT vs. FS vs. colonoscopy), Proteus 2[135] (CTC vs. FS), and SAVE[136] (FIT vs. reduced CTC vs. full CTC vs. colonoscopy), and a trial by Grobbee and colleagues that utilized screening arms from other trials (FS vs. colonoscopy) (**Appendix D Table 2**). None of these trials found a statistically significant difference in the number of cancers detected in each arm (**Figure 10**); however, they were not powered to do so.

Direct Visualization vs. Stool Testing

Eleven trials evaluated the comparative effectiveness between different direct visualization and stool tests (**Appendix D Table 3**). Nine trials evaluated a stool test versus FS (with or without stool testing). Four trials evaluated FIT versus colonoscopy or CTC: COLONPREV[133] (FIT vs. colonoscopy), SCORE III[142] (FIT vs. colonoscopy), SAVE[136] (FIT vs. [reduced and full bowel prep] CTC vs. colonoscopy), and a study by Grobbee and colleagues utilizing three screening arms from other trials (4 rounds of FIT vs. one-time colonoscopy vs. one-time FS).

Most trials demonstrated that one-time screening with direct visualization detects more CRC than stool testing. However, one study comparing four rounds of FIT to one-time colonoscopy or one-time FS found no difference in CRC detection between modalities[142] (**Figure 10**). COLONPREV found no statistically significant differences in the distribution of cancers in the colon between colonoscopy versus FIT; both screening tests found a greater number of distal than proximal cancers. The study by Grobbee and colleagues[149] found no statistically significant differences between modalities for CRC stage or location. No other subgroups were reported.

Stool Testing vs. Stool Testing

Eight studies evaluated the comparative effectiveness between stool tests (**Appendix D Table 4**). Two trials and one prospective cohort study evaluated gFOBT versus FIT: the Hol trial (Hemoccult II vs. OC-Sensor), van Rossum trial (Hemoccult II vs. OC-Sensor), and Faivre study (Hemoccult II vs. OC-Sensor, FOB Gold and Magstream). These studies showed a higher number of cancers in the FIT versus Hemoccult II test over one to three rounds of screening. Results were only statistically significant in the observational study, likely owing to larger sample sizes and outcomes. None of these studies reported interval cancers. No subgroup analyses by sex or location in colon were reported.

Three trials and one prospective cohort study evaluated one FIT versus another FIT: the Passamonti trial (OC-Sensor vs. HM-JACK), Santare and Zubero trials (OC-Sensor vs. FOB Gold), and Faivre study (OC-Sensor vs. FOB Gold vs. Magstream). Among these studies there was no statistically significant differences in cancers between FIT after one or two rounds of screening, despite some differences in test positivity among the different FITs. None of these studies reported interval cancers. The Passamonti trial[131] did not find any statistically significant differences in cancer yield by sex or location in the colon between the two FITs.

Two trials and one prospective cohort study evaluated one-sample versus two-sample FITs or FITs at different intervals of testing: the van Roon trial[145] (OC-Sensor q1 vs. q2 vs. q3 year intervals), Schreuders trial[139] (OC-Sensor, 1 vs. 2 samples), and Faivre study[123] (OC-Sensor or FOB Gold, 1 vs. 2 samples). Overall, the number of cancers detected was low and there were no statistically significant differences in the number of cancers detected between the different intervals of testing or different number of samples collected. Over four rounds of screening, the collection of two samples of OC-Sensor versus one sample resulted in a higher colonoscopy demand without a significant increase in cancer yield or decrease in interval cancers.[139] Additionally there were no meaningful differences in cancer yield by sex or location in the colon between the one-sample versus two-sample FIT.

We found no prospective studies evaluating the comparative effectiveness of sDNA screening on cancer incidence or mortality.

Serum or Urine Testing

We found no prospective studies evaluating the comparative effectiveness of serum- or urine-based screening on cancer incidence or mortality.

KQ2. What Is the Accuracy of Direct Visualization, Stool-Based, or Serum-Based Screening Tests for Detecting Colorectal Cancer, Advanced Adenomas, or Adenomatous Polyps Based on Size? Does the Accuracy of the Screening Tests Vary by Subgroups (e.g., Age, Sex, Race/Ethnicity)?

Summary of Results

Our review focuses on per-person screening test accuracy for direct visualization tests and stool-, serum- and urine-based testing to detect CRC, advanced adenomas, or both (advanced neoplasia). When available, we also include the per-person test accuracy for adenomas by size (i.e., ≥10 or ≥6 mm). Overall, we found no new studies since our prior review that add to our understanding of screening sensitivity or specificity for colonoscopy, CTC, or flexible sigmoidoscopy. We found several new studies evaluating the sensitivity and specificity of capsule endoscopy and stool-, serum-, and urine-based tests for screening.

Direct Visualization Tests

We included nine fair- to good-quality studies evaluating screening CTC, four of which also reported the test accuracy of colonoscopy generalizable to community practice (**Table 12**).

Flexible Sigmoidoscopy

There were no studies evaluating the test accuracy of screening flexible sigmoidoscopy.

Colonoscopy and CTC

Based on these studies, we know that both colonoscopy and CTC can miss cancers; however, these studies were not powered to estimate the test accuracy for CRC as the number of CRCs in these studies were low.

Based on three studies that compared colonoscopy to a reference standard of CTC-enhanced colonoscopy or repeat colonoscopy (n=2,290), the per-person sensitivity for adenomas 10 mm or larger ranged from 0.89 (95% CI, 0.78 to 0.96) to 0.95 (95% CI, 0.74 to 0.99), and the per-person sensitivity for adenomas 6 mm or larger ranged from 0.75 (95% CI, 0.63 to 0.84) to 0.93 (95% CI, 0.88 to 0.96). Specificity could only be calculated from one of the included studies; it was 0.89 (95% CI, 0.86 to 0.91) for adenomas 10 mm or larger and 0.94 (95% CI, 0.92 to 0.96) for adenomas 6 mm or larger.

Based on seven studies of CTC with bowel preparation (n=5,328), the sensitivity and specificity to detect adenomas 10 mm or larger ranged from 0.67 (95% CI, 0.45 to 0.84) to 0.94 (95% CI, 0.84 to 0.98) and 0.86 (95% CI, 0.85 to 0.87) to 0.98 (95% CI, 0.96 to 0.99), respectively. Likewise, the sensitivity and specificity to detect adenomas 6 mm or larger ranged from 0.73 (95% CI, 0.58 to 0.84) to 0.98 (95% CI, 0.91 to 0.99) and 0.80 (95% CI, 0.77 to 0.82) to 0.93 (95% CI, 0.90 to 0.96), respectively. Although there is some variation in estimates of sensitivity and specificity among included studies, it is unclear whether the variation of test performance is due to differences in study design, populations, CTC imaging, or in reader experience or reading of protocols.

Capsule Endoscopy

Based on two fair-quality studies (n=920) evaluating screening capsule endoscopy, the sensitivity to detect adenomas 10 mm or larger ranged from 0.92 to 1.0 (95% CI range, 0.70 to 1.0) and specificity ranged from 0.95 to 0.98 (95% CI range, 0.93 to 0.99). For adenomas 6 mm or larger, one study reported a sensitivity of 0.91 (95% CI, 0.85 to 0.95) and specificity of 0.83 (95% CI, 0.80 to 0.86). However, in both studies, there was a high proportion of persons with inadequate or incomplete capsule endoscopy.

Stool Tests

Stool tests to screen for CRC include HSgFOBT (Hemoccult Sensa), FIT (e.g., OC-Sensor, OC-Light), and sDNA-FIT (Cologuard). We included five fair-quality studies evaluating Hemoccult

Sensa (two of which used a colonoscopy reference standard for all participants), 44 fair- to good-quality studies evaluating different FITs (25 of which used a colonoscopy reference standard for all), and four fair-quality studies evaluating Cologuard (all 4 used a colonoscopy reference standard) (**Table 13**).

High-Sensitivity gFOBT

Based on two studies (n=3,503) of Hemoccult Sensa using colonoscopy as a reference standard, sensitivity to detect CRC ranged from 0.50 to 0.75 (95% CI range, 0.09 to 1.0) and specificity ranged from 0.96 to 0.98 (95% CI range, 0.95 to 0.99). Sensitivity to detect CRC from two studies (n=10,170) employing a cancer registry followup ranged from 0.62 to 0.79 (95% CI range, 0.36 to 0.94). Hemoccult Sensa was not sensitive to detect AA (sensitivity range 0.06 to 0.17; 95% CI range, 0.02 to 0.23).

FIT

A wide variety of FITs are available. Those most commonly evaluated in our review were part of the OC-Sensor family (Polymedco in the United States or Eiken Chemical outside of the United States); in the included studies they were referred to as: OC FIT-CHEK, OC-Auto, OC-Micro, OC-Sensor, and OC-Sensor Micro. Additionally, the OC-Light test (also by the same manufacturer but using a different methodology) and the OC-Hemodia (also by the same manufacturer but discontinued) tests were evaluated in more than two studies. Twenty-one other tests were evaluated in two or fewer studies. Based on nine studies (n=34,352) using OC-Sensor tests to detect CRC with a colonoscopy reference standard and the manufacturer-recommended cutoff of 20 μg Hb/g feces, pooled sensitivity was 0.74 (95% CI, 0.64 to 0.83; I^2=31.6%) and pooled specificity was 0.94 (95% CI, 0.93 to 0.96; I^2=96.6%). As expected at lower cutoffs (10 and 15 μg Hb/g feces), sensitivity increased and the corresponding specificities decreased. Based on 10 studies (n=40,411) using OC-Sensor tests to detect AA with a colonoscopy reference standard, sensitivity and specificity using a cutoff of 20 μg Hb/g feces were 0.23 (95% CI, 0.20 to 0.25; I^2=47.4%) and 0.96 (95% CI, 0.95 to 0.97; I^2=94.8), respectively. Based on three studies (n=31,803), OC-Light had similar sensitivity and specificity to detect CRC and AA compared with OC-Sensor. Only four studies using registry follow-up reported test accuracy of FITs over multiple rounds of testing; in two of these studies, sensitivity to detect cancer was lower in the second round of screening, however estimates were imprecise with confidence intervals widely overlapping. While studies examining differences in test accuracy by age, sex, and race/ethnicity were limited, we found no consistent differences by subgroup. Overall, in 10 studies there were no significant differences in test accuracy by age strata, although 2 studies suggest possible lower specificity to detect CRC in older persons (age 70 years and older). Six studies reporting test accuracy by sex had inconsistent findings, with two studies of OC-Sensor which suggest higher sensitivity with lower specificity in men compared with women.

sDNA

Currently, the only available sDNA screening test is one with a FIT assay marketed as Cologuard (Exact Sciences; Madison, WI), sometimes referred to as a multitarget stool DNA test. Based on four studies (n=12,424) to detect CRC using a colonoscopy, pooled sensitivity and specificity was 0.93 (95% CI, 0.87 to 1.0) and 0.85 (95% CI, 0.84 to 0.86), respectively; pooled sensitivity and specificity to detect AA was 0.43 (95% CI, 0.40 to 0.46) and 0.89 (95% CI, 0.86 to 0.92), respectively. Based on one study, the specificity to detect CRC and AA decreases with increasing age.

Serum Test

Currently, one serum test—Epi proColon (Epigenomics, Germantown, MD)—is available to screen average-risk adults for CRC through detection of circulating methylated *SEPT9* DNA. Based on one fair-quality nested case-control study (n=6857), sensitivity and specificity to detect CRC were 0.68 (95% CI, 0.53 to 0.80) and 0.79 (95% CI, 0.77 to 0.81), respectively. The sensitivity and specificity to detect AA were 0.22 (95% CI, 0.18 to 0.24) and 0.79 (95% CI, 0.76 to 0.82), respectively.

Urine Test

We identified one urine test to detect adenomas, a metabolomic-based urine test called PolypDx (Metabolomic Technologies Inc., Edmonton, Canada) that combines three clinical features (age, sex, and smoking status) with three urine metabolites (succinic acid, ascorbic acid, and carnitine). Based on one fair-quality study (n=685) in average and high-risk participants (i.e., personal or family history of CRC or polyps), the sensitivity and specificity to detect AN in the testing dataset (n=228) were 0.43 (95% CI range, 0.30 to 0.57) and 0.91 (95% CI range, 0.87 to 0.96), respectively; however, multiple thresholds were evaluated and higher sensitivities could be obtained with a tradeoff in specificity.

Detailed Results for Direct Visualization Tests

Flexible Sigmoidoscopy

We identified no studies evaluating the test performance of FS with a colonoscopy reference standard in average-risk screening populations.

CT Colonography

We found nine test accuracy studies[169, 172, 177, 178, 181, 184, 188, 195, 205] in 10 articles[169, 172, 177, 178, 181, 184, 188, 195, 205, 350] that evaluated CTC as a screening test to detect colorectal lesions in asymptomatic average-risk people (**Table 12**). All of these studies were included in the previous review.[82, 83]

Study and Population Characteristics

Six (n=5,453) of the nine studies were conducted in the United States (**Table 14**).[169, 177, 178, 188, 195, 205] Three of them (n=4,369) were multicenter trials.[177, 195, 205] The sample sizes for the nine studies ranged from 68 to 2,531. While four studies included people age 40 years and older,[169, 178, 181, 195] two of them[181, 195] required a family history for people ages 40 to 50 years. The mean age spanning all studies ranged from 55 to 65 years. All trials excluded people with familial hereditary CRC syndromes, and two trials also explicitly excluded people with family history of CRC in first-degree relatives.[172, 188] The baseline prevalence of cancer in the populations ranged from 0.16 to 1.1 percent. The proportion of female participants ranged from 41 to 60 percent, except for one small trial (n=68) conducted exclusively in men in a VA medical center setting.[188] Four studies reported race/ethnicity;[169, 177, 178, 205] 83 to 91 percent of participants in those studies were white.

All included studies evaluated multidetector CTC using supine and prone imaging positions, although protocols for bowel preparation, imaging, and reading images varied among studies. Seven studies (n=5,328) evaluated CTC with bowel preparation with[177, 184, 195] or without fecal tagging,[172, 178, 181, 188] and two studies (n=1,169) evaluated CTC without bowel preparation and with fecal tagging.[169, 205] Bowel preparation varied among studies (from full preparation with polyethylene glycol and magnesium citrate to more limited preparation using sodium phosphate and/or sodium picosulfate). One study[181] administered intravenous contrast as part of the CTC protocol. There was also variation in the number of detectors, reconstruction interval, collimation, and slice thickness. One trial[177] used a large sample of CTC readers (15 radiologists). While readers generally used a combination of two- and three-dimensional reading strategies, the primary reading strategy varied. The test positivity (at least one lesion 5 or 6 mm or larger) for people undergoing screening CTC ranged from 10 to 30 percent.

All nine studies used colonoscopy as the reference standard. Only three of the studies,[172, 195, 205] however, used CTC-enhanced colonoscopy (i.e., colonoscopy with segmental unblinding). Colonoscopies were generally provided by staff gastroenterologists with cecal intubation ranging from 94 to 100 percent.

Five studies were good quality[169, 172, 177, 195, 205] and the remaining four were fair quality. Limitations of fair-quality studies included limited reporting on study details (e.g., attrition, exclusions due to inadequate CTC or colonoscopy), a small number of included participants, and, in one study, attribution of lesions seen on CTC but not colonoscopy as false-positives.

CT Colonography With Bowel Preparation

Test Accuracy for CRC

Six studies reported the per-person sensitivity of CTC with bowel preparation to detect CRC; however, the number of cancers was low, ranging from one to seven (**Table 15**). Sensitivity ranged from 0.86 to 1.0 (95% CI range, 0.21 to 1.0).

Test Accuracy for AA

Three studies[172, 181, 184] evaluating CTC with bowel preparation (n=1,044) reported accuracy to detect advanced adenomas, although only two of the studies[172, 184] reported both sensitivity and specificity. The per-person sensitivity and specificity to detect advanced adenomas ranged from 0.88 to 1.0 (95% CI range, 0.66 to 1.0) and 0.39 to 0.87 (95% CI range, 0.34 to 0.90), respectively.[172, 181, 184] Test accuracy specifically for SSLs were not reported.

Test Accuracy for Adenomas by Size

Among five included studies using bowel preparation (n=4,764), the per-person sensitivity for adenomas 10 mm or larger ranged from 0.67 to 0.94 (95% CI range, 0.45 to 0.99) and specificity ranged from 0.86 to 0.98 (95% CI, 0.85 to 0.99). The pooled estimate for sensitivity was 0.89 (95% CI, 0.83, 0.96; I^2=41.7%) and for specificity was 0.94 (95% CI, 0.89 to 1.0; I^2=98.3%) (**Figure 11**).

The per-person sensitivity for adenomas 6 mm or larger among five included studies using bowel preparation (n=4,808) ranged from 0.73 to 0.98 (95% CI range, 0.57 to 1.0).[172, 177, 181, 184, 195] Among four studies using bowel preparation (n=4,567), the per-person specificity for adenomas 6 mm or larger ranged from 0.80 to 0.93 (95% CI range, 0.77 to 0.96).[172, 177, 184, 195] The pooled estimate for sensitivity was 0.86 (95% CI, 0.78 to 0.95; I^2=87.4%) and for specificity was 0.88 (95% CI, 0.83 to 93; I^2=94.9%) (**Figure 12**).As described above, there is variation among CTC imaging and reading protocols, as well as variation in the study design and population characteristics among the studies. Because of the limited number of studies and the number of variables contributing to clinical heterogeneity, the key determinants accounting for the variation in test performance are still unclear. There is some evidence to suggest that fecal tagging improves sensitivity. It is unclear from this body of evidence whether primary two- or three-dimensional reading strategy or radiologist choice of primary reading strategies improves sensitivity.

By Stage or Location

Four studies of CTC with bowel preparation reported on the distribution of lesions in the colon.[172, 177, 184, 195] The percent of adenomas 10 mm or larger in the distal colon was 49 to 73 percent, and the percent of adenomas 6–9 mm was 48 to 66 percent. Only one study reported sensitivity and specificity of lesions by location in the colon[172]; the sensitivity for advanced adenomas did not vary significantly by location (proximal, 0.89% [95% CI, 0.59 to 0.99] vs. distal, 0.92 [95% CI, 0.76 to 0.98]).

By Age, Sex, Race/Ethnicity, or Family History

One study[177] reported post hoc analyses for sensitivity and specificity by age in a subsequent publication.[350] This study found nonstatistically significant lower per-person sensitivities for the detection of adenomas or cancers in people age 65 years and older (n=477) compared with those younger than age 65 years (n=2,054). The per-person sensitivity for adenomas or cancers 10 mm or larger in older adults compared with middle-aged adults was 0.82 (95% CI, 0.64 to 0.94) and 0.92 percent (95% CI, 0.84 to 0.97), respectively. Likewise, the per-person sensitivity for adenomas or cancers 6 mm or larger in older adults compared with middle-aged adults was 0.72 (95% CI, 0.56 to 0.85) and 0.81 (95% CI, 0.74 to 0.88), respectively. The authors noted that there were differences in bowel preparation and distention by age group.

No other subgroups were reported.

CTC Without Bowel Preparation

Two studies (n=1,169) evaluated CTC performance without bowel preparation but with fecal tagging (**Tables 13 and 14**).[169, 205] Both studies were good quality and conducted in the United States. Neither study was designed to estimate the test accuracy to detect CRC, as the total number of CRC cases was very low (4 cancers). One study (n=564), which was conducted by Fletcher and colleagues,[169] reported per-person sensitivity and specificity for detection of adenomas 6 mm or larger and for adenomas 10 mm or larger that appeared comparable to those studies using bowel preparation, although the sensitivity for detection of advanced neoplasia was lower at 65.3 percent (95% CI, 44.3 to 82.8). In the second study (n=605), conducted by Zalis and colleagues,[205] the per-person sensitivity and specificity for detection of adenomas 10 mm or larger appeared comparable to those studies using bowel preparation, although the sensitivity for adenomas 6 mm or larger was lower (57.7% [95% CI, 45.4 to 69.4]). This study did not report test performance for advanced adenomas or advanced neoplasia. Given the clinical heterogeneity among studies with and without bowel preparation, it is unclear from these two studies whether lower sensitivities for detection of certain lesions are due to lack of bowel preparation use or other differences in study design, population, or CTC protocol. No additional results by stage, location, or subgroups were reported.

Colonoscopy

We found no tandem colonoscopy studies that met our inclusion criteria requiring screening colonoscopy performance representative of community practice. Seven of the included diagnostic accuracy studies evaluating CTC also reported on sensitivity and/or specificity of colonoscopy. Four of these studies (n=4,821) included a larger number of endoscopists and have greater applicability to colonoscopy performance in community practice (**Table 12**).[177, 178, 195, 205] All of these studies were included in the previous review.

Study and Population Characteristics

All four of the included studies were conducted in the United States (**Table 14**). Three of these studies (n=4,369) were multicenter.[177, 178, 205] All studies recruited similar populations of asymptomatic, average-risk adults age 50 years or older. Two studies also included people age 40 years and older with or without a family history.[178, 195] The mean age in studies ranged from 58 to 65 years. The baseline prevalence of cancer in the populations ranged from 0.16 to 1.1 percent. Two studies included more than 15 percent nonwhite participants.[177, 178]

One study reported the number of endoscopists; the others either suggested a large number of endoscopists without reporting the actual number or were conducted in multiple clinical sites. All studies stated that colonoscopies were conducted (or supervised) by an experienced gastroenterologist or surgeon. Two studies reported the cecal intubation rate (both ≥99%).[178, 195]

Studies were rated as fair- to good quality. The studies primarily aimed at determining the test accuracy of CTC, which also provided data to calculate the per-person and/or per-lesion sensitivity for CRC and adenomas. Two studies used colonoscopy enhanced with CTC as their criterion standard.[195, 205] In this study design, colonoscopy was performed after CTC examination and interpretation, with unblinding of CTC results after examination of each segment of the colon. For any suspected lesion on CTC that measured larger than 5 mm and was not seen on the initial “blinded” colonoscopy, the endoscopists re-examined that segment and could review the CTC image for guidance. In the other two studies, participants could have a repeat colonoscopy if indicated by CTC.[177, 178] Despite this approach, however, not all participants advised to have a repeat colonoscopy received one. In the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial, for example, only 12 of the 27 people who were recommended to receive a repeat colonoscopy for lesions detected on CTC actually received the second colonoscopy.[177]

Test Accuracy for CRC

In two trials (n=1,685), colonoscopy missed CRCs (**Table 16**).[178, 195] In one fair-quality study (n=452) conducted by Johnson and colleagues, the colonoscopy was performed or supervised by one of 50 staff gastroenterologists or surgeons blinded to CTC findings.[178] In this study, repeat colonoscopy was performed on six patients in whom lesions 10 mm or larger were missed that were deemed by consensus to have a high likelihood of being a true neoplasm. Because four of the missed lesions were later determined to be adenocarcinomas, the index colonoscopy only detected one of the five CRC cases. In another study (n=1,233), conducted by Pickhardt and colleagues, colonoscopy was conducted by one of 17 experienced gastroenterologists or surgeons blinded to CTC findings.[195] In this study, index colonoscopy results were compared with colonoscopy with segmental unblinding. Colonoscopy detected one of two CRC cases.

Test Accuracy for AA

Sensitivity and specificity for AN or AA were not reported.

Test Accuracy for Adenomas by Size

Per-person and per-lesion sensitivity and specificity for adenomas did not differ significantly by study, and per-lesion accuracy was more commonly reported (**Table 16**). The per-person sensitivity for adenomas 10 mm or larger ranged from 0.89 to 0.95 (95% CI range, 0.70 to 0.99) and the per-person sensitivity for adenomas 6 mm or larger ranged from 0.75 to 0.93 (95% CI range, 0.63 to 0.96). The per-lesion (per-person sensitivity not reported) sensitivity of colonoscopy in ACRIN for adenomas 10 mm or larger was 0.98 percent (95% CI, 0.93 to 1.0).[177] Specificity could only be calculated in one of the included studies. This good-quality study (n=605) by Zalis and colleagues[205] observed a per-person specificity for adenomas 10 mm or larger of 0.89 (95% CI, 0.86 to 0.91) and 0.94 (95% CI, 0.92 to 0.96) for adenomas 6 mm or larger.[205]

By Stage, Location, Age, Sex, Race/Ethnicity, or Family History

No subgroup results by age, sex, race/ethnicity, or family history were reported.

Capsule Endoscopy

We identified two studies evaluating the test performance of the second-generation colon capsule endoscopy, or PillCam™ COLON 2 (Given Imaging Ltd., Yoqneam, Israel) in participants scheduled for a screening colonoscopy.[198]

Study and Population Characteristics

One study took place in the United States and Israel and analyzed 695 participants (of 884 recruited); the other was conducted in the Czech Republic and analyzed 225 participants (of 236 recruited). Mean age ranged from 57 to 59 years, and 47 to 56 percent were female. Participants with a family history were excluded from both studies. Prevalence of CRC ranged from 0.6 to 0.9 percent, and 4.0 to 6.2 percent had an adenoma 10 mm or larger.

Both studies were rated fair quality, primarily because a large proportion of the enrolled samples could not complete the capsule endoscopy procedure (e.g., inadequate cleansing, problem with transit time). The reference standard consisted of colonoscopy. The capsule endoscopy findings were unblinded when a significant finding was identified with the capsule endoscopy but not the conventional colonoscopy.

Test Accuracy for CRC

Capsule endoscopy identified all patients with CRC, with a per-person sensitivity of 1.00 for both studies (95% CI range, 0.34 to 1.0). Specificity was reported in one study, at 1.0 (95% CI, 0.98 to 1.0).

Test Accuracy for Adenomas by Size

Per-person sensitivity of capsule endoscopy to detect adenomas 10 mm or larger ranged from 0.92 to 1.0 (95% CI range, 0.70 to 1.0) and specificity ranged from 0.95 to 0.98 (95% CI range, 0.93 to 0.99). One study reported test accuracy for adenomas 6 mm or larger; sensitivity was similar at 0.91 (95% CI, 0.85 to 0.95), but specificity was lower at 0.83 (95% CI, 0.80 to 0.86).

By Stage, Location, Age, Sex, Race/Ethnicity, or Family History

No subgroup results by age, sex, race/ethnicity, or family history were reported.

Detailed Results for Stool-Based Tests

High-Sensitivity gFOBT

Five studies[151-153, 185, 200] (n=19,472) reported results of a HSgFOBT (Hemoccult Sensa, manufactured by Beckman Coulter) in adults at average risk for CRC (**Table 17**). Three of these studies[152, 153, 185] were included in the previous systematic review.

Study and Population Characteristics

Four studies took place in the United States; the fifth was in Israel and the United Kingdom (**Table 17**). All five were cross-sectional test-accuracy studies reporting the performance of a one-time Hemoccult Sensa. The number of people screened ranged from 1,006 to 7,904. All studies recruited only adults 50 years or older; a mean age was reported in one study (60 years). Race/ethnicity was reported in four studies in which the majority of participants were white (54 to 93%). One study[200] reported 13 percent of participants had a first-degree relative with CRC, and a second study[151] excluded people with two or more first-degree relatives with colorectal neoplasia. Prevalence of CRC ranged from 0.2 to 0.6 percent. Two studies[151, 200] had followup to accurately ascertain advanced adenoma prevalence; prevalence of advanced adenomas ranged from 5.3 to 5.8 percent.

Two studies used colonoscopy as the reference standard to identify colorectal lesions, regardless of the result of the gFOBT. The other three studies used a cancer registry with 2 years of followup; one also used a colonoscopy for patients with abnormal gFOBT results, another used colonoscopy for patients with abnormal gFOBT results and an FS for the other patients, and the third used a FS for all abnormal tests.

All five studies were rated fair quality due to differential verification, unclear or no blinding of the gFOBT results for those performing the colonoscopy (or other direct visualization method), or unclear methods of patient selection. Additionally, in one study[151] a subgroup of randomized patients were not given dietary restrictions, which may have increased the rate of false positives for Hemoccult Sensa.

Test Accuracy for CRC

Two studies[151, 200] (n=3,503) with colonoscopy followup for all participants reported test accuracy for CRC; sensitivity ranged from 0.50 to 0.75 (95% CI range, 0.09 to 1.0) and specificity ranged from 0.96 to 0.98 (95% CI range, 0.95 to 0.99) (**Table 17**).

Test Accuracy for AN and AA

The same two studies[151, 200] (n=3,503) with colonoscopy followup for all participants reported test accuracy of Hemoccult Sensa to detect AN (including SSL for one study[200]); sensitivity ranged from 0.07 to 0.21 (95% CI range, 0.02 to 0.27) and specificity ranged from 0.96 to 0.99 (95% CI range, 0.96 to 0.99) (**Table 17**). The same studies also reported test accuracy for AA; sensitivity to detect AA ranged from 0.06 to 0.17 (95% CI range, 0.02 to 0.23) and specificity ranged from 0.96 to 0.99 (95% CI range, 0.96 to 0.99). One study[200] reported sensitivity for SSL at 0.03 (95% CI, 0.0 to 0.09).

Alternate Study Designs

Two studies[152, 185] (n=10,170) with registry followup reported test accuracy of HSgFOBT to detect CRC; sensitivity ranged from 0.62 to 0.79 (95% CI range, 0.36 to 0.94) and specificity ranged from 0.87 to 0.96 (95% CI range, 0.86 to 0.97) (**Table 17**).

By Stage or Location

One study[153] (n=5,799) with registry and FS followup reported only distal CRC (**Table 17**). Sensitivity of Hemoccult Sensa to detect distal CRC was 0.64 (95% CI, 0.36 to 0.86). No other studies reported stage or location subgroups.

By Age, Sex, Race/Ethnicity, or Family History

No subgroups by age, sex, race/ethnicity, or family history were reported.

FIT

We identified 45 studies (in 61 articles) evaluating the test accuracy of a FIT to detect CRC, AN, and/or AA; 20 of these studies were newly identified (**Table 19**).

Study and Population Characteristics

Eight studies were conducted solely in the United States, and one study was conducted in the United States and Canada (**Table 19**). The remaining studies were conducted in Taiwan (k=7), Germany (k=4), Japan (k=4), the Netherlands (k=5), South Korea (k=4), Spain (k=3), and Hong Kong (k=2), and one study each was conducted in Italy, Denmark, France, Slovenia, Sweden, in both Israel and the United Kingdom, and in both Australia and Asia. Twenty-eight studies were cross-sectional test accuracy studies examining a one-time FIT; these studies had sample sizes ranging from 307 to 9,989 participants except for one large study (n=21,805) recruiting people over a period of 20 years for a comprehensive health examination in Japan. Seventeen studies were conducted within the context of a screening program and their sample sizes ranged from 2,235 to 956,005 participants. One study was a nested case-control design with a sample of 516. Most studies recruited participants 40 or 50 years or older, but three studies allowed adults of any age. Mean age was reported in 24 studies and ranged from 47 to 68 years. Participants with a family history of CRC—typically defined as a first-degree relative with CRC, but not always specified—were specifically excluded in six studies. Eight studies reported that 3 to 13 percent of participants had a family history of CRC, while the remaining studies did not have any specific exclusion criteria related to family history or did not report the proportion with a family history. Race/ethnicity was sparsely reported (k=10); percent white ranged from 0 to 96. Prevalence of CRC was very low and when present, ranged from 0.001 to 1.7 percent (with the exception of 3.1% for the nested case-control study). Prevalence of advanced adenomas varied widely and ranged from 0.08 to 11.8 percent (39% for the nested case-control study).

There is wide variation in the characteristics of available FITs (**Appendix D Table 1**). They are available as quantitative or qualitative tests, as laboratory or point-of-care tests, and they differ in methodology. The most commonly used FITs in our included studies were part of the OC-Sensor family (Polymedco in the United States or Eiken Chemical outside of the United States); in the included studies they were referred to as OC FIT-CHEK, OC-Auto, OC-Micro, OC-Sensor Micro, and OC-Sensor. The OC-Light test—by the same manufacturer but using a different methodology—was used in four studies. The OC-Hemodia test, also manufactured by Eiken Chemical, was used in three studies; however, the test is no longer available. Many other FITs were also represented, but not robustly studied, including A Clearview, CAREprime Hb, Eurolyser FOB test, FlexSure OBT, FOB Gold, Hb ELISA, HemeSelect, Hemo Techt NS-Plus C system, Hemosure, HM-Jack, I Clearview, ImmoCARE-C, InSure FIT, Magstream tests (including Magstream 1000, Magstream 1000/Hem SP), Monohaem, QuantOn Hem, QuickVue, QuikRead go iFOBT, RIDASCREEN Hb, RIDASCREEN Hemoglobin-Haptoglobin Complex, and SENTiFIT-FOB Gold. Two studies whose results were published after the previous review accounted for seven new FITs; however, six of them were examined in one nested case-control study,[171] and the reported test performance is likely not representative of what would be seen among average-risk adults in primary care. One multisite study[164] used OC-Sensor plus a variety of other stool tests for different study sites and analyzed them together. Most of the sites that did not use OC-Sensor were in countries that did not meet our inclusion criteria, and we will not discuss their combined results.

Two different reference standards were used to identify colorectal lesions. In 26 studies, the FIT was followed by a colonoscopy for all participants (in one study,[172] colonoscopy with segmental unblinding from CTC was used), regardless of the results of the FIT. Nineteen studies employed a combination of cancer registries for all participants and direct visualization for participants with an abnormal FIT result. In those studies, direct visualization was usually achieved with a colonoscopy, but sometimes CTC, FS, and/or BE were used. The studies using cancer registries to identify colorectal cancer were completed in the context of a large screening program (country, state, city, or region), sometimes using an initial round of FIT screening in a location where a colorectal cancer screening program had not yet been initiated, sometimes using a single round of screening where a cancer screening program had already been in place, and sometimes using more than one round of a screening program with the findings collapsed together.

Nine studies were rated good quality. Studies at higher risk of bias and rated as fair quality were those with differential verification, unclear or no blinding of the FIT results for those performing the colonoscopy (or other direct visualization method), unclear methods of patient selection, and concerns about patient attrition (such as a high proportion of unreadable screening tests). One new study was rated as poor quality and excluded, primarily due to a lack of reporting and therefore an inability to ascertain the risk of bias.

OC-Sensor Family

Test Accuracy for CRC

Nine studies (n=34,352)[156, 164, 167, 174, 175, 180, 194, 197, 200] using OC-Sensor tests to detect CRC with a colonoscopy reference standard for all participants were pooled at the manufacturer-recommended cutoff of 20 μg Hb/g feces; sensitivity to detect CRC was 0.74 (95% CI, 0.64 to 0.83; I^2=31.6%) and specificity was 0.94 (95% CI, 0.93 to 0.96; I^2=96.6%) (**Figure 13, Appendix E Figure 1, and Table 20**). At lower cutoffs (15 and 10 μg Hb/g feces), the sensitivity to detect CRC increased (0.92 and 0.99, respectively) and the corresponding specificities decreased (0.92 and 0.90, respectively). These lower cutoffs, however, had few studies to pool (k=3), and the confidence intervals overlapped with those from the other cutoffs; thus, the pooled results should be interpreted with caution. Higher cutoffs for OC-Sensor tests were also reported (23, 25, 30, and 40 μg Hb/g feces), but by only one study each.

Test Accuracy for AN and AA

Twelve studies (n=38,689)[156, 164, 166, 167, 174, 175, 180, 187, 194, 197, 200, 206] using OC-Sensor tests to detect AN with a colonoscopy reference standard for all participants were pooled at a cutoff of 20 µg Hb/g feces; sensitivity to detect AN was 0.25 (95% CI, 0.21 to 0.30; I^2=78.1%) and specificity was 0.96 (95% CI, 0.95 to 0.97; I^2=93.9%) (**Figure 14 and Table 20**). Similar to the results for CRC, at lower cutoffs sensitivity increased and specificity decreased. Again, few studies per cutoff and overlapping confidence intervals mean these results should be interpreted with caution.

Ten studies (n=40,411)[156, 158, 164, 167, 174, 175, 180, 194, 197, 200] using OC-Sensor tests to detect advanced adenomas with a colonoscopy reference standard for all participants were pooled at a cutoff of 20 µg Hb/g feces; sensitivity to detect AA was 0.23 (95% CI, 0.20 to 0.25; I^2=47.4%) and specificity was 0.96 (95% CI, 0.95 to 0.97; I^2=94.8) (**Figure 15 and Table 20**). All but one of these studies[158] also reported test accuracy to detect AN. Since most of the lesions were advanced adenomas and not cancers, the AA data are similar to the AN data. Advanced adenomas were usually defined as adenomas 1 cm or larger in size, with tubulovillous or villous components, or high-grade dysplasia, but three studies[175, 197, 200] also grouped SSL with advanced adenomas. For the three studies including SSLs, sensitivity was similar to the other studies (ranging from 0.16 to 0.24) and their removal from the pooled analysis did not affect the overall sensitivity (0.24 [95% CI, 0.20 to 0.28]).

Four studies[158, 166, 175, 200] also reported sensitivity for sessile serrated lesions alone (with one study[175] examining only sessile serrated polyps 1 cm or larger). At a cutoff of 20 µg Hb/g feces, sensitivity to detect SSLs ranged from 0.02 to 0.07 (95% CI range, 0.0 to 0.15).

Alternate Study Designs

Eight studies (n=2,476,032)[154, 159-161, 170, 173, 179, 189] using OC-Sensor tests to detect CRC, with cancer registry followup to identify CRC, were pooled at a cutoff of 20 µg Hb/g feces (**Appendix D Table 5 and Appendix E Figure 2**). The pooled estimate of sensitivity to detect CRC (0.81 [95% CI 0.74 to 0.88]) for these studies with registry followup was higher than that of the studies with colonoscopy provided to all participants; however, the confidence intervals overlapped. The pooled specificity was consistent with the studies with colonoscopy for all participants (0.95 [95% CI, 0.94 to 0.96]). Two of the studies reported cutoffs at 10 and/or 15 µg Hb/g feces; one study reporting all three cutoffs (10, 15, and 20 µg Hb/g feces) showed the same trend of increasing sensitivity and decreasing specificity as the cutoff was lowered. In another study[173] with multiple cutoffs (2.2, 2.8, 4.4, 7.2, 9, and 10 µg Hb/g feces) sensitivity appeared to increase for lower test cutoffs as well.

One nested case-control study[171] in Germany compared the performance of nine quantitative FITs, including OC-Sensor. The sensitivity of OC-Sensor to detect colorectal lesions was lower than that found in our other included studies. However, within that study, OC-Sensor had similar test performance compared with the other FITs and the confidence intervals for all FITs overlapped with one another. The authors reported that a desired specificity could be achieved with similar sensitivities for all tests by adjusting cutoffs.

Three studies[173, 199, 202] using OC-Sensor reported sensitivity for more than one round of screening. Two of these studies[173, 202] suggested that the sensitivity to detect CRC in the second round of screening was lower than in the initial round of screening; however, estimates of sensitivity were imprecise with 95 percent confidence intervals for both rounds widely overlapping.

By Location or Stage

Three studies[167, 189, 202] examined the test accuracy of OC-Sensor tests to detect CRC by location in the colon (distal or proximal). The findings were inconsistent among the three studies. One of the studies[167] had colonoscopy followup for all participants, but the number of cancers was low (6 distal CRCs and 2 proximal CRCs). The other two studies utilized cancer registries to identify cancers (11 and 419 distal CRCs; 9 and 153 proximal CRCs). Confidence intervals for sensitivity to detect proximal and distal CRC were very wide and overlapped in the two studies with a low number of cancers, but point estimates indicated OC-Sensor was more sensitive for proximal cancers. The largest study indicated OC-Sensor had a higher sensitivity to detect distal CRC at 20 µg Hb/g feces (0.91 [95% CI, 0.88 to 0.93]), than for proximal CRC (0.74 [95% CI, 0.66 to 0.80]).

Two studies[189, 202] presented the test accuracy of OC-Sensor to detect CRC by stage; both studies used cancer registries to identify cancers. In general, there appeared to be a trend of decreasing sensitivity as stage increased, but confidence intervals overlapped and one of the studies[202] had a very low number of CRCs (9 Stage I, 3 Stage II, 6 Stage III, 2 Stage IV), prohibiting making any definitive conclusions.

By Age, Sex, Race/Ethnicity, or Family History

Six studies[154, 159, 161, 180, 189, 199] using either colonoscopy or registry reference standards reported the test accuracy of OC-Sensor for a variety of age groups (i.e., 40-49 years, <50 years, ≥50 years, 50-59 years, 50–75 years, 50–54 years, 55–59 years, 60–64 years, 60-69 years, ≥65 years, 65–69 years, 70–75 years); only two studies[159, 180] stratified their results by age groups under 50 years. Among all studies, there were no patterns or differences in the sensitivity and specificity to detect CRC among different age groups, although one study[199] demonstrated that programmatic sensitivity and specificity both decreased with age.

Three studies reported test accuracy for OC-Sensor by sex.[159, 167, 199] Two large registry followup studies reported the test accuracy of OC-Sensor to detect CRC had different findings. At a cutoff of 20 µg Hb/g feces, one study found no differences between male and female subgroups.[159] A second study consistently found an increased sensitivity and decreased specificity in men compared with women at a variety of cutoffs ($p<0.05$ for sensitivity and specificity at a cutoff of 20 µg Hb/g feces).[199] One additional study with a colonoscopy reference standard reported the test accuracy of OC-Sensor to detect AN, generally reporting higher sensitivities and lower specificities for males at a variety of cutoffs, but these results were not statistically significant.[167]

One study[166] provided a direct within study comparison of Black and white race, although one additional study[197] was limited to Alaska Natives and another[158] was limited to ethnic Chinese.

All three studies used colonoscopy reference standards. When stratified by Black and white race, there were no differences between groups for OC-Sensor detection of advanced neoplasia.

No studies provided test accuracy stratified by family history of CRC.

Other FITs

Test Accuracy for CRC

Nine additional FITs to detect CRC were assessed in 11 studies[155, 156, 162, 163, 165, 183, 190, 192, 193, 200, 204] with a colonoscopy reference standard for all participants (**Figure 16 and Table 20**). OC-Light was the only FIT reported in more than one study (k=3),[162, 163, 165] with pooled sensitivity to detect CRC of 0.81 (95% CI, 0.70 to 0.91; I^2=0%) and specificity of 0.93 (95% CI, 0.91 to 0.96; I^2=99.0%). For other FITs, cutoffs varied from 2 to 100 ug/g and sensitivity ranged from 0.50 to 0.97 (95% CI range, 0.09 to 1.00). Specificity had less variation, ranging from 0.83 to 0.97 (95% CI range, 0.82 to 0.97).

Test Accuracy for AN

We identified 13 studies[155, 156, 162, 163, 165, 183, 186, 190, 192, 193, 200, 201, 204] with 13 FITs to detect advanced neoplasia with a colonoscopy reference standard for all participants (**Table 20**). OC-Light was used in four studies,[162, 163, 165, 186] with pooled sensitivity to detect AN of 0.27 (95% CI, 0.16 to 0.38; I^2=91.4%) and specificity of 0.95 (95% CI, 0.92 to 0.98; I^2=98.8%) at a cutoff of 10 µg Hb/g feces. The only other FIT reported in more than one study was Hemosure (k=2). For the other tests cutoffs varied from 6 to 100 µg Hb/g feces, and the sensitivity to detect AN ranged from 0.02 to 0.66 (95% CI range, 0.01 to 0.99) and specificity ranged from 0.60 to 0.99 (95% CI range, 0.58 to 1.0).

Test Accuracy for AA

Nine studies[155, 156, 162, 163, 165, 190, 193, 200, 204] reported the test accuracy of seven FITs to detect advanced adenomas (**Table 20**). Two studies grouped SSPs with advanced adenomas. Two FITs were reported in more than one study: OC-Light (k=3) and Hemosure (k=2). The pooled sensitivity and specificity of OC-Light to detect AA were 0.28 (95% CI, 0.19 to 0.37; I^2=86.3%) and 0.94 (95% CI, 0.91 to 0.97; I^2=99.2%), respectively. For the other FITs, cutoffs varied from 2 to 100 µg Hb/g feces and sensitivity to detect AA ranged from 0.18 to 0.50 (95% CI range, 0.13 to 0.56), but specificity was more consistent between studies (range 0.85 to 0.98 [95% CI range, 0.84 to 0.98]).

Alternate Study Designs

We identified ten additional studies using eight FITs (OC-Hemodia, OC-Sensor combined with FOB Gold, FOB Gold, HM-Jack, Monohaem, Magstream, HemeSelect, and FlexSure OBT) to screen for CRC with cancer registry followup to identify CRC cases (**Appendix E Figure 3 and Appendix D Table 5**); only OC-Hemodia tests were reported in more than one study (k=2).[176] The cutoff for the OC-Hemodia tests ranged from 2.2 to 20 µg Hb/g feces, and sensitivity to detect CRC ranged from 0.81 to 0.87 (95% CI range, 0.75 to 0.92). The remaining FITs had sensitivity to detect CRC ranging from 0.69 to 0.90 (95% CI range, 0.45 to 0.94) and specificity ranging from 0.84 to 0.96 (95% CI range, 0.84 to 0.96).

One study[153] reported the sensitivity of a FIT (FlexSure OBT) to detect distal CRC only, with a sensitivity of 0.82 (95% CI, 0.48 to 0.97) and a specificity of 0.97 (95% CI, 0.96 to 0.97). One nested case-control study[171] in Germany (described earlier for OC-Sensor) compared the performance of nine quantitative FITs. The authors reported that a desired specificity could be achieved with similar sensitivities for all FITs by adjusting cutoffs.

One study[154] using OC-Sensor combined with FOB Gold reported sensitivity over two rounds of screening. The sensitivity to detect CRC was similar in the initial and subsequent round of screening.

By Location or Stage

No clear patterns were identified for distal versus proximal CRC detection. One study[204] using Hemosure with colonoscopy followup reported higher sensitivity for proximal versus distal CRC detection, but the confidence intervals overlapped. A study[165] using OC-Light reported higher distal sensitivity, but confidence intervals again overlapped. Two additional studies (one using FOB Gold with colonoscopy followup[155] and the other using OC-Sensor or FOB Gold with registry followup[203]) did not find differences in distal and proximal sensitivity. One other study[153] only reported distal sensitivity for FlexSure OBT (no proximal sensitivity reported); the sensitivity was consistent with the other registry followup study. For advanced neoplasia, five studies[155, 156, 165, 190, 204] of five FITs with colonoscopy followup consistently showed higher sensitivity to detect distal versus proximal neoplasia; three of these studies did not have overlapping confidence intervals. Similarly, sensitivity of distal advanced adenomas was higher than proximal advanced adenomas.

One study[203] using OC-Sensor or FOB Gold for four rounds of screening with registry followup reported higher sensitivity for Stage I versus Stage IV detection, however, there were few Stage IV CRC cases (n=13) and the confidence intervals overlapped.

By Age, Sex, Race/Ethnicity, or Family History

No clear difference in test accuracy by age was found. One study[203] using OC-Sensor or FOB Gold for four rounds of screening with registry followup reported no difference in sensitivity by age groups. OC-Light had lower sensitivity at younger ages in one study,[162] but the study was limited by few CRC cases (n=5 for ages 40–49, n=16 for older ages) and confidence intervals overlapped. For advanced neoplasia and advanced adenomas, two studies with colonoscopy followup[190, 201] reported sensitivity by age; no statistically significant difference was found by age groups.

One study[203] using OC-Sensor or FOB Gold for four rounds of screening with registry followup reported no differences by sex. One study[208] using FOB Gold with registry followup found that sensitivity to detect CRC for females was lower than males at higher cutoffs, but did not differ at lower cutoffs. Two studies[190, 201] with colonoscopy followup also reported no differences in sensitivity for the detection of AA or AN by sex.

There were no race/ethnicity or family history subgroup results reported for other FITs.

sDNA

We identified four studies[166, 175, 197, 209] reporting test accuracy for a sDNA test; all were evaluating a multitarget sDNA test known as Cologuard from a single manufacturer (Exact Sciences). This test evaluates 10 DNA methylation and mutation markers plus the hemoglobin protein using immunochemical testing, therefore in this report is referred to as sDNA-FIT. Three studies[166, 197, 209] published their results after the 2016 review (**Table 13**).

Study and Population Characteristics

Three of the four studies were conducted fully or partially in the United States, the other was conducted in the Netherlands as part of the COCOS trial[209] (**Table 21**). One study had a large sample size of 9,989 participants; the other three studies were smaller and had sample sizes ranging from 661 to 1,014. Prevalence of CRC ranged from 0.3 to 1.5 percent, and prevalence of advanced adenomas ranged from 6.7 to 13.9 percent. Mean or median age ranged from 55 to 64 years; two of the smaller U.S.-based studies recruited participants age 40 years and older; the other two studies recruited participants age 50 years and older. Participants in the largest study and the study conducted in the Netherlands were primarily white (84% and 96%, respectively). This was also true in one of the smaller studies (65% white), which also had a large proportion of Black participants (35%). The remaining study was conducted exclusively among Alaska Natives.

All four studies used colonoscopy as the reference standard for all participants, and all three conducted in the United States were rated as fair quality. These studies were at a higher risk of bias due to patient selection or patient attrition (small differences in the participants who were evaluated versus those who did not have evaluable data). The study conducted in the Netherlands was rated as good quality.

Test Accuracy for CRC

Three studies reported the test accuracy of Cologuard to identify CRC (**Figure 17 and Table 22**). The pooled sensitivity to detect CRC was 0.93 (95% CI, 0.87 to 1.0; I^2=0%) and the pooled specificity was 0.85 (95% CI, 0.84 to 0.86; I^2=37.7%).

Test Accuracy for AN and AA

Four studies reported the test accuracy of Cologuard to identify AN (three studies[175, 197, 209] categorized SSLs—as well as advanced adenomas and CRC—as advanced neoplasia). The pooled sensitivity was 0.47 (95% CI, 0.44 to 0.50; I^2=0%) and the pooled specificity was 0.89 (95% CI, 0.87 to 0.92; I^2=88.8%) (**Figure 17**).

Three studies[175, 197] reported the test accuracy of Cologuard to detect AA. Advanced adenomas were defined as adenomas 1 cm or larger, containing >25% villous component, or high-grade dysplasia, or SSL 1 cm or larger. The pooled sensitivity to detect AA was 0.43 (95% CI, 0.40 to 0.46; I^2=0%) and the pooled specificity was 0.89 (95% CI, 0.86 to 0.92; I^2=87.8%) (**Figure 17 and Table 22**). For large SSL (sessile serrated adenomas or polyps 1 cm or larger plus serrated polyps with dysplasia in one study[209]) alone, three studies[166, 175] reported sensitivity ranging from 0.40 to 0.42 (95% CI range, 0.22 to 0.61). For any size SSL, one study[166] reported a sensitivity of 0.28 (95% CI, 0.16 to 0.43).

By Location or Stage

One study[175] reported sensitivity of Cologuard to detect advanced adenomas by location. For distal advanced adenomas, sensitivity was 0.54 (95% CI, 0.49 to 0.60) and for proximal advanced adenomas, sensitivity was 0.33 (95% CI, 0.29 to 0.38).

By Age, Sex, Race/Ethnicity, or Family History

The largest study[175, 351] on Cologuard reported test accuracy by age, sex, and race/ethnicity groups, although it was not designed to examine these differences. This study found that the specificity to detect CRC and AA decreases with increasing age, but there was not a clear pattern for increasing sensitivity with increasing age. Differences in test accuracy by sex—higher sensitivity and lower specificity in men compared to women— were not statistically significant. Findings were inconsistent in two studies reporting test accuracy for white participants compared to Black participants; one study[175, 351] reported lower sensitivity for Black participants and the other[166] found no statistically significant differences between white and Black participants.

Subgroups results by family history were not reported.

Detailed Results for Serum-Based Tests

We identified one fair-quality study[196] that reported the test characteristics of a blood serum test to screen for CRC in average-risk adults (**Table 13**). This nested case-control study included participants from the PRESEPT study (Prospective Evaluation of Septin 9) and evaluated the mSEPT9 marker using Epi proColon. Our previous review[82, 83] included the original prospective analysis of PRESEPT,[352] which examined the first generation of Epi proColon. The first generation of the test is no longer available, and results from that article are not discussed further here.

Study and Population Characteristics

The PRESEPT study enrolled 7,941 participants from the United States and Germany; 6,857 participants met all criteria and had samples that could be re-analyzed in this retrospective analysis. All valid available samples from participants with CRC (44 of 50) and advanced adenoma (621 of 653) were selected and a stratified random sample was selected of participants of those with small polyps (435 of 2,369) and those with no evidence of disease (444 of 3,785). Among the 6,857 participants, CRC prevalence was 0.7 percent and prevalence of advanced adenomas was 9.5 percent. For the final case-control sample (n=1,544), prevalence of CRC was 2.8 percent and prevalence of advanced adenomas was 40.2 percent. Participants were all 50 years or older, 47 percent were female, and 73 percent were white. Eighty-one percent were recruited from the United States.

Test Accuracy for CRC

Sensitivity of Epi proColon to detect CRC was 0.68 (95% CI, 0.53 to 0.80) and specificity was 0.79 (95% CI, 0.77 to 0.81).

Test Accuracy for AN and AA

For the detection of AN, sensitivity was 0.25 (95% CI, 0.22, 0.28) and specificity was 0.79 (95% CI, 0.76 to 0.82). Due to the low number of CRCs, the sensitivity and specificity to detect AA were similar to those for AN, at 0.22 (95% CI, 0.18 to 0.24) and 0.79 (95% CI, 0.76 to 0.82), respectively.

By Stage or Location

In general, sensitivity of Epi proColon to detect CRC by stage increased as the stage of CRC increased; however, confidence intervals for the sensitivity to detect CRC at all stages overlapped. For Stage I, sensitivity was 0.41 (95% CI, 0.22 to 0.64) and for Stage IV sensitivity was 1.00 (95% CI, 0.57 to 1.00). Location-specific results were not reported.

By Age, Sex, Race/Ethnicity, or Family History

No subgroup results by age, sex, race/ethnicity, or family history were reported.

Detailed Results for Urine-Based Tests

We identified one study[168] in two publications[168, 353] that developed a metabolomic-based urine test, PolypDx, to detect adenomas (**Table 13**). Originally the test was developed on a nuclear magnetic resonance (NMR) platform and found 14 metabolites to distinguish people with adenomas from people without adenomas.[353] Since NMR is mainly used for research and is less suitable for clinical tests due to cost and expertise required, a mass spectrometry-based urine metabolomic test was subsequently developed using three clinical features (age, sex, and smoking status) and three metabolites (succinic acid, ascorbic acid, and carnitine).[168]

Study and Population Characteristics

The study used urine samples from 685 average- and high-risk participants recruited to SCOPE (Stop Colorectal Cancer through Prevention and Education), a regional colon cancer screening program in Edmonton, Canada. Fifty-nine percent were high-risk participants, defined as having a personal or family history of CRC or polyps. Results are not reported separately for non-high-risk participants. All participants provided a mid-stream urine sample and a stool sample, and completed a colonoscopy. The mean age for the 685 participants was 57 years, and 54 percent were female. Only one participant was diagnosed with CRC (0.1%); colonoscopy identified adenomas for 22.5 percent of participants.

The study was rated fair quality. Risk of bias concerns included unclear blinding of the endoscopist and patient attrition (loss of urine samples no longer valid for analysis).

Test Accuracy for AN and AA

The authors split the sample into a training data set with two-thirds of the sample (n=457) and a testing data set with the remaining one-third (n=228). The two datasets were balanced for age, sex, and class. Among the testing dataset, sensitivity to detect AN at various thresholds ranged from 0.43 to 0.92 (95% CI range, 0.30 to 1.00) and specificity ranged from 0.19 to 0.91 (95% CI range, 0.13 to 1.00). Thresholds were selected to obtain either high sensitivity (0.7, 0.8, or 0.9) or high specificity (0.7, 0.8, or 0.9); when high sensitivity was selected, the corresponding specificity was low, and when high specificity was selected, the corresponding sensitivity was low. The study compared the test performance of PolypDx to two FITs (Immune ICT and Immune MagSt); at similar specificities (>0.90), PolypDx had higher sensitivity (0.43, 95% CI: 0.30, 0.57) and similar specificity (0.91; 95% CI: 0.87, 0.96) compared with the FITs (sensitivity: 0.18 and 0.21, specificity: 0.97 and 0.92), but confidence intervals for the FITs and statistical significance of the differences between tests were not reported.

By Stage, Location, Age, Sex, Race/Ethnicity, or Family History

No subgroup results by age, sex, race/ethnicity, or family history were reported.

KQ3. What Are the Serious Harms of the Different Screening Tests? Do the Serious Harms of Screening Tests Vary by Subgroups (e.g., Age, Sex, Race/Ethnicity)?

Summary of Results

We included 131 fair- or good-quality studies (in 162 articles) (**Table 4**). Among these were 18 studies that evaluated serious harms from screening flexible sigmoidoscopy, 67 studies on screening colonoscopy, 21 studies on followup colonoscopy (colonoscopy that follows an abnormal result from a stool test, FS, or CTC), and 38 studies that evaluated CTC. Of the studies evaluating CTC, seven provided estimates of radiation exposure and 27 reported extracolonic findings. Sixty-eight studies included asymptomatic (screening) populations, and 63 studies included both asymptomatic and symptomatic (mixed) populations. Thirty-seven studies are new since the previous review.

Serious adverse events from colonoscopy are estimated at 3.1 perforations (95% CI, 2.3 to 4.0) and 14.6 major bleeds (95% CI, 9.4 to 19.9) per 10,000 procedures for screening populations. Serious adverse events from screening FS alone are less common, with a pooled estimate of 0.2 perforations (95% CI, 0.1 to 0.4) and 0.5 major bleeds (95% CI, 0 to 1.3) per 10,000 procedures.

However, the pooled estimates are 12.0 perforations (95% CI, 7.5 to 16.5) and 20.7 major bleeds (95% CI, 8.2 to 33.2) per 10,000 colonoscopy procedures following an abnormal FS screening result. Serious adverse events from colonoscopy following stool testing with an abnormal result are estimated at 5.4 perforations (95% CI 3.4 to 7.4) and 17.5 serious bleeds (95% CI, 7.6 to 27.5) per 10,000 colonoscopy procedures.

Twenty-three studies provided analyses of differential harms of colonoscopy by age. These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding.

Other harms besides bleeding and perforation, such as cardiopulmonary events or infections, may result from screening but are best assessed in studies with comparison groups since they may occur for reasons other than screening. Only four studies[125, 294, 304, 309] reported harms in a cohort that received colonoscopy compared with a cohort that did not. These studies did not find a higher risk of serious harms associated with colonoscopy.

Data from 17 studies show there is little to no risk of serious adverse events (e.g., symptomatic perforation) for screening CTC. While CTC may also require followup or therapeutic colonoscopy, we did not find sufficient evidence to estimate serious adverse events from colonoscopy followup. CTC also entails exposure to low-dose ionizing radiation (range 0.8 to 5.3 mSv) which may increase the risk of malignancy. Additionally, extracolonic findings on CTC are very common. Approximately 1.3 to 11.4 percent of examinations have extracolonic findings that necessitate diagnostic followup. From empirical evidence to date, it remains unclear whether detection of extracolonic findings represents an overall true benefit (from detection and treatment of clinically significant disease) or harm (from unnecessary diagnostic workup or identification of disease without clinical intervention).

No serious harms were reported in one small study of capsule endoscopy. We found no studies examining the harms of stool, serum, or urine testing, but neither do we hypothesize serious harms for these noninvasive tests other than diagnostic inaccuracy (i.e., false-positive or false-negative testing) or downstream harms of followup testing.

Detailed Results for the Harms of Direct Visualization Tests

Harms of Flexible Sigmoidoscopy Screening

We found 18 fair- or good-quality studies (n=395,077) that evaluated serious harms from screening FS in a general-risk population (**Table 23**). Five studies[130, 249, 264, 297, 301] were conducted in the United States. The length of followup was not commonly reported, but when reported was approximately 1 month. No studies reported harms in comparison groups. One additional study[129] (n=2,108) reported perforations associated with FS post FOBT/FIT.

Bleeding and Perforations

Serious bleeds from FS, from either screening or mixed populations, were rare. Based on 10 studies (n=179,854), the pooled estimate was 0.5 bleeds per 10,000 procedures (95% CI, 0 to

1.3, I^2=19.4%) (**Figure 18**).

Perforations following FS were also rare. In 11 studies (n=359,679) of mixed populations, the pooled estimate was 0.2 perforations per 10,000 procedures (95% CI, 0.1 to 0.4; range 0, 1.0 per 10,000; I^2=0%).

The single study[129] (n=2,108) reporting perforations associated with FS post gFOBT/FIT reported three perforations.

Other Serious Harms

Other commonly reported harms included mortality, MI, GI complications, and hospitalizations. However, no studies of screening FS reported harms in unscreened comparison groups, so it is uncertain if and/or to what degree these events were due to screening.

Harms by Age, Sex, Race/Ethnicity, or Family History

No studies reported harms of screening FS by any of these subgroups.

Harms of Screening Colonoscopy

We included 67 fair- or good-quality studies that evaluated serious harms from colonoscopy as a primary screening procedure (**Table 24, Table 25**). The majority of studies were fair quality, primarily due to lack of a comparison group. Thirty-four studies were conducted in the United States. Twenty-nine of 67 studies were conducted exclusively in screening populations or reported harms specific to the screening subgroup; the remaining 38 studies were conducted in mixed populations (including both screening populations and populations receiving colonoscopies due to symptoms or abnormal screening tests). Followup time, when reported, was 1 to 30 days for most studies. Four studies reported harms in addition to bleeds or perforations in unscreened comparison groups.[125, 294, 304, 309]

Bleeding and Perforations

Rates of serious bleeding were similar across colonoscopy indication. Based on 22 studies (n=5.4 million) reporting serious bleeding complications in people receiving screening colonoscopies, the pooled estimate was 14.6 bleeds per 10,000 procedures (95% CI, 9.4 to 19.9; I^2=99.5%, range of estimates from individual studies 0 to 68.7 bleeds per 10,000) (**Figure 19**). In the single study that was an outlier,[306] the older age of the study population (mean 74.4 years; range 66–104 years) may reflect the increasing risk of colonoscopy bleeds with increasing age. Serious bleeds in populations with both screening and followup or diagnostic colonoscopies (mixed populations) were similar: based on 22 studies with mixed populations (n=10.6 million) the pooled estimate was 16.4 serious bleeds per 10,000 (95% CI, 12.1 to 20.8; I^2=99.8%) (**Figure 20**). Study estimates were generally similar to the pooled estimate, with the exception of three studies that had small sample sizes,[258] much older populations,[304] or used a broader definition of major bleeding.[232]

Based on 23 studies (n=5.4 million) in screening populations, the pooled estimate for perforations was 3.1 per 10,000 (95% CI, 2.3 to 4.0; I^2=93.6%) (**Figure 21**). Results were similar across studies (range 0 to 22.1 per 10,000). Based on 33 studies (n=14.4 million) of mixed screening and symptomatic populations, the pooled estimate was similar at 5.0 perforations per 10,000 procedures (95% CI, 4.0 to 6.0; I^2=98.3%) (**Figure 22**).

Other Serious Harms

Serious harms from screening colonoscopy other than bleeding and perforation were not routinely reported. Other serious harms reported included cardiopulmonary events other gastrointestinal events, infections (including diverticulitis), and unspecified serious complications (**Table 24, Table 25**). The most commonly reported events were infection and gastrointestinal events (other than bleeding or perforation); events reported more rarely were cardiovascular events. Because these were not commonly reported, we do not provide a summary estimate of their likelihood of occurrence. Six studies[215, 221, 235, 283, 295, 307] in screening populations (n= 2,896,553) reported frequency of mortality related to colonoscopy screening. Across these studies, two deaths were reported, for a mortality rate of 0.007 per 10,000 people screened. Four studies[223, 243, 285, 291] in mixed populations (n=166,998) reported a total of 16 screening-related deaths, for a mortality rate of 0.96 per 10,000 people screened.

Since most studies had no comparator arm (unscreened group), it is unclear whether serious harms were related to the receipt of colonoscopy. Only three studies in screening populations (n=705,048)[294, 304, 309] and one study in mixed populations (n=3,468,901)[125] compared other serious harms (such as cardiovascular events, stroke, and mortality) in people who had a colonoscopy versus those who did not. These studies found either similar or less frequent serious adverse events in the screened group compared with the control group (**Table 24, Table 25**). For example, one study in screening populations (n=10,698) found the rate of cardiovascular events was 99 per 10,000 people in the screening group compared with 150 per 10,000 people in the unscreened group.[304] Another study in screening populations (n=17,316) found the rate of stroke was 3 per 10,000 people in the screened group compared with 10 per 10,000 people in the unscreened group, and the mortality rate was 6 per 10,000 people in the screened group compared with 24 per 10,000 people in the unscreened group.[294] In an intention-to-treat analysis, a Polish population-based screening study[309] (n=677,034) reported similar mortality rates in screened and unscreened groups (10 per 10,000 people in the screened group compared with 9 per 10,000 people in the unscreened group, not statistically significant). In the study's as-screened analysis (n=109,486), mortality rates were lower in the screened group (2.0 per 10,000 people) compared with the unscreened group (9.0 per 10,000 people, $p<0.001$). The single study in mixed populations with a comparison arm (n=3,468,901) found the rate of cardiovascular events was 130 per 10,000 people in the screened group compared with 93 per 10,000 people in the unscreened group.

Harms of Screening Colonoscopy by Age, Sex, Race/Ethnicity, or Family History

Twenty-three studies[125, 212, 216, 219, 225, 227, 229, 235, 237, 241, 250, 257, 261, 265, 283, 285, 288, 303, 304, 306, 310, 312, 313] provided data by age subgroups (**Appendix D, Tables 6 and 7**).

Based on 19 studies[125, 212, 216, 219, 225, 227, 235, 237, 241, 257, 261, 283, 288, 303, 304, 306, 310, 312, 313] reporting harms in people up to age 80, risk for bleeds, perforation, or other harms appeared to increase with age. For example, a study[237] of colonoscopy in a mixed population conducted in Sweden (n=593,315) found 0.24 percent of people ages 70 to 80 years experienced a serious bleed, higher than the 0.17 and 0.13 percent in age groups 60–70 years and 50-60 years, respectively. Similar patterns were observed for perforation (0.16% vs. 0.12% and 0.07%, respectively).

Six studies[212, 219, 237, 241, 261, 313] assessed perforations in people under age 50 years who received colonoscopy (all were in mixed populations), and generally found the risk of perforations increased with increasing age. For example, one of these studies[219] suggested a higher odds of perforations in people age 60 to 69 relative to people under age 40 years (OR 2.89; 95% CI 1.66, 5.05).

Sex differences in serious harms, when reported, suggested little differential risk between males and females. One study[235] in a screening population provided bleeding and perforation estimates by sex, finding slightly higher rates of serious bleeds for male compared with female participants (0.18% for males, 0.06% for females) and slightly higher rates of perforations (0.009% for males, 0.004% for females); another study in a screening population[229] reported a similar bleeding risk by sex (OR 1.0001 [95% CI, 1.0001, 1.0002] for female vs. male participants). Two studies[237, 285] in mixed populations demonstrate that males had a higher risk of bleeding compared with females while another study[313] in a mixed population found male sex was associated with a lower risk of bleeding compared with female sex; no significant differences by sex were found for perforations. However, in seven studies[210, 216, 219, 225, 241, 265, 286] of mixed populations, no differences in either bleeds or perforations were observed.

Four studies reported harms stratified by race/ethnicity, with mixed findings.[212, 225, 257, 303] A study[225] in a mixed population reported that participants of Hispanic ethnicity (OR: 1.23, 95% CI 1.08, 1.39) and Black race had higher risks of bleeding compared with whites (OR 1.32, 95% CI 1.13, 1.53), while two studies in mixed populations found similar frequencies of perforations (<1%)[212] and similar rates of colonoscopy-related hospitalizations (<0.5%)[257]among white, Black, Hispanic, and other groups. One study [303] in a screening population reported a higher risk of risk of infection-related hospitalization among Black [OR: 1.57 (1.22, 2.01)] compared with white people.

No studies reported serious harms stratified by family history.

Harms of Followup Colonoscopy

We included 14 fair- or good-quality studies that evaluated serious harms from colonoscopy following an abnormal stool test result, six studies that evaluated harms from colonoscopy following an abnormal flexible sigmoidoscopy result, and one study that evaluated harms from colonoscopy following an abnormal CTC result (**Table 26**). Eighteen of these studies (n=131,455) were part of included screening programs for KQ1.[119, 121, 124, 125, 127, 129, 130, 133-136, 138, 140-144, 147] Three studies reported harms from a gFOBT/FIT screening program but did not report the number of participants receiving a followup colonoscopy. Followup time, when reported, was 30 days for most studies.

Bleeding and Perforations

Following abnormal stool testing. Based on 11 studies of colonoscopy conducted after abnormal gFOBT/FIT result (n=78,793), the pooled estimate was 17.5 serious bleeds per 10,000 (95% CI, 7.6 to 27.5, I^2=89.3%) (**Figure 23**). Serious bleeding was slightly higher in two studies[136, 290] that were conducted postpolypectomy, but the confidence intervals were wide, likely due to smaller sample size. Based 12 studies (n=341,922), the pooled estimate of perforations following abnormal gFOBT/FIT was 5.4 per 10,000 procedures (95% CI, 3.4 to 7.4; I^2=47.8%).

Following abnormal flexible sigmoidoscopy. Six studies reported serious bleeds or perforations in populations receiving colonoscopy following an abnormal FS result. Based on four of these where data could be pooled (n=23,022), the pooled estimate was 12.0 perforations (95% CI, 7.5 to 16.5, I^2=0%) (**Figure 24**). Based on four studies (n=5,790), the pooled estimate is 20.7 major bleeds (95% CI, 8.2 to 33.2, I^2=8.2%) (**Figure 25**) per 10,000 followup colonoscopy procedures after abnormal screening FS.

Following abnormal CTC. One study[136] (n=126) conducted in Italy reported no cases of serious bleeds, perforation, or other serious adverse events.

Other Serious Harms

Following abnormal stool testing. There were limited data on other serious harms related to colonoscopy following an abnormal gFOBT/FIT result—and no studies with a comparator group. Based on three studies[133, 260, 290] in screening populations (n=34,478), cardiopulmonary events were rare. In two of these studies[287, 290] (n=2984), infectious events were also rare (<0.5% of procedures). Two[248, 270] of four studies reporting mortality found zero screening-related deaths; one death due to perforation was reported in one study[231] (n=263,129); and one death was reported in another study[290] (n=2,984), but it was not clear whether it was screening-related.

In three studies[134, 142, 272] of stool-based testing used as a primary screening test, either hospitalizations, screening-related mortality, or other unspecified serious adverse events were reported. No mortality, serious bleeds, perforations, or other serious adverse events were reported, and no comparison hospitalization rates for unscreened individuals were provided that would allow attribution of hospitalization to screening.

Following abnormal flexible sigmoidoscopy. In six studies, a single mortality event was reported in one study (n=2,051) that the authors judged was possibly related to screening.[119] One other study[127] (n=2,524) reported 24 cases of post-polypectomy syndrome (defined as abdominal pain, fever, leukocytosis, and peritoneal inflammation after polypectomy with electrocoagulation, in the absence of bowel perforation[354]).

Following abnormal CTC. One study[136] (n=126) conducted in Italy reported no cases of serious bleeds, perforation, or other serious adverse events.

Harms by Age, Sex, Race/Ethnicity, or Family History

Two studies[231, 287] reported perforation of bleeding harms stratified by age or sex, finding no difference between subgroups. One study[248] reported similar rates of severe complications (not specified) between age and sex subgroups.

No studies reported serious harms stratified by race/ethnicity or family history.

Harms of CTC

We identified 17 studies (n=89,073) assessing harms related to CTC (i.e., perforations, serious bleeds, and other serious events) and seven studies that reported radiation exposure from the CTC. Twenty-seven studies reported the prevalence of extracolonic findings on CTC, which may be either a benefit or a harm.

Serious Bleeds, Perforations, or Other Serious Adverse Events

In the 17 studies assessing harms related to CTC (**Table 26**), eight [177, 205, 222, 253, 254, 276, 279, 306] were U.S.-based. The mean age ranged from 51 to 77 years. No studies included unscreened comparison groups. The most commonly reported serious adverse event was perforation, which can happen due to insufflation of the colon. The pooled estimated risk of perforations based on seven studies was 1.3 per 10,000 procedures (95% CI, 0 to 2.9; I^2=38.9%) (**Figure 26**).

In four studies reporting serious bleeds (n=3,285), four such bleeds were reported, all in a single U.S.-based study.[306]

Of the 14 studies reporting other harms, 10 found no serious harms or mortality associated with CTC screening. Other harms (e.g., cardiopulmonary events, other GI events) were uncommonly reported and no comparisons were provided for unscreened controls. One study reported two cases of contrast-induced urticaria.[181]

Radiation Exposure

Seven included studies[169, 172, 184, 205, 211, 234, 272] reported radiation exposure associated with one CTC examination (**Table 27**).

Based on two included test accuracy studies of CTC, the estimated radiation dose for one full-screening CTC examination (dual positioning supine and prone) ranged from 4.5 to 5.3 mSv. Three additional CTC screening studies reported estimated radiation dose ranging from 0.8 to 5 mSv.[211, 234, 272] Two test accuracy studies reported the radiation output from the CT scanner, ranging from 6 to 10.56 mGy.

We did not identify any study that directly measured the risk for stochastic effects (e.g., cancer) caused by radiation exposure from CTC. For context, we briefly consider the indirect evidence for the potential adverse effects of low-dose ionizing radiation in the Discussion section.

Harms by Age, Sex, Race/Ethnicity, or Family History

We found no studies that reported on differential risk for serious harms or radiation exposure of CTC by age, sex, race/ethnicity, or family history.

Extracolonic Findings

We found 27 fair- to good-quality studies that addressed extracolonic findings (ECFs) associated with screening CTC (**Table 28**). Twenty-three studies (n=59,044) were conducted in screening populations, while three[239, 268, 280] (n=3149) were in mixed populations and one[238] (n=75) was conducted in a screen-positive population. The number of examinations ranged from 264 to 10,286. The largest study (n=10,286) represented people included in other studies but focused on different extracolonic malignancies only.[279] Followup time was not frequently reported, but when it was ranged from 6 months to 6 years, most typically 1 to 3 years. Most studies reported ECFs using the CT Colonography Reporting and Data System (C-RADS) classification system, a well-recognized standard for reporting CTC findings. There are five categories of C-RADS findings: E0=limited examination, E1=normal examination or normal variant, E2=clinically unimportant finding for which no workup is required, E3=likely unimportant or incompletely characterized finding for which workup may be required, and E4=potentially important finding requiring followup.[355] Alternatively, some studies instead describe extracolonic findings in terms of “high,” “moderate,” or “low” clinical significance. “High” generally includes findings that require surgical treatment, medical intervention, or further investigation (e.g., indeterminate solid organ masses or chest nodules, abdominal aortic aneurysms ≥3 cm). Findings of “moderate” clinical significance do not require immediate medical attention but likely require recognition, investigation, or treatment sometime in the future (e.g., calculi, small adrenal masses). Findings of “low” clinical significance do not require further investigation or treatment.

The most common ECF was E2 (clinically unimportant requiring no further workup). In 10 studies reporting E2 findings, ECFs occurred in 19.9 to 53.3 percent of examinations. ECFs requiring further workup of potentially important findings (E4) ranged from 1.3 to 11.4 percent in 11 studies. In six studies reporting E3 and E4 findings combined, the findings occurred in 4.4 to 16.9 percent of examinations. E3-level findings occurred in 3.4 to 26.9 percent of examinations in 10 studies. Based mostly on indirect comparisons, we did not find large differences in the prevalence of extracolonic findings (any or clinically significant) between studies limited to screening populations and those in asymptomatic people.

Twenty of 27 studies reported clinical followup of ECFs, typically limited to E4 findings. Among studies adequately reporting subsequent treatment, a minority of individuals screened (≤3%) required definitive medical or surgical treatment. Extracolonic cancers were not common and occurred in only 0.5 percent of people undergoing CTC examinations. In the largest series of examinations (n=10,286), which had about 4 years of followup, 36 (0.35%) examinations found an extracolonic malignancy, 32 of which received definitive treatment.[279] Abdominal aortic aneurysm occurred in up to 1.4 percent of people. Only seven of the studies reported clinical followup beyond the diagnosis of ECF. The clinical followup varied in terms of length of followup and details of the followup (e.g., curative resection for malignancy, cancer treatment received, successful surgery for abdominal aneurysm). In the largest study (n=10,286), of the 36 people diagnosed with extracolonic malignancy, two people with lung cancer and one person with renal cell cancer died, and the rest were alive at up to 56 months.[279] From this limited reporting of longer-term clinical followup, it is difficult to assess the net benefit to patients with incidental ECF on screening CTC.

Extracolonic Findings by Age, Sex, Race/Ethnicity, or Family History

Extracolonic findings may be more common with increasing age. The mean age in these studies ranged from 57 to 75 years. In the two studies with a mean age of 65 years or older, the percent with E3–E4 extracolonic findings was on average higher than in studies with younger mean ages.[222, 253] Two studies[177, 268] compared extracolonic findings in people younger than age 65 years with those of people age 65 years and older. Both studies found a higher prevalence of both any extracolonic finding and extracolonic findings that warranted further workup (E3–E4). Three studies[224, 238, 256] reported ECF by sex, finding similar rates of ECFs in both groups.

Harms of Capsule Endoscopy

Only one study[198] (n=689) for screening capsule endoscopy reported harms. Zero serious adverse events and three nonserious adverse events related to the capsule procedure. These events, which were all resolved on the same day, included gagging, vomiting, and abdominal cramping. One large retrospective study[356] (n=5,428) of diagnostic capsule endoscopy was excluded because it was conducted in people with upper and lower GI symptoms; this study found approximately 0.5 percent serious adverse events (e.g., aspiration, capsule retention).

Chapter 4. Discussion

Overall

We conducted this review to support the USPSTF in updating its recommendation on screening for CRC. Since the previous recommendation was published in 2016, we have included 70 new studies. Among them are 13[119, 122, 125, 127, 130-132, 135-137, 139, 149, 150] studies that assessed the effectiveness or comparative effectiveness of screening on CRC incidence and/or mortality, 28 new studies[154, 155, 158, 159, 161, 162, 164, 166, 168, 170, 171, 173, 179, 180, 187, 189, 196-200, 202-204, 206-209] that assessed the diagnostic accuracy of screening tests, and 37 new studies[119, 125, 127, 130, 135, 136, 150, 198, 217, 218, 221, 226, 231, 237, 240, 244, 248, 250, 260-262, 270, 271, 281, 282, 287, 290, 298, 302, 303, 307-313] that assessed harms.

Numerous tests have been studied for their use in screening for CRC in average-risk adults, including FS, colonoscopy, CTC, capsule endoscopy, gFOBT, FIT, and sDNA-FIT, as well as serum- and urine-based tests (**Table 29**). These tests have different levels of evidence to support their use, of proven ability to detect cancer and/or precursor lesions, and of risk of serious adverse events. At this time, most trials comparing screening modalities are limited in their study design and power to evaluate the comparative effectiveness on the reduction of CRC incidence/mortality or comparative harms. Therefore, they cannot answer questions on the relative benefit and harms (tradeoffs) between the tests. Currently seven randomized controlled trials of CRC screening are underway (**Appendix I**). Two trials have a usual care arm: SCREESCO (n=200,000), comparing FIT and colonoscopy to usual care and NordICC comparing colonoscopy to usual care (n=66,000). The other five trials are comparing various screening strategies: FIT versus colonoscopy (COLONPREV, CONFIRM), FOBT versus FS (Norwegian trial), CTC versus FS (Italian trial), FOBT versus FOBT and colonoscopy (Japanese trial). Three trials have reported baseline detection rates,[135, 221, 357] but the primary results from these trials are unlikely to be published over the next few years, due to the long followup time needed to assess differences between groups in CRC incidence and mortality rates. Notably, only one of these trials recruited adults younger than 50 years (Japanese trial); but with a smaller sample size (n=10,000), it is unlikely to inform any decisions about the age to begin screening. With that in mind, this systematic review of the available evidence will be used in tandem with microsimulation modeling conducted by CISNET CRC, which addresses issues around the comparative effectiveness of available tests, as well as decisions around age to start/stop screening.

Robust data from well-conducted, population-based screening RCTs demonstrate that both intention to screen with Hemoccult II and FS can reduce CRC mortality. However, Hemoccult II and FS are no longer routinely used for screening in the United States. Therefore, we have limited empirical data on true programs of CRC screening and screening modalities used in clinical practice today. Expensive, large population-based trials of newer tests may not be necessary, as evidence-based reasoning supports the theory that screening with endoscopy or stool tests with a sensitivity as good as, or better than existing tests (without a tradeoff in specificity) will result in CRC mortality reductions similar or better than reductions shown in existing trials.[358] Our review reveals that newer stool tests meet those requirements, including single-sample testing via FITs (e.g., OC-Sensor and OC-Light FIT families) and three-sample testing via HSgFOBT (i.e., Hemoccult Sensa). Stool tests that maximize sensitivity, such as FITs that use lower cutoffs or sDNA-FIT(i.e., Cologuard), have lower specificity and therefore require new trials or modeling exercises to understand the tradeoff of more false-positive test results. Other non-invasive testing (i.e., serum or urine tests) with test performance similar to or better than stool tests (i.e., based on test accuracy and adherence to screening) would also be expected to result in CRC mortality reductions similar to or better than reductions in existing trials. Thus, if the spectrum of disease detected by sDNA, serum, or urine testing is similar to that detected by stool testing checking for occult blood, then large population-based trials may not be necessary to evaluate their effectiveness in screening average-risk adults for CRC. Although imperfect, colonoscopy remains the criterion standard for assessing the test performance of other screening tests and is widely regarded as the standard for colorectal cancer screening in the United States. However, the mortality benefit of colonoscopy has not been evaluated in trials and the superiority of colonoscopy compared with other tests in a screening program has not been established. Colonoscopy is also significantly more invasive, with greater accompanying procedural harms, and potential harms of overdetection (unnecessary polypectomy/surveillance) than other available testing. CTC has evidence to support the adequate detection for CRC and larger potential precursor lesions. Although risk of immediate harms from screening CTC (such as bowel perforation from insufflation) is very low, it is unclear what (if any) true harm is posed by cumulative exposure to low doses of radiation or detection of extracolonic findings. Noninvasive serum and urine tests are promising given the potential for better patient acceptability (and therefore adherence) than stool-based testing.[359] Serum testing for circulating mSEPT9 in one study appears to have slightly lower sensitivity and lower specificity to detect CRC than commonly evaluated/employed FITs. And a metabolomic urine test shows promise for similar detection of AA than serum testing, but no evidence yet exists for its test performance to detect CRC in a screening population. Likewise, evidence for use of capsule endoscopy in a screening population is limited to very small test accuracy studies with high incompletion or inadequate study rates. Below we summarize the evidence and implementation concerns for direct visualization tests (FS, colonoscopy, and CTC) and stool tests (gFOBT, FIT, sDNA-FIT) with evidence to support their use in screening.

Direct Visualization Tests

Endoscopy

FS and Colonoscopy Benefits

Four large population-based RCTs evaluating screening FS showed that intention to screen with one-time FS (or, in the PLCO trial, two rounds of FS) was consistently associated with a decrease in CRC incidence (IRR 0.78 (95% CI, 0.74 to 0.83) and CRC-specific mortality (IRR 0.74 (95% CI, 0.68 to 0.80) compared with no screening at 11 to 17 years of followup. Despite this robust evidence, recent utilization data in the United States suggest that FS (with or without stool testing) is very uncommon (<1%).[360] Public and clinician perceptions of accuracy of colonoscopy versus FS, given the reach of endoscopy, also play an important role in the low utilization of FS compared with colonoscopy.[361] Although from included studies, FS is associated with a reduction in CRC incidence and mortality for both proximal and distal cancers, albeit greater reductions for distal cancers. We found no studies estimating the test accuracy of FS compared with a colonoscopy reference standard. Estimates of FS sensitivity and specificity are based on a limited number of relatively small studies with suboptimal study designs (e.g., tandem FS studies, simulated studies using colonoscopy and assumed FS reach to splenic flexure).[90] Sensitivity of FS to detect CRC calculated from the PLCO trial is 69.6 percent[362]; however, the test accuracy of FS to detect CRC may depend on the referral criteria, as criteria resulting in greater followup colonoscopy may detect a greater number of cancers—particularly proximal cancers. For example, the PLCO trial used nonbiopsy referral-based criteria for followup colonoscopy and had the highest referral rate to colonoscopy (about 33%) of all the trials.

Only one prospective cohort study has evaluated the association of the receipt of screening colonoscopy and CRC mortality in average-risk adults.[21] However, this study is part of a larger evidence base of population-based case control studies and retrospective cohort studies demonstrating an association of screening colonoscopy and reduction in CRC incidence and/or mortality.[19, 20, 156, 363-367] This included study using data from the Nurses' Health Study and the Health Professionals Follow-Up Study found that CRC mortality was lower in people with at least one screening colonoscopy versus those who never had a screening endoscopy (adjusted HR, 0.32 [95% CI, 0.24 to 0.45]) at 24 years of followup. Another included study conducted among Medicare beneficiaries found that receipt of screening colonoscopy was associated with a lower incidence of CRC after 8 years as compared with no screening colonoscopy in people ages 70 to 74 years; this study did not report CRC mortality outcomes.[128] This magnitude of association from observational studies should not be compared with the magnitude of effect in CRC mortality in intention to treat analyses from RCTs of screening FS. Currently, one large screening RCT in average risk adults, NordICC, evaluating the impact of screening colonoscopy to usual care on CRC incidence and mortality in Norway, Sweden, Poland, and the Netherlands, is underway.[368]

We included only four studies for which we could derive community-based relevant estimates of test accuracy, evaluating screening colonoscopy against a criterion standard. However, none of them were designed to estimate the test performance for CRC. Based on three studies, the per-person sensitivity for colonoscopy to detect adenomas 10 mm or larger ranged from 89.1 to 94.7 percent and the per-person sensitivity to detect adenomas 6 mm or larger ranged from 74.6 to 92.8 percent. Colonoscopies in these studies were conducted by experienced endoscopists; test performance will vary in clinical practice based on the adequacy of bowel preparation and colonoscopist performance/experience. A separate body of evidence addressing adenoma miss rates from tandem colonoscopy studies, not included in our review, confirms that colonoscopies can miss adenomas. A 2019 systematic review of 43 studies of over 15,000 tandem colonoscopies demonstrated that miss rates for adenomas and AA are higher than previously appreciated.[95] Both the effectiveness and test accuracy of colonoscopy may vary depending on a number of factors including the examiner quality. The American Society for Gastrointestinal Endoscopy, American College of Gastroenterology, and U.S. Multi-Society Task Force have issued guidance and recommendations for the technical performance and quality improvement targets for colonoscopy.[369, 370] In addition, there is a growing body of evidence, not included in this review, that evaluates whether technological advancements in colonoscopy to improve adenoma detection, namely chromoendoscopy or digital/virtual chromoendoscopy (e.g., narrow band imaging, flexible spectral imaging color enhancement), endoscopic technologies to increase mucosal surface area inspection (e.g., wide-angle lens or full-spectrum endoscopy, through-the-scope retrograde viewing device), and computer aided detection using artificial intelligence can improve detection, but data are limited to support widespread adoption in screening or average-risk populations.[371-375]

FS and Colonoscopy Harms

Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons are estimated at 14.6 serious bleeds (95% CI, 9.4 to 19.9) and 3.1 perforations (95% CI, 2.3 to 4.0) per 10,000 procedures. This estimate of serious bleeds is higher than appreciated in the prior review to support the 2016 USPSTF recommendation (8.2 serious bleeds per 10,000 procedures, 95% CI, 5.0 to 13.5).[1] Overall, it appears the risk of major bleeding and perforation is higher with increasing age. Other serious harms (e.g., infections, other GI events, cardiopulmonary events) were not consistently reported, and four studies evaluating harms in people who received colonoscopy versus those who did not found no increased risk of serious harms (including MI, CVA, or other cardiovascular events) as a result of colonoscopy. Serious adverse events from screening FS are rare (0.5 [95% CI, 0 to 1.3] serious bleeds and 0.2 perforations [95% CI, 0.1 to 0.4] per 10,000 procedures); however, screening FS may require followup colonoscopy. Serious harms of colonoscopy following screening FS are estimated at 20.7 serious bleeds (95% CI, 8.2 to 33.2) and 12.0 perforations (95% CI, 7.5 to 16.5) per 10,000 colonoscopies.

Case reports of fatal or near-fatal outcomes in average-risk people undergoing routine colonoscopy include splenic rupture, retroperitoneal or intra-abdominal hemorrhage, retroperitoneal gas gangrene, bowel infarction or ischemic colitis, small bowel perforation, colonic gas explosion with electrocautery, and appendicitis or appendiceal abscess.[82] In addition, there have been case reports of transmission of communicable diseases (i.e., hepatitis C virus, human papillomavirus) using unsanitized colonoscopes and chemical colitis from glutaraldehyde, which is used to disinfect endoscopes.[82]

We found no studies directly assessing the harms of cancer overdiagnosis (i.e., cancer detected through screening that would have not otherwise clinically manifested during a person's lifetime). One Markov modeling study using data from over 4 million screening colonoscopies from Germany's national screening colonoscopy registry, found that the risk of overdiagnosis was very low in people ages 55 to 79 years and 28 percent of the overdiagnoses occurred in people older than age 75 years.[376] Another potential harm is the overdetection of adenomas (i.e., adenomas detected through screening that would not develop into cancer and/or otherwise clinically manifested during a person's lifetime) leading to unnecessary procedures or more intensive colonoscopy surveillance.

CTC

CTC Benefits

While we found no studies examining the impact of screening CTC on cancer incidence or mortality, there is a robust evidence base evaluating the test performance of screening CTC in average-risk adults. However, none of these studies were designed to estimate test performance to detect cancer. Based on seven studies of CTC with bowel preparation, the per-person sensitivity and specificity to detect adenomas 10 mm or larger ranged from 66.7 to 93.5 percent and 86.0 to 97.9 percent, respectively; and to detect adenomas 6 mm or larger ranged from 72.7 to 98.0 percent and 79.6 to 93.1 percent, respectively. It is unclear whether the variation in test performance is due to differences in study design or populations studied or differences in bowel preparation, CTC imaging, reading protocols, and radiologist experience. In the included studies and current practice there is variation in bowel preparation (e.g., full, partial, none) and CTC technical enhancements (e.g., increasing detectors, fecal tagging, electronic cleansing, computer aided detection, insufflation techniques). Because some variation in accuracy is likely due to CTC protocol and/or radiologist ability, both the American College of Radiology and the International Collaboration for CT Colonography Standards have recommended practice guidelines and quality metrics, as well as specifications for training and certification.[377-379] In practice, the standard appears to be dry preparation (sodium phosphate, magnesium citrate, bisacodyl) rather than wet preparation (PEG) because of patient preferences and because PEG can leave liquid in the colon that can potentially obscure lesions.[380] Fecal tagging now appears to be routinely employed (oral ingestion of high-density oral contrast agent so that residual colonic contents can be differentiated from polyps) and appears to decrease the need for cathartic preparation. Additionally, there are different contrast agents, either barium- or iodine-based (ionic and nonionic), and the selection of which to use is largely based on local experience. Current practice centers on multidetector row CT scanners, which uses much thinner slices with faster scan times, resulting in better imaging and decreased radiation dose. Finally, there are differences in reading software. Commonly used reading software allows for both two- and three-dimensional display. The selection of the primary method appears to depend on radiologist preference. Other practice variations that influence the impact and implementation of screening CTC includes colonoscopy referral or surveillance criteria, as well as coordination with colonoscopy resources. Currently, there is consensus that large lesions (≥10 mm) should be referred to colonoscopy for polypectomy. There is variation in practice for smaller lesions, such that 6- to 9-mm lesions may be referred to colonoscopy for polypectomy or be monitored with CTC surveillance (with a followup CTC in 3 years), and the smallest lesions (≤5 mm) may be ignored or monitored. The American College of Radiology states that people with lesions of 6–9 mm should be offered colonoscopy and lesions smaller than 5 mm need not be reported.[205, 378, 381, 382] Preference for CTC over colonoscopy may be, in part, due to difference in bowel preparation. Ideally, while same-day colonoscopy could avoid duplicate preparation, it may result in suboptimal colonoscopy if limited bowel preparation is used for CTC and would require close coordination between radiology and gastroenterology departments/services.

CTC Harms

Immediate serious adverse events from screening CTC appear to be uncommon. Perforations were the most commonly reported harms (estimated at 1.3 per 10,000 examinations [95% CI, 0 to 2.9]); however, these perforations were detected radiographically (not symptomatic) and sustained by room-air manual insufflation which is no longer used in practice. However, like FS, CTC may require followup or therapeutic colonoscopy, and we did not find sufficient evidence to estimate serious adverse events from colonoscopy followup procedures.

Potential harms from CTC include exposure to radiation, especially if used in a program of screening that requires repeated examinations. Radiation dose in our included studies ranged from 0.8 to 5.3 mSv, consistent with a 2012 survey of academic and nonacademic institutions which found that the median radiation dose per screening CTC examination was 4.4 mSv,[383 384, 385]and a 2018 narrative review reporting the typical radiation exposure associated with a CTC examination at ≤3 to 6 mSv (which is higher than radiation exposure from digital mammography or CT for lung cancer screening).[386]

Given that the average amount of radiation exposure from background sources in the United States is about 3.0 mSv per year,[387] ionizing radiation from a single CTC examination is low. Even low doses of ionizing radiation, however, may convey a small excess risk of cancer.[388, 389] We identified no studies directly measuring the risk for stochastic effects (i.e., cancer) caused by radiation exposure from CTC. We can indirectly estimate these adverse effects, however, based on the range of effective radiation dose for CTC reported in the literature and estimates of lifetime attributable risk of malignancy (i.e., all solid cancers and leukemia) from the National Research Council report "Health Risks From Exposure to Low Levels of Ionizing Radiation."[387] Based on this report, the council predicts that approximately one additional individual per 1,000 would develop cancer (solid cancer or leukemia) from an exposure of 10 mSv above background using the linear no-threshold (LNT) model. In comparison, 420 individuals per 1,000 would be expected to develop cancer from other causes over their lifetimes. Because of limitations in the data used to develop risk models, the risk estimates are uncertain, and variation by a factor of 2 or 3 cannot be excluded.[387] Multiple organizations support the LNT model to estimate potential harms of radiation exposure of less than 100 mSv, including the Nuclear Regulatory Commission, the International Commission on Radiological Protection, the U.S. National Council on Radiation Protection and Measurements, the United Nations Scientific Committee on the Effects of Atomic Radiation, and the U.K. National Radiological Protection Board. Other organizations, however, believe that the LNT model is an oversimplification and likely overestimates potential harms of low-dose radiation exposure, including the Health Physics Society, the France Academy of Sciences/National Academy of Medicine, and the American Nuclear Society.[390] The effective radiation dose in CTC targets the abdomen and would not likely increase the risk of certain prevalent cancers (e.g., cancers of the breast, thyroid, or lung), although the risk for leukemia or abdominal organ cancer may remain. This risk estimate is consistent with other published literature on radiation exposure risk from CT.[388, 391]

Modeled data based on the National Research Council's assumptions, and using a mean dose of 8 mSv for women and 7 mSv for men per CTC examination, found that the benefits of CTC screening every 5 years (from ages 50 to 80 years) far outweigh any potential radiation risks, with 15 cases of radiation-related cancers per 10,000 persons screened (95% CI, 8 to 28) versus 358 to 519 CRC cases prevented per 10,000 persons screened.[392]

Extracolonic Findings

CTC also detects extracolonic findings, which could be a benefit (e.g., detection of intervenable extracolonic cancer, abdominal aortic aneurysm) or harm (e.g., overdiagnosis, procedural harms from subsequent testing). Extracolonic findings are very common and increase with age. Approximately 1.3 to 11.4 percent of CTC exams have extracolonic findings that necessitate actual diagnostic followup. Only a small proportion of CTC exams have findings that ultimately require any type of definitive treatment (≤3%). Therefore, judicious handling of the reporting and diagnostic workup of extracolonic findings is crucial to minimize the burden of testing (and associated cost and harms of testing), as many findings ultimately prove to be of no clinical consequence. Additional reading software may allow for repurposing CTC examinations to obtain bone mineral density from the lumbar spine to screen for osteoporosis if desired/indicated.[393, 394] It remains unclear whether detection of extracolonic findings represents a true overall benefit or harm based on empirical evidence.

Harms of Bowel Preparation

Common bowel preparation agents for FS include enemas and occasionally oral laxatives, while bowel preparation agents for colonoscopy and CTC include PEG solution, oral sodium phosphate solution, and sodium picosulphate, with or without additional oral laxatives. Common minor adverse events include nausea, vomiting, abdominal pain, abdominal distention/bloating, anal irritation, headache, dizziness, electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, hyper- or hypophosphatemia), and poor sleep. Therefore, the necessity of bowel preparation can affect adherence to endoscopy or CTC. However, serious adverse events (e.g., severe dehydration, symptomatic electrolyte abnormalities) are generally limited to people with major predisposing illnesses, and the selection of a bowel preparation agent may depend, in part, on underlying comorbidities (e.g., sodium phosphate use is generally avoided in people with renal, cardiovascular and GI motility impairment, sodium picosulfate is generally avoided in older adults).[82] Overall, existing systematic reviews on bowel preparation for endoscopy suggest similar tolerability based on the number of minor adverse events, no difference in efficacy of preparation, and no clinically significant adverse events with PEG or sodium phosphate.[395, 396] Case reports of serious adverse events from bowel preparation from PEG or sodium phosphate in average-risk people undergoing colonoscopy include acute renal failure and acute phosphate nephropathy, ischemic colitis, symptomatic hypokalemia, seizure secondary to hyponatremia, and Boerhaave syndrome (barogenic esophageal rupture).[82]

Stool Tests

To date Hemoccult and Hemoccult II are the only stool CRC screening tests that has been evaluated in RCTs. These trials demonstrate that intention to screen with gFOBT can decrease CRC-specific mortality by 9 to 22 percent (biennial screening, five studies) or by 32 percent (annual screening, one study) in a program of screening after 11 to 30 years of followup compared with no screening. However, only one of these trials demonstrated a reduction in CRC incidence.[143] In general gFOBT has been replaced for the most part by more sensitive stool based tests (i.e, HSgFOBT or various FITs). In the United States, many health systems and coordinated screening programs now use FITs, as opposed to gFOBT, to screen for CRC.[397-401] FITs usually require only one sample and eliminate dietary and medicinal restrictions, which generally improves ease of and adherence to testing.[402, 403]

We found one prospective cohort study that evaluated a national screening program in Taiwan in which one to three rounds of biennial FIT were associated with lower CRC mortality compared with no screening at up to 6 years followup (adjusted RR 0.90 [95% CI, 0.84 to 0.95]). We excluded one large (n=192,261) RCT conducted in rural China that compared single FIT screening to no screening because of its applicability to US practice,[404] and another ongoing RCT of FIT screening to no screening in Thailand.[405] In this trial, a single round of FIT testing had no statistically significant impact on CRC mortality (RR, 0.88 [95% CI, 0.72 to 1.07]) at 8 years of followup. Other studies evaluating national FIT screening programs were excluded because they did not have an unscreened contemporaneous comparator arm, they had very limited followup, and/or their analyses were at high risk of bias. In general, studies with a contemporaneous control group demonstrated that an invitation to FIT screening resulted in a greater number of cancers detected than no invitation to screening and/or a higher proportion of early-stage CRC with an invitation to FIT screening compared with no invitation to screening.[347, 349, 406] One additional excluded study of a FIT screening program conducted in the United States (Kaiser Permanente Northern California) that had a historical control group found that implementation of organized annual screening with a FIT (OC-Sensor) in people ages 51 to 75 years compared with usual care was associated with higher screening participation and decreased CRC mortality over time.[407]

Despite the lack of trials on stool tests used in clinical practice, tests that identify the same spectrum of disease as Hemoccult II do not need to be evaluated in large population-based RCTs if they have the same or better performing sensitivity and specificity. Both Hemoccult Sensa and FITs have higher sensitivity than Hemoccult II without a tradeoff in specificity. However, Hemoccult Sensa has more limited data, significant imprecision around test accuracy and requires three stool samples. Based on 2 studies with colonoscopy as the reference standard, the sensitivity to detect CRC ranged from 0.50 to 0.75 (95% CI range, 0.09 to 1.0) and the specificity ranged from 0.96 to 0.98 (95% CI range, 0.95 to 0.99) for Hemoccult Sensa. Based on 13 studies with colonoscopy as the reference standard, the OC-Sensor FIT family had a sensitivity to detect CRC of 0.74 (95% CI, 0.64 to 0.83) and a specificity of 0.94 (95% CI, 0.93 to 0.96) using the manufacturer recommended cut-off of 20 μg Hb/g feces. The OC-Light test, by the same manufacturer but with a different methodology, also performed similarly in four studies. Findings from comparative effectiveness studies in which Hemoccult II was compared with various FIT assays are consistent with this thinking as test positivity and CRC detection with FIT were consistently higher than Hemoccult II. It is possible that the sensitivity of FIT to detect CRC is lower in subsequent rounds of screening, but this is based on a small number of studies with methodologically limited study design and smaller numbers of cancers in subsequent rounds. Although sensitivity and specificity of a screening tests should not theoretically vary with disease prevalence, the variation in test accuracy may be due to a change in disease spectrum (e.g., stage of cancer) which is happening alongside a change in prevalence.[408]

Cologuard (sDNA-FIT) has greater sensitivity but lower specificity than OC-Sensor when applying manufacturer-recommended cutoff of 20 μg Hb/g feces. Based on four studies, the sensitivity to detect CRC was 0.93 (95% CI, 0.87 to 1.0), and the specificity was 0.85 (95% CI, 0.84 to 0.86). Lowering the threshold of FITs also maximizes sensitivity with a tradeoff in specificity. For example, when a cutoff of 10 or 15 μg Hb/g feces was applied, OC-Sensor had a similar sensitivity and specificity to detect CRC as Cologuard. Our findings are consistent with a 2019 systematic review[94] of the test accuracy of FITs. Decision models help in determining optimal sensitivity and specificity of stool (or other non-invasive screening tests) in a program of screening for CRC, and to understand the trade-offs of optimizing sensitivity. In addition, the value of current sDNA-FIT testing in practice remains uncertain when compared with FITs using lowered cutoffs to maximize sensitivity, because of the higher rate of unsatisfactory samples and 10-fold higher cost of the sDNA-FIT compared with FITs.

Harms of Stool Testing

There are no hypothesized serious adverse events resulting from noninvasive stool testing other than the risk of missed cancers (false negatives). However, serious adverse events may result from followup colonoscopy for abnormal stool testing. Serious harms of colonoscopy following abnormal stool testing are estimated at 17.5 serious bleeds (95%, CI 7.6 to 27.5) and 5.7 perforations (95% CI 2.8, 8.7) per 10,000 colonoscopies.

Contextual Issues

Adherence

Overall adherence to CRC screening in the United States has increased but remains suboptimal, and has consistently lagged behind recommended screenings for other cancers.[73] Adherence to a single round of serum testing appears to be highest, followed by stool testing (FIT greater than gFOBT), and lowest for a single CTC or colonoscopy, although estimates of adherence to screening vary widely across studies, setting, and populations.[75, 82, 409,359] While adherence to a single stool test is greater than a single colonoscopy, it requires annual or biennial testing, adherence to repeated stool-based screening varies widely between studies, although generally declines over multiple rounds of screening, and screening is highest in people who have already completed one initial screening test.[410-424] Additionally, completion of colonoscopy following abnormal stool-based screening tests ranges widely, from as low as 50 to up to almost 90 percent in the United States, with variation by health care setting and type of stool test.[414, 425-431] Last, adherence is variable by age, sex, and race/ethnicity; however, much of this variation is explained by health insurance generosity and access to preventive care.[76, 411, 432-436] The evidence on adherence to initial CRC screening, repeated screening, and colonoscopy following abnormal stool testing is detailed in **Appendix G**.

Differential adherence to screening tests influences the benefits and harms of screening program and may influence the selection of a preferred strategy. To illustrate the impact of adherence on screening, one microsimulation modeling analysis compared the benefits and life years gained (LYG) assuming 100 percent adherence versus reported adherence to initial screening.[437] This analysis evaluated strategies recommended by the USPSTF in 2016 (i.e., flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, annual FIT, annual HSgFOBT, sDNA-FIT every 3 years, CTC every 5 years) and serum testing for mSEPT9 every 1, 2, or 3 years, starting at age 50 years and ending at age 75 years. The analysis assumed a 35 percent adherence to flexible sigmoidoscopy, 38 percent to colonoscopy 42.6 percent to FIT and sDNA-FIT, 33.4 percent to HSgFOBT, 22 percent to CTC, and 85 percent to serum testing. Estimates were derived from the literature, with the exception of the estimate for sDNA-FIT which was assumed to be the same as

FIT. This analysis also assumed a 76.2 percent adherence to colonoscopy following an abnormal screening test, but 100 percent adherence to subsequent surveillance colonoscopies. The model was then calibrated to the National Health Interview Survey data that suggests 62.4 percent of individuals are up to date for CRC screening. While this analysis had some limitations, it demonstrated that when reported adherence was taken into account, serum testing averted 23 deaths per 1000 individual screened compared to 20 deaths averted using colonoscopy, and 11 to 16 deaths averted for using flexible sigmoidoscopy, CTC or stool-based testing. This modeling study concluded that adherence rates above 65 to 70 percent would be required for any stool- or serum-based screening tests to match the benefits of colonoscopy with 38 percent adherence.

Tailored Screening

In addition to considering the age to start and stop screening, some current CRC screening recommendations are tailored by race/ethnicity, family history, and multivariable risk assessment (**Table 3**). No screening recommendations are tailored by sex or gender, although sex is included in multivariable risk assessment.

Age

Because of the higher incidence of CRC in adults under age 50 years over time, in 2018 the ACS issued a qualified recommendation to start screening at age 45 years. Earlier age to initiate screening is primarily based on the epidemiology of disease and modeling studies accounting for the incidence of CRC by age. To date, we have little to no empiric evidence evaluating potential differences in the effectiveness of screening, test performance of screening tests, and the harms of screening in younger age groups (i.e., <50 years vs. older than 50 years). While a few studies of effectiveness (KQ1) recruited adults less than 50 years, none of these studies report stratified analyses by younger age subgroups. Any age differences in older gFOBT and FS screening trials were not statistically significant. Any differences in the effectiveness of screening in younger ages would be attributable to varying the underlying risk/incidence of CRC and/or natural history of disease, as well as differences in test accuracy by age. Limited studies demonstrate no difference in test performance (KQ2) of stool testing or harms of colonoscopy in people younger than 50 years. Although we do not hypothesize that colonoscopy or CTC are more harmful in younger adults than older adults, starting screening at younger ages will accrue more procedural harms and ECF, which should be weighed against any incremental benefit of earlier start to screening.

It is yet unclear whether the spectrum of sporadic CRC in younger adults mimics that seen in a traditionally screened age group, as there is evidence to suggest that a large proportion of the increase in CRC in those under age 50 is rectal versus colon cancer, and those with earlier onset CRC tend to have distinctive clinical features, have a more advanced stage at diagnosis, and poorer overall survival rates, which may be due to a difference in screen- versus symptom-detected disease and/or a more aggressive natural history.[438]

Current recommendations also differ on the age to stop screening; they range from ages 74 to 85 years. Few studies include older adults age 75 years and older to conduct robust subgroup analyses for the effectiveness, test accuracy and harms of screening. Limited empiric evidence suggests that screening colonoscopy may not result in the same benefit in reduction of CRC incidence in adults ages 75 to 79 years compared with those ages 70 to 74 years.[128] In addition, limited evidence suggests that CTC has lower sensitivity in older adults[350] and the specificity of sDNA-FIT decreases with advancing age[351] (higher false positive screening). And more robust evidence consistently demonstrates increasing serious harms from colonoscopy (as well as ECF on CTC exams) with advancing age.

Race/Ethnicity

Due to the higher incidence of CRC in Black people compared with white people (and other races/ethnicities), the USMSTF in 2017 recommended screening African Americans at age 45 years, and others at age 50 years. To date, we have little to no empiric evidence evaluating potential differences in the effectiveness of screening, test performance of screening tests, and the harms of screening by race/ethnicity (i.e., Black versus white). While effectiveness studies (KQ1) include nonwhite adults, none report stratified analyses by racial/ethnic subgroups. Again, any differences in the effectiveness of screening would be attributable to varying underlying risk/incidence of CRC and/or natural history of disease. We do not hypothesize that there are any differences in test performance or harms of screening tests by race/ethnicity; and as expected there are limited studies demonstrate no difference or inconsistent findings in test performance (KQ2) of stool testing or harms of colonoscopy by race/ethnicity.

Most of the evidence to date suggests that differences in risk of CRC and CRC mortality between Black and white adults is primarily driven by differences in receipt of good quality screening and subsequent care of cancer rather than inherent biological differences.[439] Furthermore, race is a social construct reflecting much more than heritable disease risk, and therefore confounded by may other factors increasing risk for developing cancer and progression of cancer, not limited to behavioral and environmental risk factors.[440] However, there remains uncertainty on the differences in carcinogenic mechanisms contributing to observed disparities in outcomes between Black and white adults.[441] While there is some evidence for a difference in the distribution of adenomas in the proximal versus distal colon, and in tumor markers in Black versus white people, the clinical significance of this difference on CRC incidence and mortality is unclear.

Sex

Although no recommendations tailor screening by sex, there is evidence to suggest differences in the effectiveness of screening, test performance of screening tests, and harms of screening in men versus women. Screening FS and selected gFOBT trials suggest a greater benefit in CRC mortality reduction in men than women. These results may be explained by the differences in sex-specific CRC incidence and mortality, as well as differences in the distribution of CRC in the colon (i.e., distal versus proximal) between men and women.[442, 329] Results were somewhat inconsistent for the FIT test accuracy, with some evidence to suggest that sensitivity may be higher (with lower specificity) to detect CRC in men compared with women. A 2019 systematic review evaluating the effect of sex (and age and positive threshold) on FIT test accuracy found that the 95% CI intervals overlapped between men and women.[443] Likewise, results were inconsistent for serious harms from colonoscopy, with some, albeit limited, evidence to suggest slightly higher rates of complications in men compared with women from screening colonoscopy.

Family History

Family history of CRC represents an approximation of genetic risk and is typically characterized in terms of the number of affected relatives, the degree of relatedness, and their age at CRC diagnosis. Individuals at the highest risk are those from families with known genetic syndromes, multiple affected relatives, and/or relatives with early age cancer diagnosis, particularly before age 50 years. At more moderate risk levels are people with one or more FDR or second degree relative (SDR) with later onset cancer. A systematic review of eight large population-based cohorts found that the prevalence of family history of one FDR with early-onset cancer was approximately 0.3 percent, while the prevalence of a single FDR with history of late-onset (after age 60) CRC was more than 3 percent.[68] Because our review focuses on the evidence to support screening in generally average risk adults, our discussion about the evidence for screening focuses on those at "moderate risk" as opposed to those with the highest hereditary risk for whom most U.S. guidelines recommend early and more frequent colonoscopy (i.e., colonoscopy is typically recommended at age 40 or 10 years before the relative's age at diagnosis and repeated at 5–10 year intervals).[63, 444] (**Appendix H Table 1**) The evidence on initiation of earlier screening in people with moderate familial risk for CRC is summarized below and detailed in **Appendix H**.

A large body of observational evidence spanning multiple countries and populations suggests that CRC risk increases as intensity of family history of CRC increases (more relatives, closer in relation, younger age at diagnosis), providing a plausible hypothesis for a screening benefit at earlier ages in these groups. Pooled risk estimates for a single FDR with CRC over age 60 are elevated compared to people with no family history (1.83, 95% CI, 1.47-2.25).[63] A systematic review of risk for CRC associated with family history found that the risk for CRC increased from 1.8 percent for a 50 year old with no family history to 3.4 percent with at least one affected relative and to 6.9 percent with two or more affected relatives.[445] A review of reviews conducted for the Canadian guidelines found similar increased levels of risk across nearly all types of studies and populations.[444]

There is limited empiric evidence on the effectiveness of screening, test performance of screening tests and harms in people at moderately increased risk of CRC due to family history and no evidence in this group under age 50 years. Although some studies do include people with a family history of CRC, most do not report results stratified by familial risk. One included observational colonoscopy study in health professionals found that in people with a FDR family history of CRC, the association with CRC mortality was no longer statistically significant after 5 years (multivariate HR 0.91; 95% CI, 0.55 to 1.52) compared with a sustained association beyond 5 years in people without a family history (multivariate HR 0.43; 95% CI, 0.32 to 0.58) (p=0.04 for interaction).[21] One excluded population-based case-control study found that previous colonoscopy was associated with decreased CRC risk in people with all levels of family history. Regardless of family history status, colonoscopy was associated with a lower CRC risk (OR 0.25 [95% CI, 0.22 to 0.28] for people without family history and OR 0.45 [95% CI, 0.36 to 0.56] for people with family history).[446] Neither of these studies report results for adults under age 50 years. No included studies reported variation of test accuracy or harms by family history.

Multivariable Risk Assessment

Although the concept of individualizing CRC screening recommendations has become more compelling as we have learned more about modifiable and non-modifiable risk factors, multivariate risk assessment for CRC risk is not commonly used in clinical practice[70, 447] and currently there is no commonly used/accepted risk assessment tool to help tailor CRC screening.[69] In 2019, one international guideline panel, as part of the BMJ Rapid Recommendations series, issued a weak recommendation against screening in asymptomatic adults ages 50 to 79 years with an estimated 15-year CRC risk below 3 percent using a validated multivariate risk assessment tool (QCancer) which includes a number of variables in addition to age, sex, race/ethnicity, and family history.[80] In theory, multivariate risk assessment could also identify persons at higher risk for CRC and in whom to initiate screening earlier than age 50 years.

While many risk models or scores have been developed to predict the risk of CRC and/or advanced neoplasia, there are no trials evaluating the benefits and harms of implementing risk assessment to guide CRC screening. Two recent systematic reviews summarize the performance (mainly discrimination) of risk prediction models for CRC and/or advanced neoplasia in asymptomatic general risk adults.[447, 448] A 2016 systematic review identified 52 models described in 40 studies for assessing risk of CRC or advanced neoplasia in average-risk populations; in aggregate these 52 models considered 87 different risk factors obtained through medical records, self-reported questionnaires, and laboratory testing inclusive of genetic biomarkers.[447] Commonly included factors were age, sex, family history (generally specified as FDR), BMI, and lifestyle factors (e.g., smoking, alcohol, diet, exercise). Overall, the discrimination of the models ranged from an area under the curve (AUC) of 0.65 to 0.70. The authors found that, in general, models including lifestyle behaviors (obtained by questionnaire) and genetic biomarkers did not have better discrimination than models with risk factors that could be routinely obtained through medical records (i.e., age, sex, family history, smoking, +/- alcohol). In external validation studies, 10 of these models showed acceptable discrimination, AUC 0.71 to 0.78. These include two models containing only three variables (age, sex, and BMI or family history).[447] A 2018 review focused on multivariate risk tools for advanced neoplasia only and identified 17 original risk scores described in 22 unique studies.[448] Findings from this review were consistent with the 2016 review in the commonly included factors and discrimination (AUC) of the risk tools. This review also demonstrated a substantial variation in discrimination even for the same risk score across different studies. The review conducted meta-analyses of discrimination for each risk score evaluated in more than one study and found that the most evaluated risk scores (4 or more studies) had less optimal discrimination (AUC 0.61 [95% CI, 0.59 to 0.64] to 0.64 [95% CI, 0.60 to 0.68]. The risk tool with the highest discrimination (AUC 0.70 [95% CI, 0.61 to 0.79]) was only evaluated in two studies.

Two publications externally validated a series of risk models identified in the 2016 review in large population-based cohorts in the United Kingdom and Europe.[449, 450] One study externally validated 14 different risk models to predict CRC in a large (n=373,112) population-based cohort in the UK (UK Biobank).[449] Another study externally validated 16 different risk models for CRC in two large population-based cohorts, the European Prospective Investigation into Cancer and Nutrition (EPIC) (n=491,992) and United Kingdom Biobank n=475,629).[450] These two studies externally validated overlapping risk models. Overall these two studies found that the performance of published risk models for CRC varied widely. Both studies concluded that there are several models (including QCancer) with easily identifiable risk factors that possess good calibration and discrimination, and thus are promising for implementation. Both studies call for modeling plus or minus clinical impact studies to further evaluate their promise for clinical practice.

Only four studies examined risk prediction for advanced colorectal neoplasia specifically in adults younger than age 50 years.[451-454] These studies were development and initial validation studies in large generally asymptomatic populations in Korea. The models demonstrated that a combination of risk factors similar to those in other models (e.g., age, sex, BMI, family history, smoking, laboratory tests) can identify people at higher risk for advanced neoplasia (AUC from 0.66 to 0.72). These models do not appear to be externally validated. In general, these studies included populations with lower average BMI (when reported) than U.S. populations, and given the 10-fold difference in CRC incidence internationally, there is a need to validate in broader populations applicable to U.S. populations.

Limitations of the Review

Our review focused on the benefit of CRC screening on mortality, the test accuracy of generally available CRC screening tests, and the potential serious harms of these screening tests in average-risk adults. We therefore excluded studies in symptomatic people and people with the highest hereditary risk; this exclusion criteria resulted in very scant evidence for certain technologies such as capsule endoscopy and newer serum- and urine-based testing. We also narrowly included trials or prospective cohort studies designed to evaluating the impact of screening on CRC incidence or mortality. We acknowledge that excluded well-designed nested case-control studies may be at lower risk of bias than included prospective cohort studies (e.g., more accurately capture screening history, exam indication). While our review addressed some important contextual issues related to screening (e.g., adherence to testing, risk assessment to tailor screening, test acceptability and availability), we did not include an assessment of the mechanism of benefit of the different screening tests (primary prevention vs. early detection), methods to increase screening adherence, prevalence of interval cancers between screenings, potential harms of overdetection of adenomas or unnecessary polypectomy, technological enhancements to improve the diagnostic accuracy of colonoscopy, and surveillance after screening. Our review was commissioned along with microsimulation decision models from CISNET, which address the comparative effectiveness and tradeoffs of screening strategies that vary in ages to start and stop, interval of screening, and screening modality; therefore, we do not include modeling studies in our review. At the request of the USPSTF, we did however summarize recent decision modeling analyses, other than those conducted by CISNET, that addressed the comparative effectiveness and tradeoffs of various screening strategies, with a particular attention to those analyses evaluating age to start screening (**Appendix F**). Given our U.S. centric focus, we limited our review to evidence conducted in countries with the highest applicability to U.S. practice and given resource limitations, only articles published in English were considered for inclusion.

Emerging Issues and Future Research Needs

Screening for CRC is a complex and active area of research. Unlike other routinely recommended and conducted cancer screening, there are multiple viable options for CRC screening, with: 1) varying levels of evidence to support their use, 2) intended aim to detect cancers, potential precursor lesions, or both, 3) test acceptability and adherence, 4) intervals of time to repeat screening, 5) need for followup testing (including surveillance incurred), 6) associated serious harms, 7) availability in practice, 8) associated cost, and 9) advocacy for their use. The best-quality evidence, in terms of robust study design and reduction in mortality, is limited to FS and Hemoccult II, modalities that are no longer routinely used for screening in the United States. Rigorous test accuracy studies for technologies that identify a similar spectrum of disease as endoscopy and stool testing for occult blood evaluated in trials are likely sufficient to adopt newer tests without new screening trials. Ongoing comparative RCT may also fill this evidence gap for currently used tests (**Appendix I**), and, assuming tests detect a similar spectrum of disease, modeling studies can provide valuable insight into the comparative net benefit of tests especially with (rapid) technological advancements that may improve test accuracy and/or reduce harms. Decision modeling can synthesize available data to inform the effectiveness of a wider range of testing modalities than possible in practice, including evaluation of newer tests, different test intervals, and populations with differing risk for CRC. Evidence to address gaps in our understanding of the clinical importance of smaller lesions (<10 mm), the role of sessile serrated lesions in both the natural history of disease and the performance of screening tests to detect these lesions, variation in the disease process across the large intestine (rectum, distal and proximal colon), and any variation in the natural history of disease by age, sex, race/ethnicity and family history, as well as any variation in test accuracy by age, sex, race/ethnicity and family history will inform current decision models. In addition, evidence to address gaps in understand around test accuracy and adherence to screening over sequential rounds of screening are also important to inform current decision models.

Much-needed future research should include trials or well-designed cohort studies in average-risk populations to evaluate the effects of programs of screening using colonoscopy, the best-performing FITs, CTC, and new serum- and urine-based tests on cancer mortality and incidence. Studies including adequate sampling of adults ages 40 to 49 years, people with moderate family history risk, and different race/ethnicities to allow for robust subgroup analyses, and/or employing multivariate risk assessment to guide screening would also be important in understanding how best to implement screening. In addition, studies to confirm the screening test performance of promising FITs with thus-far limited reproducibility (i.e., only one study) would be helpful to offer other FIT options to OC-Sensor and OC-Light. Likewise, test accuracy studies adequately powered for cancer detection to establish and/or confirm the screening test performance of promising serum- and urine-based tests (e.g., high sensitivity to detect CRC and/or advanced adenomas) are needed to bolster a menu of options for screening that may have greater acceptability and feasibility (and therefore adherence). In particular, promising serum tests are Epi proColon which has a single adequately powered test accuracy study with sensitivity at or below, and specificity much below commonly studied FITs, and a novel serum test for circulating tumor DNA (LUNAR-2) that has a large prospective cohort study (ECLIPSE) in progress.[455] Serum-based tests to screen for colon cancer is an active field of study with other tests at various stages of development and testing.[456-458] The metabolomic urine test, PolypDx has a single small study establishing its ability to detect advanced adenomas on par with Epi proColon but thus far no data on test accuracy to detect cancer. In general test accuracy studies to clarify any differential in detection of proximal versus distal test accuracy, and the detection of precursor lesions with more potential for malignant transformation (e.g., serrated sessile lesions) would also be informative. It is also important to understand the contribution of technological advancements to existing technology (e.g., enhancements to optical colonoscopy or CTC) on test performance in average-risk adults as well as on reducing harms (e.g., decreasing radiation exposure, less aggressive bowel preparation). Last, the clinical impact of the identifying extracolonic findings remains unknown. More complete and consistent reporting of the downstream benefits and harms of the initial detection (subsequent workup and definitive treatment) of C-RADS E3 and E4 findings need to be published in observational studies or trials with longer-term followup.

Conclusion

CRC screening continues to be a necessary and active field of research. Since the 2016 USPSTF recommendation, we have gained a greater appreciation of the increasing CRC incidence in adults under age 50 years and we have more evidence on effectiveness and test accuracy of newer stool tests (FIT and sDNA-FIT), and the test accuracy of an FDA approved serum test (Epi proColon) for use in persons declining colonoscopy, FS, gFOBT, or FIT. We have also identified a new metabolomic urine test (PolypDx) with limited test accuracy data, thus far limited to detection of adenomas. We also have more data on colonoscopy harms demonstrating higher estimates of major bleeding than previously appreciated in 2016.

Current screening modalities, including colonoscopy, FS, CTC, various high-sensitivity stool-based tests, and a serum-based test, have different levels of evidence to support their use, different test performance to detect cancer and precursor lesions, and different risks of harms. At this time, comparative studies of the various screening tests cannot answer questions of the relative benefit and harms (tradeoffs) between the tests. The use of accompanying decision analyses will help inform the comparative benefits and harms of the screening strategies. Recommendations regarding which screening tests to use, or whether there is a hierarchy of preferred screening tests, will depend on the decisionmaker's criteria for sufficiency of evidence and weighing the net benefit. Actual implementation of recommendations will depend on a number of additional factors, including patient preference and available resources.

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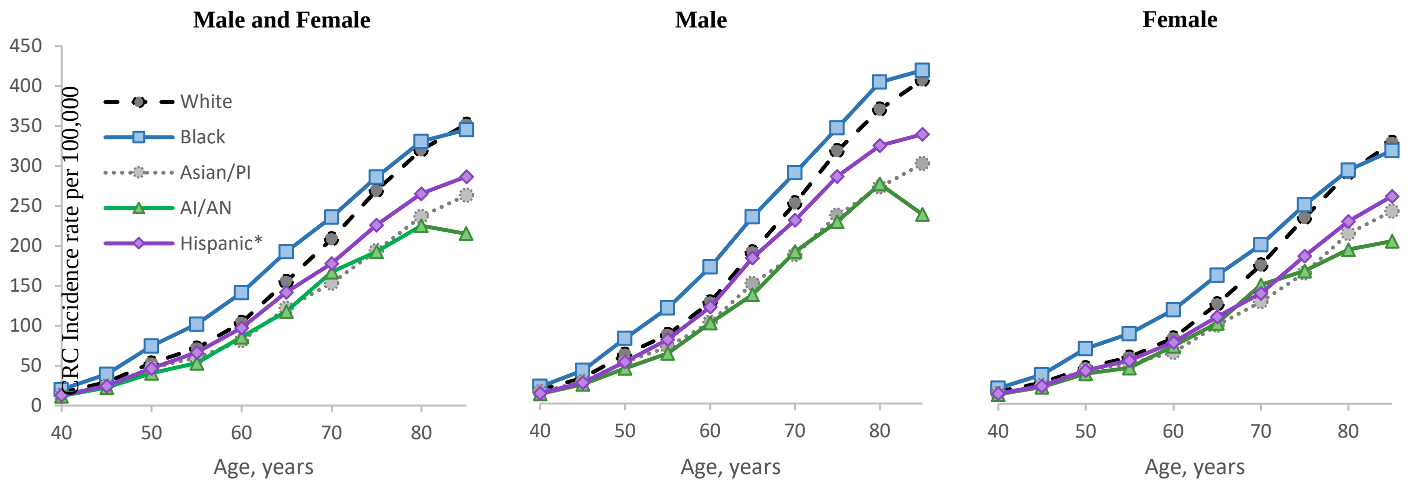
Figure 1. Age-Specific Colorectal Cancer Incidence Rates/100,000 by Race/Ethnicity, United States, 1999-2014

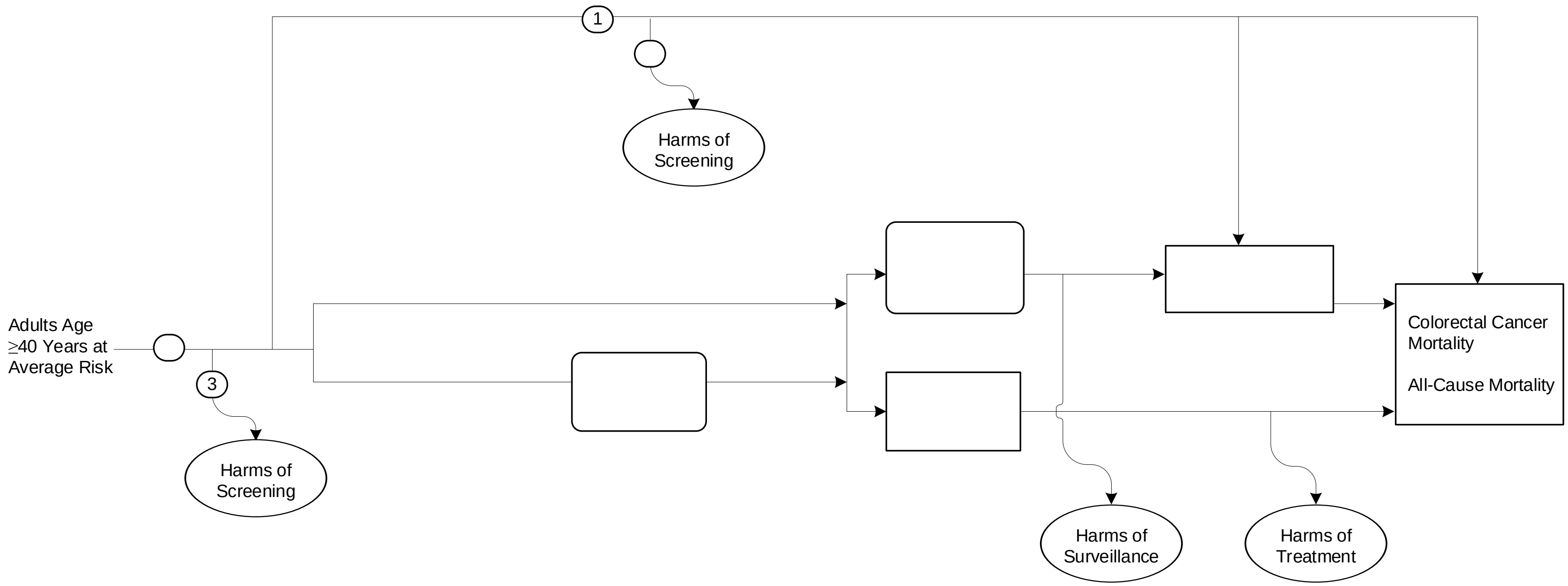


Note: Data combined from the Center for Disease Control and Prevention National Program of Cancer Registries and the National Cancer Institute Surveillance, Epidemiology and End Results Program.[459]

* Not mutually exclusive from race categories

Abbreviations: AI = American Indian; AN = Alaska Native; CRC = colorectal cancer; PI = Pacific Islander

Figure 2. Analytic Framework: Screening for Colorectal Cancer

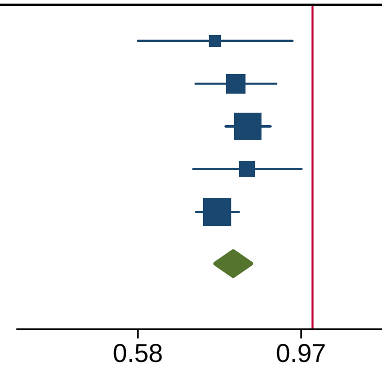


* Screening technologies with conditional approval from the U.S. Food and Drug Administration for screening for colorectal cancer.
Abbreviations: CTC = computed tomography colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac-based fecal occult blood test; m*SEPT9* = methylated septin 9 gene DNA; sDNA = stool DNA test; SSL = sessile serrated lesion.

Figure 3. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Incidence

Study	Years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
NORCCAP (50-54 years)	14.8	81.5	110.2	0.74 (0.58, 0.94)
NORCCAP (55-64 years)	14.8	162.4	206	0.79 (0.70, 0.89)
PLCO	15.8	125.5	153.3	0.82 (0.76, 0.88)
SCORE	10.5	144.11	176.43	0.82 (0.69, 0.97)
UKFSST	17	137	184	0.74 (0.70, 0.80)
Overall				0.78 (0.74, 0.83)

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 28.62\%$, $H^2 = 1.40$

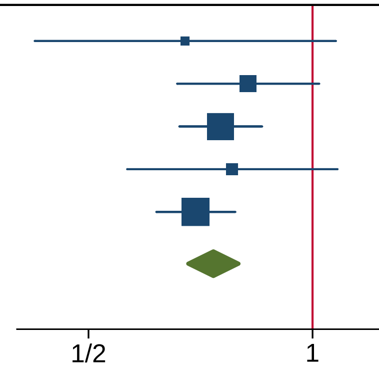


Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 4. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Mortality

Study	Years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
NORCCAP (50-54 years)	14.8	21.1	31.3	0.67 (0.42, 1.07)
NORCCAP (55-64 years)	14.8	52	63.5	0.82 (0.66, 1.02)
PLCO	16.8	33.7	44.8	0.75 (0.66, 0.85)
SCORE	11.4	34.66	44.45	0.78 (0.56, 1.08)
UKFSST	17	39	56	0.70 (0.62, 0.79)
Overall				0.74 (0.68, 0.80)

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

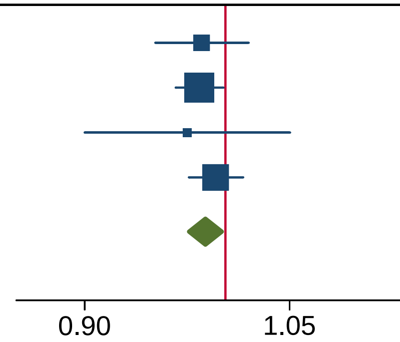


Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 5. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on All-Cause Mortality

Study	Years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
NORCCAP, Total	14.8	1309.1	1333.3	0.98 (0.95, 1.02)
PLCO, Total	16.8	1827	1853	0.98 (0.96, 1.00)
SCORE, Total	11.4	640.96	660.26	0.97 (0.90, 1.05)
UKFSST, Total	17.1	1472	1483	0.99 (0.97, 1.01)
Overall				0.98 (0.97, 1.00)

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.03\%$, $H^2 = 1.00$

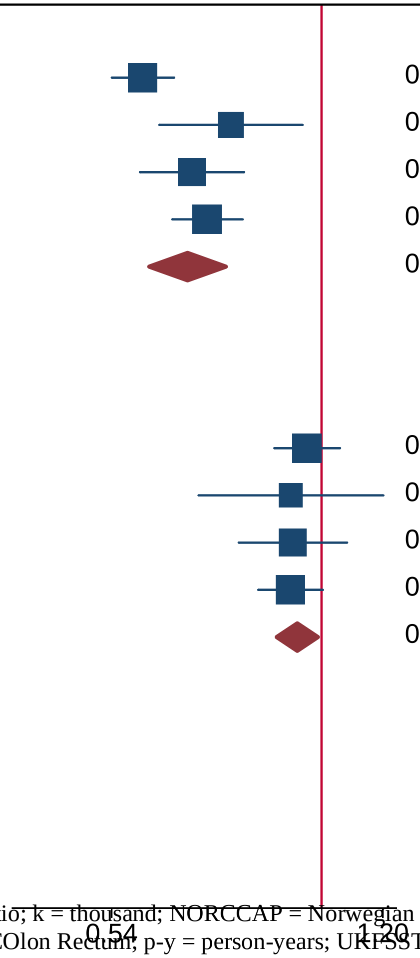


Abbreviations: CI = confidence interval; IRR = incidence rate ratio; No. = number; NORCCAP = Norwegian Colorectal Cancer Prevention trial; PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial; REML = restricted maximum likelihood; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial; SCORE = Screening for COlon Rectum

Notes: Assumed the n analyzed did not change between 11 and 15 years of followup for NORCCAP.

Figure 6. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Incidence by Location

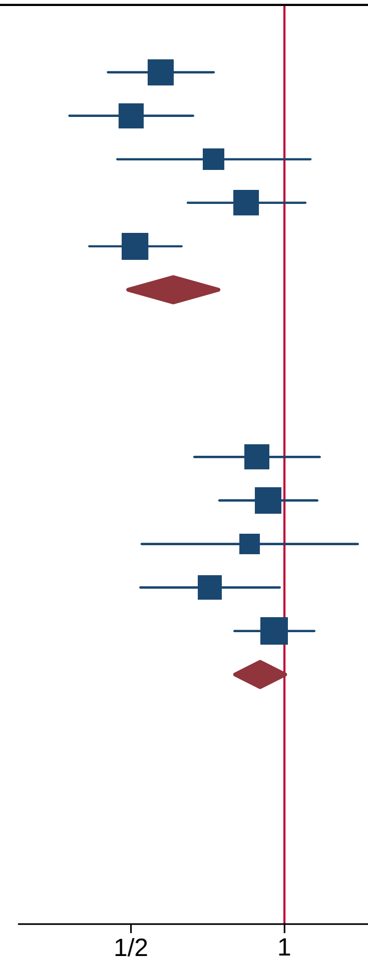
Study	Median years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
Distal				
UKFSST	17.1	66	112	0.59 (0.54, 0.65)
SCORE	10.5	87.27	114.16	0.76 (0.62, 0.94)
NORCCAP	14.8	67.1	98.5	0.68 (0.58, 0.79)
PLCO	15.8	53.2	74.6	0.71 (0.64, 0.79)
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 66.98\%$, $H^2 = 3.03$				0.67 (0.60, 0.75)
Test of $\theta_i = \theta_j$: Q(3) = 10.00, p = 0.02				
Proximal				
UKFSST	17.1	68	71	0.96 (0.87, 1.05)
SCORE	10.5	56.84	62.27	0.91 (0.69, 1.20)
NORCCAP	14.8	66.1	72	0.92 (0.78, 1.08)
PLCO	15.8	70.3	77.1	0.91 (0.83, 1.00)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$				0.93 (0.88, 0.99)
Test of $\theta_i = \theta_j$: Q(3) = 0.56, p = 0.90				



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 7. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Mortality by Location

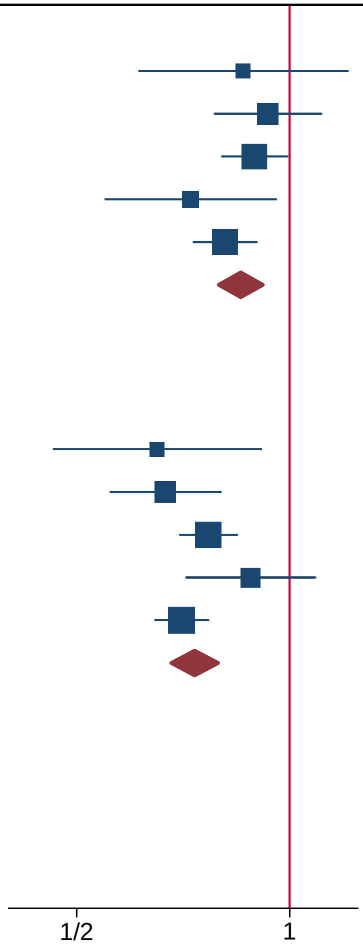
Study	Median years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
Distal				
UKFSST (60-64 years)	17.1	20	35	0.57 (0.45, 0.73)
UKFSST (55-59 years)	17.1	13	26	0.50 (0.38, 0.66)
SCORE	11.4	18.66	25.7	0.73 (0.47, 1.12)
NORCCAP	14.8	23.4	27.8	0.84 (0.65, 1.10)
PLCO	16.8	10.9	21.4	0.51 (0.41, 0.63)
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 64.60\%$, $H^2 = 2.83$				0.61 (0.49, 0.74)
Test of $\theta_i = \theta_j$: Q(4) = 11.12, p = 0.03				
Proximal				
UKFSST (55-59 years)	17.1	15	17	0.88 (0.66, 1.17)
UKFSST (60-64 years)	17.1	26	28	0.93 (0.74, 1.16)
SCORE	11.4	16	18.74	0.85 (0.52, 1.39)
NORCCAP	14.8	16.2	22.7	0.71 (0.52, 0.98)
PLCO	16.8	18.8	19.7	0.95 (0.80, 1.14)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$				0.90 (0.80, 1.00)
Test of $\theta_i = \theta_j$: Q(4) = 2.64, p = 0.62				



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 8. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Incidence by Sex

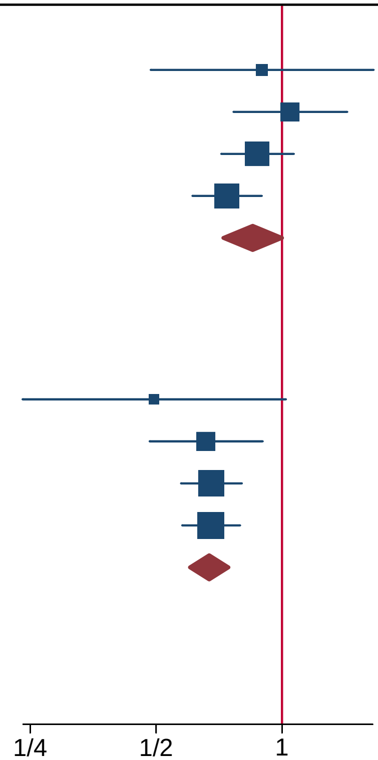
Study with years followup	Median years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
Female				
NORCCAP (50-54 years)	14.8	81	94.2	0.86 (0.61, 1.21)
NORCCAP (55-64 years)	14.8	168.7	181.1	0.93 (0.78, 1.11)
PLCO	15.8	110.5	123.9	0.89 (0.80, 0.99)
SCORE	10.5	98.54	136.05	0.72 (0.55, 0.96)
UKFSST	17.1	111	137	0.81 (0.73, 0.90)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 11.50\%$, $H^2 = 1.13$				0.85 (0.79, 0.92)
Test of $\theta_i = \theta_j$: Q(4) = 4.01, p = 0.41				
Male				
NORCCAP (50-54 years)	14.8	81.9	126	0.65 (0.46, 0.91)
NORCCAP (55-64 years)	14.8	155.6	233.1	0.67 (0.56, 0.80)
PLCO	15.8	141.3	184.1	0.77 (0.70, 0.84)
SCORE	10.5	190.94	216.83	0.88 (0.71, 1.09)
UKFSST	17.1	166	236	0.70 (0.65, 0.77)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 31.14\%$, $H^2 = 1.45$				0.73 (0.68, 0.79)
Test of $\theta_i = \theta_j$: Q(4) = 6.34, p = 0.18				



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 9. Key Question 1: Forest Plot of Flexible Sigmoidoscopy Screening vs. No Screening on Colorectal Cancer Mortality by Sex

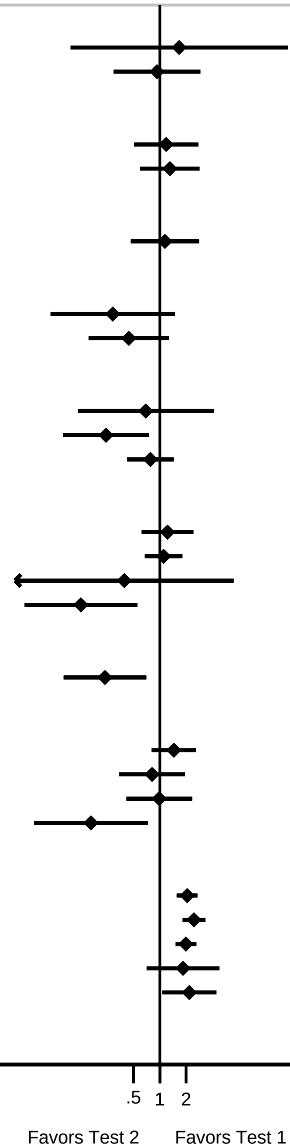
Study	Median years followup	IG events per 100k p-y	CG events per 100k p-y	IRR with 95% CI
Female				
NORCCAP (50-54 years)	14.8	24.8	27.7	0.90 (0.49, 1.65)
NORCCAP (55-64 years)	14.8	52.8	50.5	1.05 (0.77, 1.43)
PLCO	16.8	28.8	33	0.87 (0.72, 1.06)
UKFSST	17.1	31	42	0.74 (0.61, 0.89)
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 32.40\%$, $H^2 = 1.48$				0.85 (0.72, 1.00)
Test of $\theta_i = \theta_j$: Q(3) = 3.86, p = 0.28				
Male				
NORCCAP (50-54 years)	14.8	17.2	34.8	0.49 (0.24, 1.02)
NORCCAP (55-64 years)	14.8	51.1	77.7	0.66 (0.48, 0.90)
PLCO	16.8	38.8	57.3	0.68 (0.57, 0.80)
UKFSST	17.1	48	71	0.68 (0.58, 0.79)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$				0.67 (0.60, 0.74)
Test of $\theta_i = \theta_j$: Q(3) = 0.72, p = 0.87				



Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; IRR = incidence rate ratio; k = thousand; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; p-y = person-years; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 10. Key Question 1: Forest Plot of Comparative Effectiveness Studies on Colorectal Cancer Incidence

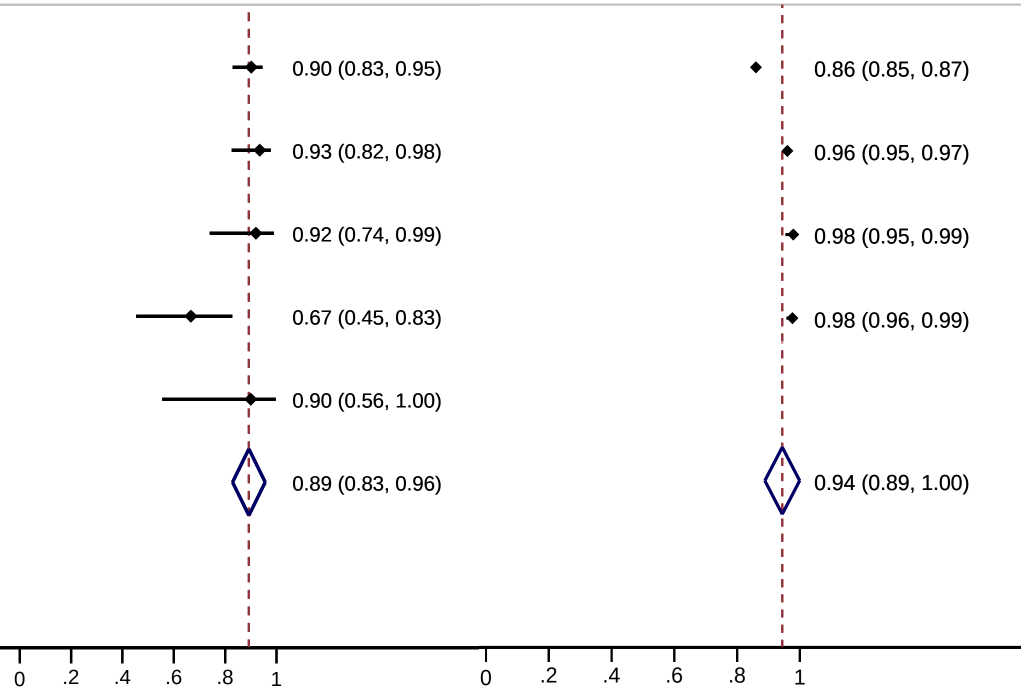
Test 1 v. Test 2, Author, year	Study	Test 1, n with CRC/n screened	Test 2, n with CRC/n screened	RR (95% CI)
CTC v. Colo				
Sali, 2016	SAVE	7/1286	0/153	1.67 (0.09, 29.21)
Stoop, 2012	COCOS	5/982	7/1276	0.93 (0.30, 2.92)
Colo v. FS				
Grobbee, 2019		9/1426	13/2435	1.18 (0.51, 2.76)
Segnan, 2007	SCORE III	13/1596	12/1922	1.30 (0.60, 2.85)
CTC v. FS				
Regge, 2017	Proteus 2	10/2595	9/2673	1.14 (0.47, 2.81)
gFOBT v. FS				
Brevinge, 1997		2/1893	5/1371	0.29 (0.06, 1.49)
Hol, 2010		6/2351	8/1386	0.44 (0.15, 1.27)
gFOBT v. FS+gFOBT				
Berry, 1997		2/3128	3/3243	0.69 (0.12, 4.13)
Rasmussen, 1999		4/3055	12/2222	0.24 (0.08, 0.75)
Steele, 2019		18/25918	23/25851	0.78 (0.42, 1.45)
FIT v. Colo				
Grobbee, 2019		83/10743	9/1426	1.22 (0.62, 2.43)
Quintero, 2012	COLONPREV	33/26599	30/26703	1.10 (0.67, 1.81)
Sali, 2016	SAVE	6/4677	0/153	0.39 (0.02, 7.00)
Segnan, 2007	SCORE III	2/1965	13/1596	0.12 (0.03, 0.55)
FIT v. CTC				
Sali, 2016	SAVE	6/4677	7/1286	0.24 (0.08, 0.70)
FIT v. FS				
Grobbee, 2019		83/10743	13/2435	1.45 (0.81, 2.59)
Hol, 2010		14/2975	8/1386	0.82 (0.34, 1.94)
Segnan, 2005	SCORE II	8/2336	14/4025	0.98 (0.41, 2.34)
Segnan, 2007	SCORE III	2/1965	12/1922	0.16 (0.04, 0.73)
FIT v. gFOBT				
Faivre, 2012 (FOB Gold)		91/32215	117/85149	2.06 (1.56, 2.70)
Faivre, 2012 (Magstream)		65/19244	117/85149	2.46 (1.82, 3.33)
Faivre, 2012 (OC-Sensor)		92/33690	117/85149	1.99 (1.51, 2.61)
Hol, 2010		14/2975	6/2351	1.84 (0.71, 4.79)
van Rossum, 2008		24/10322	11/10301	2.18 (1.07, 4.44)



Notes: The sample for Grobbee, 2019 overlaps with samples in Stoop, 2012 and Hol, 2010. In the studies with 0 events, a correction factor of 0.5 was used to allow for RR calculations.
Abbreviations: CI = confidence interval; COCOS = COlonoscopy or COlonography for Screening;; Colo = colonoscopy; CRC = colorectal cancer; CTC = computed tomography colonography; FIT; FS; gFOBT; n = number; RR = relative risk; SCORE = Screening for COlon Rectum

Figure 11. Key Question 2: Forest Plot of CT Colonography With Bowel Prep Sensitivity and Specificity for Adenomas ≥10 mm

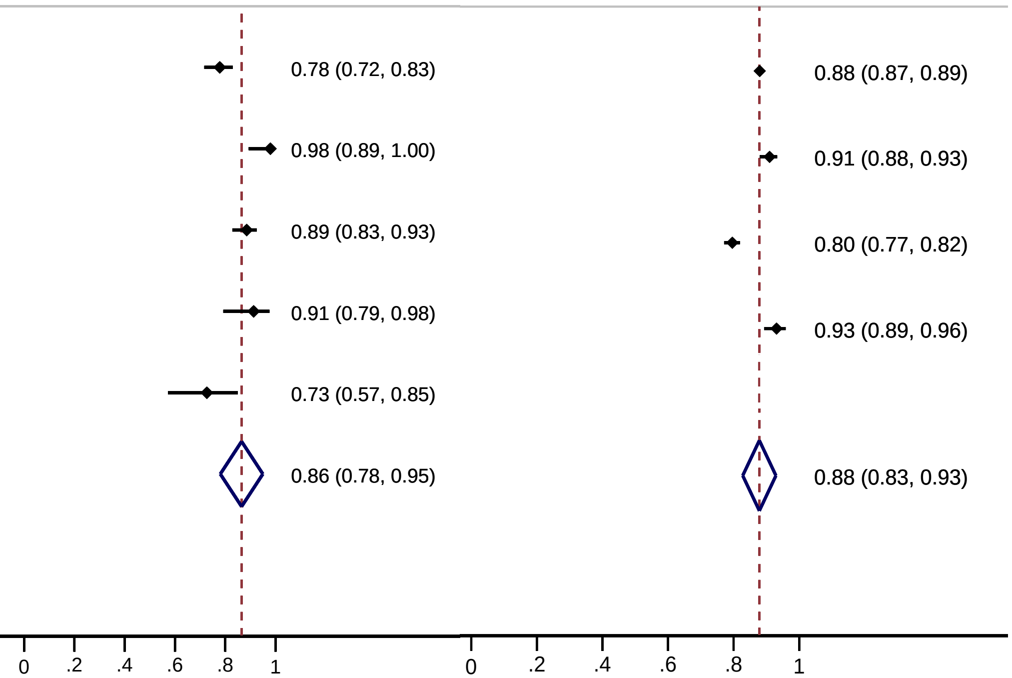
Author, year	Fecal tagging	TP	FN	TN	FP	Total	Sensitivity (95% CI)	Specificity (95% CI)
Johnson, 2008	Yes	92	10	2083	339	2524	0.90 (0.83, 0.95)	0.86 (0.85, 0.87)
Pickhardt, 2003	Yes	43	3	1138	47	1231	0.93 (0.82, 0.98)	0.96 (0.95, 0.97)
Graser, 2009	No	22	2	276	6	306	0.92 (0.74, 0.99)	0.98 (0.95, 0.99)
Johnson, 2007	No	14	7	413	10	444	0.67 (0.45, 0.83)	0.98 (0.96, 0.99)
Kim, 2008	No	9	1			241	0.90 (0.56, 1.00)	
							0.89 (0.83, 0.96)	0.94 (0.89, 1.00)



Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive
Note: I^2=41.7% for sensitivity; I^2=98.3% for specificity

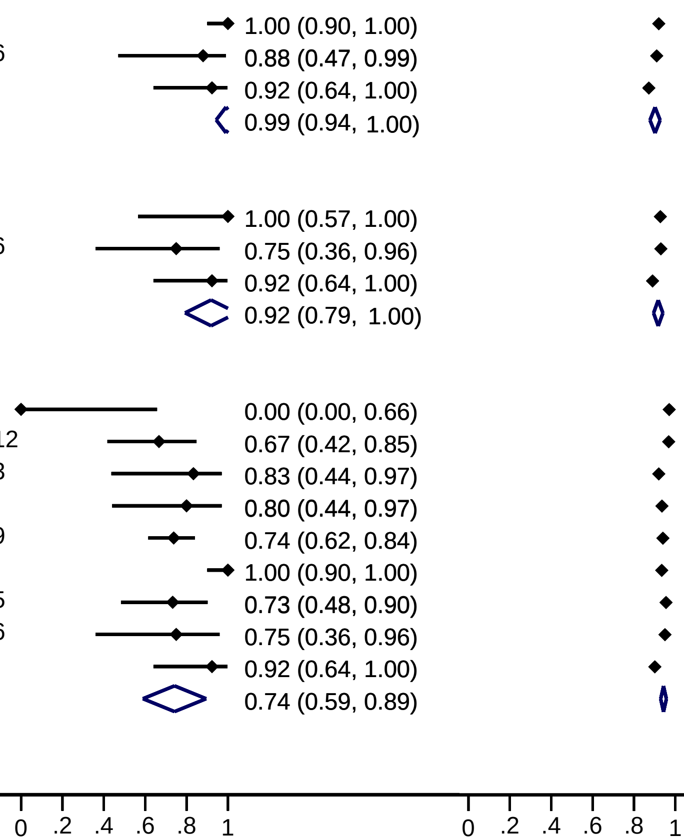
Figure 12. Key Question 2: Forest Plot of CT Colonography With Bowel Prep Sensitivity and Specificity for Adenomas ≥6 mm

Author, year	Fecal tagging	TP	FN	TN	FP	Total	Sensitivity (95% CI)	Specificity (95% CI)
Johnson, 2008	Yes	158	45	2042	279	2524	0.78 (0.72, 0.83)	0.88 (0.87, 0.89)
Lefere, 2013	Yes	48	1	403	40	492	0.98 (0.89, 1.00)	0.91 (0.88, 0.93)
Pickhardt, 2003	Yes	147	19	848	217	1231	0.89 (0.83, 0.93)	0.80 (0.77, 0.82)
Graser, 2009	No	41	4	243	18	306	0.91 (0.79, 0.98)	0.93 (0.89, 0.96)
Kim, 2008	No	32	12			241	0.73 (0.57, 0.85)	
							0.86 (0.78, 0.95)	0.88 (0.83, 0.93)



Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive
Note: I^2=87.4% for sensitivity; I^2=94.9% for specificity

Figure 13. Key Question 2: Forest Plot of OC-Sensor Sensitivity and Specificity to Detect Colorectal Cancer (All Colonoscopy Follow-Up), by Cutoff (µg Hb/g Feces)



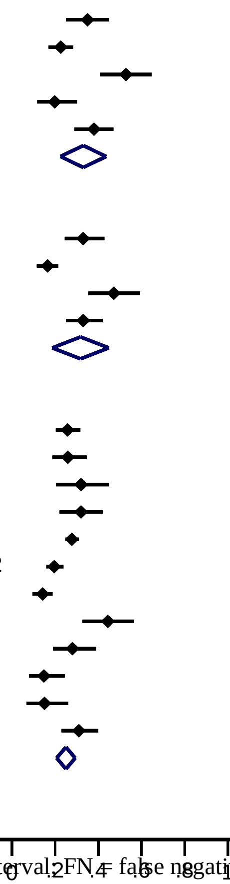
Author, year	TP	FN	TN	FP	Total	Sensitivity (95% CI)	Specificity (95% CI)
10							
Hernandez, 2014	5	0	712	62	779	1.00 (0.90, 1.00)	0.92 (0.90, 0.94)
de Wijkerslooth, 2012	7	1	1134	114	1256	0.88 (0.47, 0.99)	0.91 (0.89, 0.92)
Park, 2010	12	1	660	97	770	0.92 (0.64, 1.00)	0.87 (0.85, 0.89)
Subtotal						0.99 (0.94, 1.00)	0.90 (0.88, 0.93)
15							
Hernandez, 2014	5	0	718	56	779	1.00 (0.57, 1.00)	0.93 (0.91, 0.94)
de Wijkerslooth, 2012	6	2	1163	85	1256	0.75 (0.36, 0.96)	0.93 (0.92, 0.95)
Park, 2010	12	1	674	83	770	0.92 (0.64, 1.00)	0.89 (0.87, 0.91)
Subtotal						0.92 (0.79, 1.00)	0.92 (0.89, 0.94)
20							
Shapiro, 2017	0	2	917	28	947	0.00 (0.00, 0.66)	0.97 (0.96, 0.98)
Kim, 2017	10	5	14420	477	14912	0.67 (0.42, 0.85)	0.97 (0.97, 0.97)
Chiu, 2016	5	1	2616	181	2803	0.83 (0.44, 0.97)	0.92 (0.90, 0.94)
Redwood, 2016	8	2	599	52	661	0.80 (0.44, 0.97)	0.94 (0.93, 0.94)
Imperiale, 2014	48	17	9272	652	9989	0.74 (0.62, 0.84)	0.94 (0.92, 0.95)
Hernandez, 2014	5	0	724	50	779	1.00 (0.90, 1.00)	0.93 (0.93, 0.94)
Brenner, 2013	11	4	2121	99	2235	0.73 (0.48, 0.90)	0.95 (0.95, 0.96)
de Wijkerslooth, 2012	6	2	1183	65	1256	0.75 (0.36, 0.96)	0.95 (0.93, 0.96)
Park, 2010	12	1	682	75	770	0.92 (0.64, 1.00)	0.90 (0.88, 0.92)
Subtotal						0.74 (0.59, 0.89)	0.94 (0.93, 0.96)

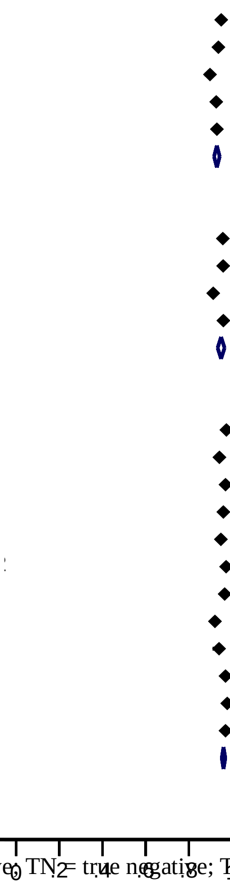
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive; µg Hb per g feces = microgram hemoglobin per gram feces

Note: For 20 µg Hb/g feces cutoff, the bivariate pooled sensitivity was 0.74 (95% CI, 0.64 to 0.83; I^2=31.6%) and specificity was 0.94 (95% CI, 0.93 to 0.96; I^2=96.6%). For 15 µg Hb/g feces cutoff, sensitivity I^2=0% and specificity I^2=77.4%. For 10 µg Hb/g feces cutoff, sensitivity I^2=0% and specificity I^2=79.1%.

Figure 14. Key Question 2: Forest Plot of OC-Sensor Sensitivity and Specificity to Detect Advanced Neoplasia (All Colonoscopy Follow-Up), by Cutoff (µg Hb/g Feces)

Author, year	TP	FN	TN	FP	Total	Sensitivity (95% CI)	Specificity (95% CI)
10							
Hernandez, 2014	34	63	649	33	779	0.35 (0.25, 0.45)	0.95 (0.93, 0.97)
Liles, 2018	48	163	2398	162	2771	0.23 (0.17, 0.28)	0.94 (0.93, 0.95)
Park, 2010	38	34	627	71	770	0.53 (0.41, 0.65)	0.90 (0.87, 0.92)
Ribbing Wilen, 2019	16	65	672	53	806	0.20 (0.12, 0.30)	0.93 (0.90, 0.94)
de Wijkerslooth, 2012	45	74	1061	76	1256	0.38 (0.29, 0.47)	0.93 (0.92, 0.95)
Subtotal						0.33 (0.22, 0.44)	0.93 (0.92, 0.94)
15							
Hernandez, 2014	32	65	653	29	779	0.33 (0.24, 0.43)	0.96 (0.94, 0.97)
Liles, 2018	35	176	2454	106	2771	0.17 (0.12, 0.22)	0.96 (0.95, 0.97)
Park, 2010	34	38	637	61	770	0.47 (0.35, 0.59)	0.91 (0.89, 0.93)
de Wijkerslooth, 2012	39	80	1088	49	1256	0.33 (0.25, 0.42)	0.96 (0.94, 0.97)
Subtotal						0.32 (0.19, 0.45)	0.95 (0.93, 0.97)
20							
Brenner, 2013	57	165	1960	53	2235	0.26 (0.20, 0.32)	0.97 (0.97, 0.98)
Chiu, 2016	29	83	2534	157	2803	0.26 (0.19, 0.35)	0.94 (0.93, 0.95)
Cooper, 2018	16	35	688	21	760	0.32 (0.20, 0.45)	0.97 (0.96, 0.98)
Hernandez, 2014	31	66	658	24	779	0.32 (0.22, 0.42)	0.96 (0.95, 0.98)
Imperiale, 2014	228	594	8695	472	9989	0.28 (0.25, 0.31)	0.95 (0.94, 0.95)
Kim, 2017	74	304	14137	397	14912	0.20 (0.16, 0.24)	0.97 (0.97, 0.98)
Liles, 2018	30	181	2474	86	2771	0.14 (0.09, 0.19)	0.97 (0.96, 0.97)
Park, 2010	32	40	643	55	770	0.44 (0.33, 0.57)	0.92 (0.90, 0.94)
Redwood, 2016	26	66	535	34	661	0.28 (0.19, 0.39)	0.94 (0.91, 0.95)
Ribbing Wilen, 2019	12	69	703	22	806	0.15 (0.08, 0.24)	0.97 (0.95, 0.98)
Shapiro, 2017	8	45	874	20	947	0.15 (0.07, 0.26)	0.98 (0.97, 0.99)
de Wijkerslooth, 2012	37	82	1103	34	1256	0.31 (0.23, 0.40)	0.97 (0.96, 0.98)
Subtotal						0.25 (0.21, 0.29)	0.96 (0.95, 0.97)



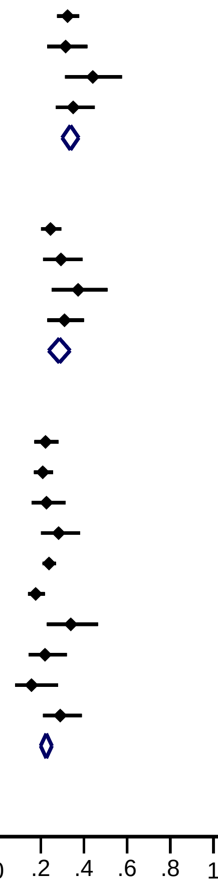


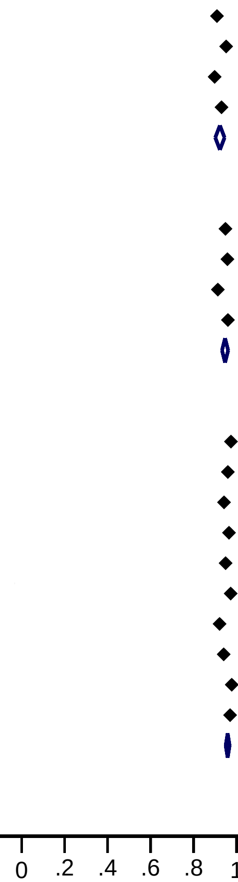
Abbreviations: AN = advanced adenoma; CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive; µg Hb per g feces = microgram hemoglobin per gram feces

Note: For 20 µg Hb/g feces cutoff, the bivariate pooled sensitivity was 0.25 (95% CI, 0.21 to 0.30; I^2=78.1%) and specificity was 0.96 (95% CI, 0.95 to 0.97; I^2=93.9%). For 15 µg Hb/g feces cutoff, the bivariate pooled sensitivity was 0.31 (95% CI, 0.21 to 0.44; I^2=89.8%) and specificity was 0.95 (95% CI, 0.93 to 0.96; I^2=89.0%). For 10 µg Hb/g feces cutoff, the bivariate pooled sensitivity was 0.33 (95% CI, 0.23 to 0.44; I^2=87.0%) and specificity was 0.93 (95% CI, 0.92 to 0.94; I^2=77.8%).

Figure 15. Key Question 2: Forest Plot of OC-Sensor Sensitivity and Specificity to Detect Advanced Adenomas (All Colonoscopy Follow-Up), by Cutoff (µg Hb/g Feces)

Author, year	TP	FN	TN	FP	Total	Sensitivity (95% CI)	Specificity (95% CI)
10							
Chang, 2017	110	229	5325	534	6198	0.32 (0.28, 0.38)	0.91 (0.90, 0.92)
Hernandez, 2014	29	63	649	33	774	0.32 (0.23, 0.42)	0.95 (0.93, 0.97)
Park, 2010	26	33	627	71	757	0.44 (0.31, 0.58)	0.90 (0.87, 0.92)
de Wijkersllooth, 2012	38	73	1061	76	1248	0.35 (0.27, 0.45)	0.93 (0.91, 0.94)
Subtotal						0.34 (0.30, 0.38)	0.92 (0.90, 0.94)
15							
Chang, 2017	83	256	5556	303	6198	0.25 (0.20, 0.29)	0.95 (0.94, 0.95)
Hernandez, 2014	27	65	653	29	774	0.29 (0.21, 0.39)	0.96 (0.94, 0.97)
Park, 2010	22	37	637	61	757	0.37 (0.25, 0.51)	0.91 (0.89, 0.93)
de Wijkersllooth, 2012	34	77	1088	49	1248	0.31 (0.23, 0.40)	0.96 (0.94, 0.97)
Subtotal						0.29 (0.24, 0.34)	0.95 (0.93, 0.96)
20							
Brenner, 2013	46	161	1960	51	2220	0.22 (0.17, 0.28)	0.97 (0.97, 0.98)
Chang, 2017	71	268	5622	237	6198	0.21 (0.17, 0.26)	0.96 (0.95, 0.96)
Chiu, 2016	24	82	2534	157	2797	0.23 (0.16, 0.31)	0.94 (0.93, 0.95)
Hernandez, 2014	26	66	658	24	774	0.28 (0.20, 0.38)	0.96 (0.95, 0.98)
Imperiale, 2014	180	577	8695	472	9924	0.24 (0.21, 0.27)	0.95 (0.94, 0.95)
Kim, 2017	64	299	14137	397	14897	0.18 (0.14, 0.22)	0.97 (0.97, 0.98)
Park, 2010	20	39	643	55	757	0.34 (0.23, 0.47)	0.92 (0.90, 0.94)
Redwood, 2016	18	64	535	34	651	0.22 (0.14, 0.32)	0.94 (0.92, 0.96)
Shapiro, 2017	8	43	874	20	945	0.16 (0.08, 0.28)	0.98 (0.97, 0.99)
de Wijkersllooth, 2012	34	80	1103	34	1248	0.29 (0.21, 0.39)	0.97 (0.95, 0.98)
Subtotal						0.23 (0.20, 0.25)	0.96 (0.95, 0.97)

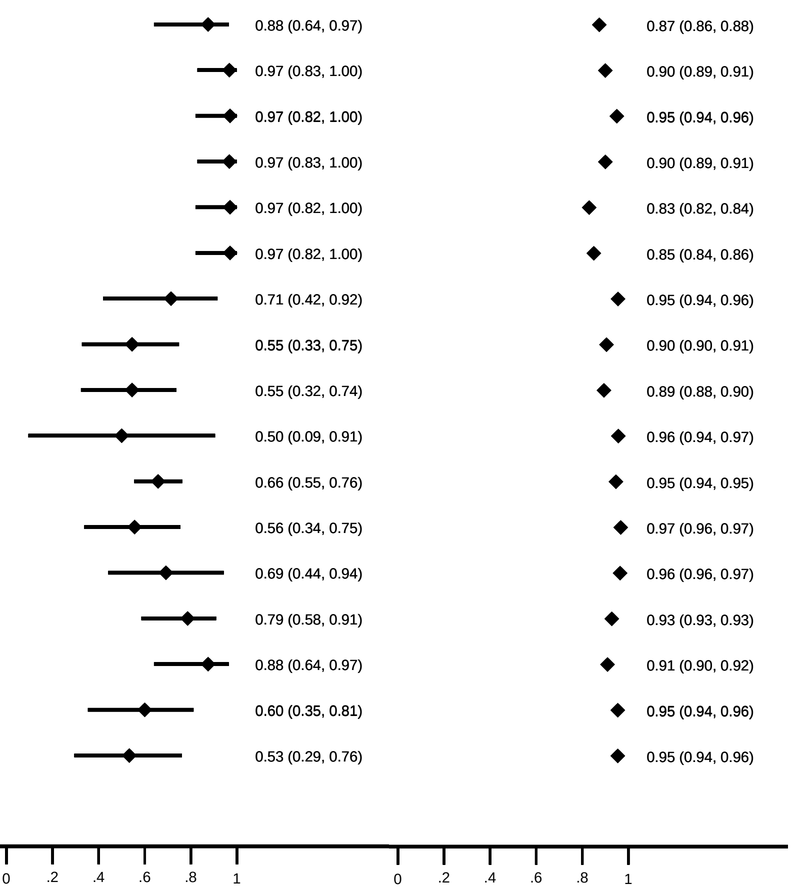




Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive; µg Hb per g feces = microgram hemoglobin per gram feces

Note: For 20 µg Hb/g feces cutoff, the bivariate pooled sensitivity was 0.23 (95% CI, 0.20 to 0.25; I^2=47.4%) and specificity was 0.96 (95% CI, 0.95 to 0.97; I^2=94.8%). For 15 µg Hb/g feces cutoff, sensitivity I^2=34.4% and specificity I^2=78.7%. For 10 µg Hb/g feces cutoff, sensitivity I^2=0% and specificity I^2=89.1%.

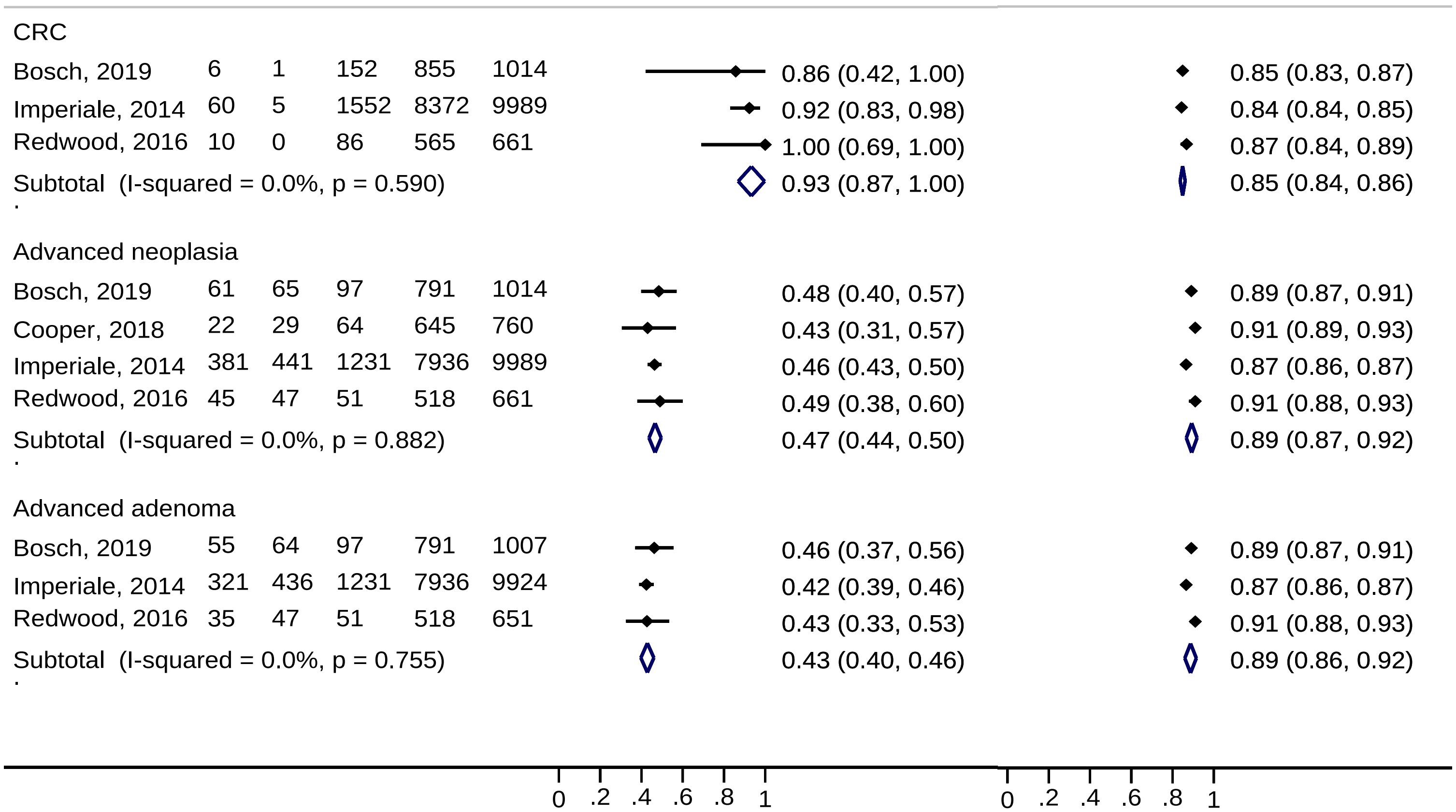
Figure 16. Key Question 2: Forest Plot of Other FITs Sensitivity and Specificity to Detect Colorectal Cancer (All Colonoscopy Follow-Up)



Author, year	FIT	No. CRC	Total	Cutoff, ug Hb per g feces	Sensitivity (95% CI)	Specificity (95% CI)
Chiu, 2016	Combination	16	3889		0.88 (0.64, 0.97)	0.87 (0.86, 0.88)
Brenner, 2017	FOB Gold	30	3494	8.5	0.97 (0.83, 1.00)	0.90 (0.89, 0.91)
Brenner, 2017	FOB Gold	29	3466	8	0.97 (0.82, 1.00)	0.95 (0.94, 0.96)
Brenner, 2017	FOB Gold	30	3494	17	0.97 (0.83, 1.00)	0.90 (0.89, 0.91)
Brenner, 2017	FOB Gold	29	3466	12	0.97 (0.82, 1.00)	0.83 (0.82, 0.84)
Brenner, 2017	FOB Gold	29	3466	27	0.97 (0.82, 1.00)	0.85 (0.84, 0.86)
Lee, 2014	Hemo Techt NS-Plus C system			19	0.71 (0.42, 0.92)	0.95 (0.94, 0.96)
Wong, 2015	Hemosure	22	5343	10	0.55 (0.33, 0.75)	0.90 (0.90, 0.91)
Ng, 2013	Hemosure	22	4539	50	0.55 (0.32, 0.74)	0.89 (0.88, 0.90)
Shapiro, 2017	InSure FIT	2	987	50	0.50 (0.09, 0.91)	0.96 (0.94, 0.97)
Morikawa, 2005	Magstream 1000/Hem SP	79	21805	100	0.66 (0.55, 0.76)	0.95 (0.94, 0.95)
Nakama, 1999	Monohaem	18	4611		0.56 (0.34, 0.75)	0.97 (0.96, 0.97)
Chen, 2014	OC-Light	13	6096	10	0.69 (0.44, 0.94)	0.96 (0.96, 0.97)
Chiu, 2013	OC-Light	28	18296	10	0.79 (0.58, 0.91)	0.93 (0.93, 0.93)
Cheng, 2002	OC-Light	16	7411	10	0.88 (0.64, 0.97)	0.91 (0.90, 0.92)
Brenner, 2013	RIDASCREEN Hemoglobin	15	2235	2	0.60 (0.35, 0.81)	0.95 (0.94, 0.96)
Brenner, 2013	RIDASCREEN Hemoglobin-Haptoglobin Complex	15	2235	2	0.53 (0.29, 0.76)	0.95 (0.94, 0.96)

Abbreviations: CI = confidence interval; CRC = colorectal cancer; µg Hb per g feces = microgram hemoglobin per gram feces

Figure 17. Key Question 2: Forest Plot of Cologuard Sensitivity and Specificity to Detect Colorectal Cancer, Advanced Neoplasia, and Advanced Adenomas



Author, year	TP	FN	FP	TN	Total	Sensitivity (95% CI)	Specificity (95% CI)
CRC							
Bosch, 2019	6	1	152	855	1014	0.86 (0.42, 1.00)	0.85 (0.83, 0.87)
Imperiale, 2014	60	5	1552	8372	9989	0.92 (0.83, 0.98)	0.84 (0.84, 0.85)
Redwood, 2016	10	0	86	565	661	1.00 (0.69, 1.00)	0.87 (0.84, 0.89)
Subtotal (I-squared = 0.0%, p = 0.590)						0.93 (0.87, 1.00)	0.85 (0.84, 0.86)
Advanced neoplasia							
Bosch, 2019	61	65	97	791	1014	0.48 (0.40, 0.57)	0.89 (0.87, 0.91)
Cooper, 2018	22	29	64	645	760	0.43 (0.31, 0.57)	0.91 (0.89, 0.93)
Imperiale, 2014	381	441	1231	7936	9989	0.46 (0.43, 0.50)	0.87 (0.86, 0.87)
Redwood, 2016	45	47	51	518	661	0.49 (0.38, 0.60)	0.91 (0.88, 0.93)
Subtotal (I-squared = 0.0%, p = 0.882)						0.47 (0.44, 0.50)	0.89 (0.87, 0.92)
Advanced adenoma							
Bosch, 2019	55	64	97	791	1007	0.46 (0.37, 0.56)	0.89 (0.87, 0.91)
Imperiale, 2014	321	436	1231	7936	9924	0.42 (0.39, 0.46)	0.87 (0.86, 0.87)
Redwood, 2016	35	47	51	518	651	0.43 (0.33, 0.53)	0.91 (0.88, 0.93)
Subtotal (I-squared = 0.0%, p = 0.755)						0.43 (0.40, 0.46)	0.89 (0.86, 0.92)

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FN = false negative; FP = false positive; TN = true negative; TP = true positive
Note: For CRC, sensitivity I^2=0% and specificity I^2=37.7%. For advanced neoplasia, sensitivity I^2=0% and specificity I^2=88.8%. For advanced adenoma, sensitivity I^2=0% and specificity I^2=87.8%.

Figure 18. Key Question 3: Serious Bleeding Events From Flexible Sigmoidoscopy Screening

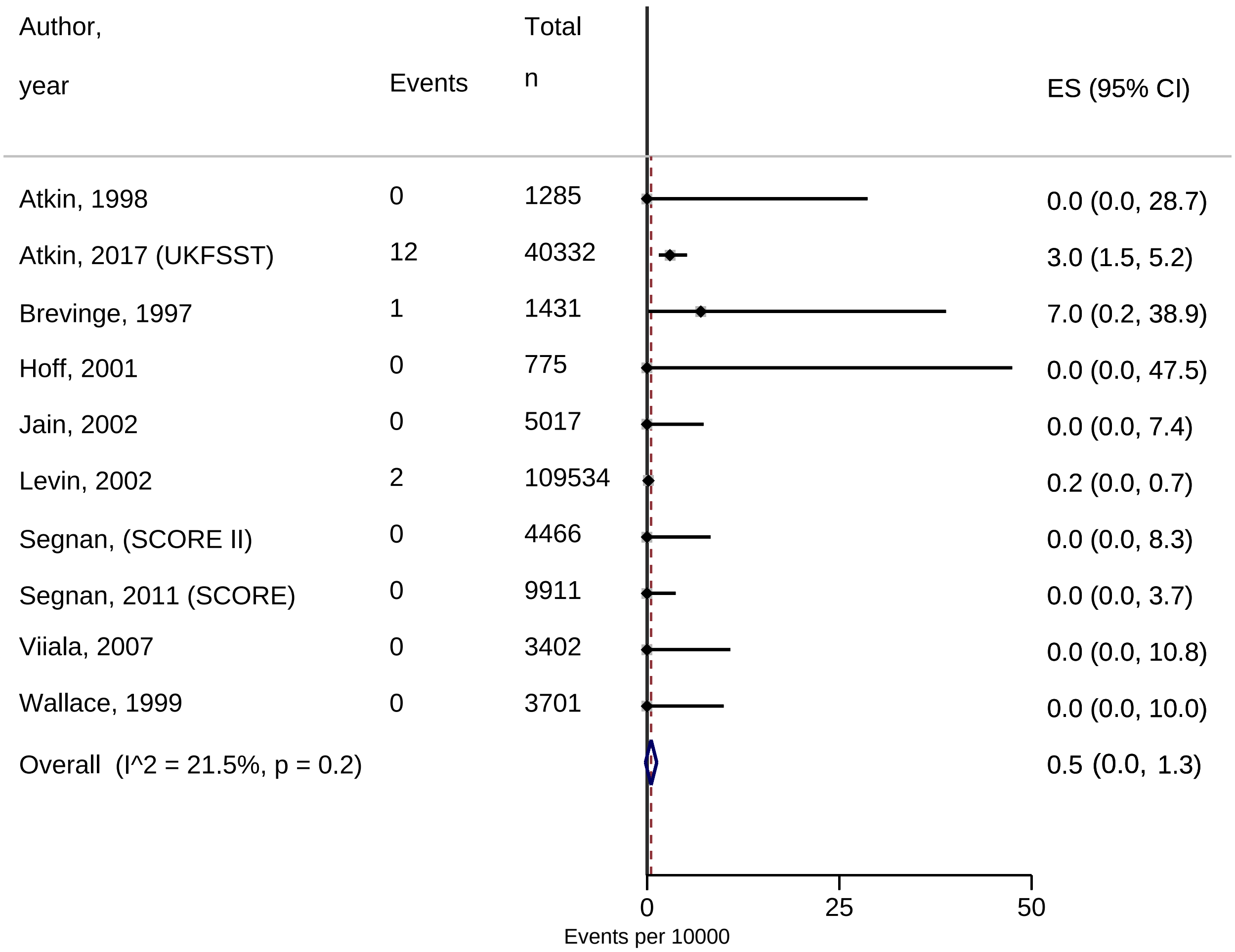
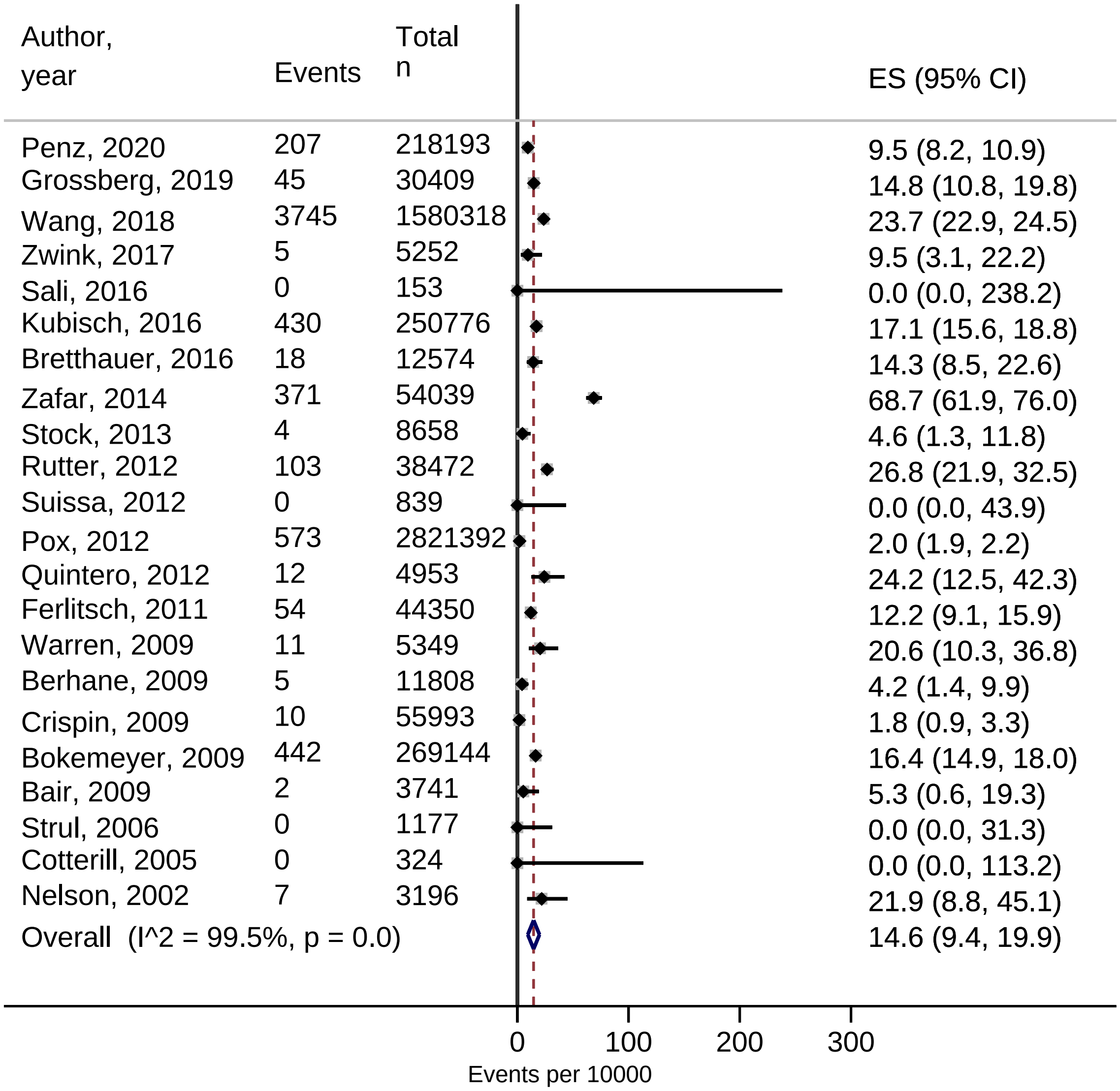
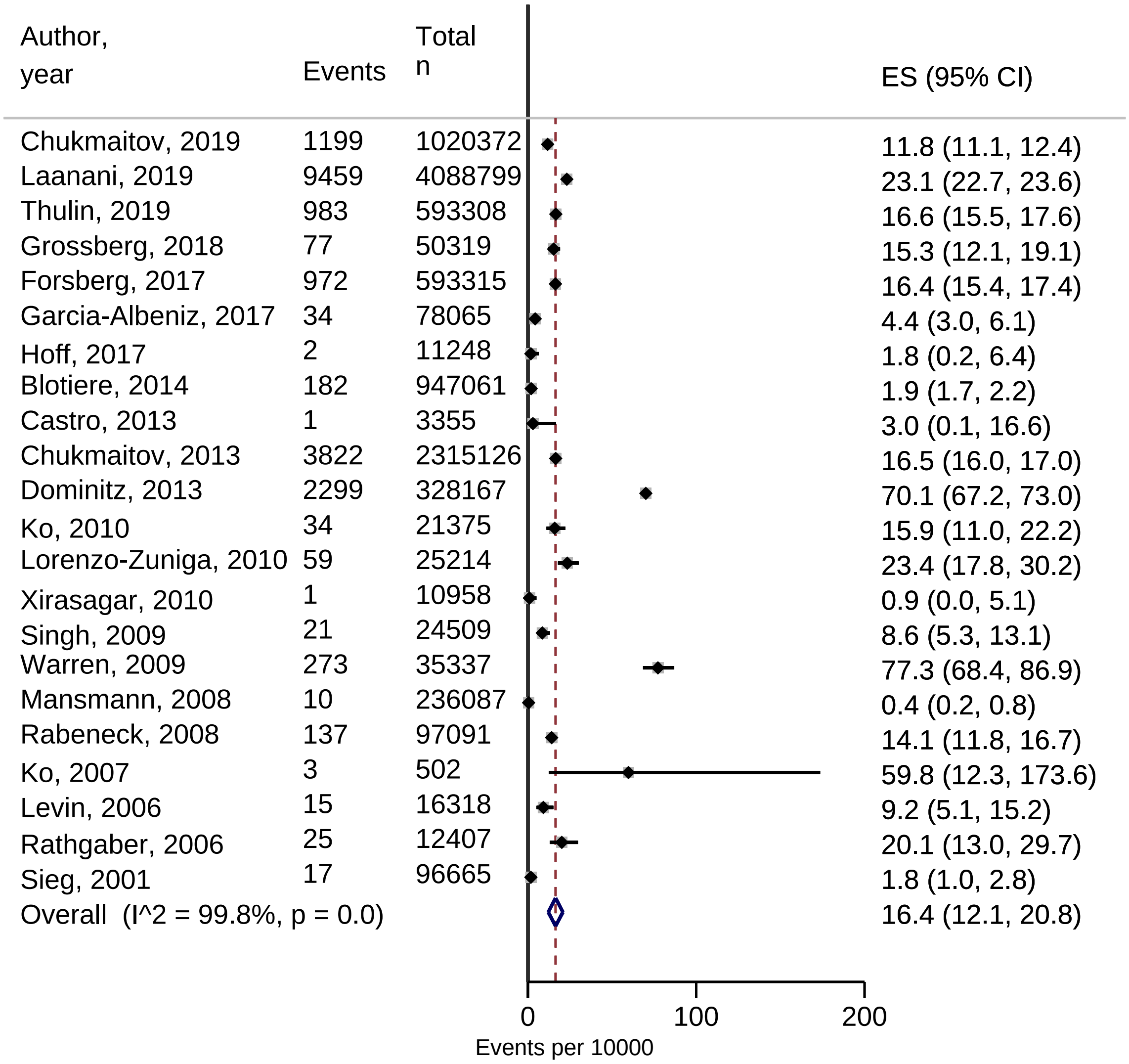


Figure 19. Key Question 3: Serious Bleeding Events From Screening Colonoscopy



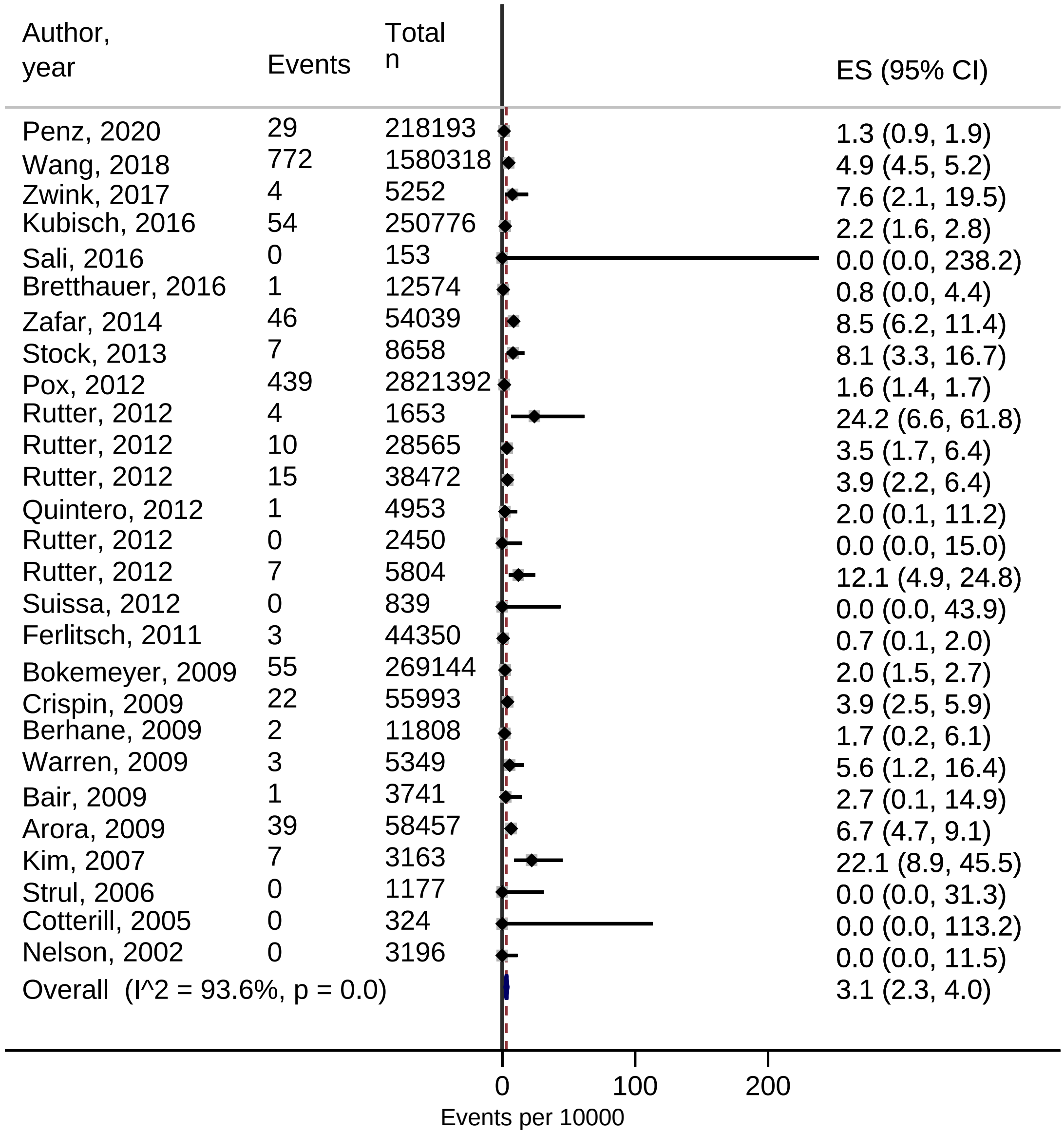
Abbreviations: CI = confidence interval; ES = effect size; n = number

Figure 20. Key Question 3: Serious Bleeding Events From Mixed Colonoscopies*



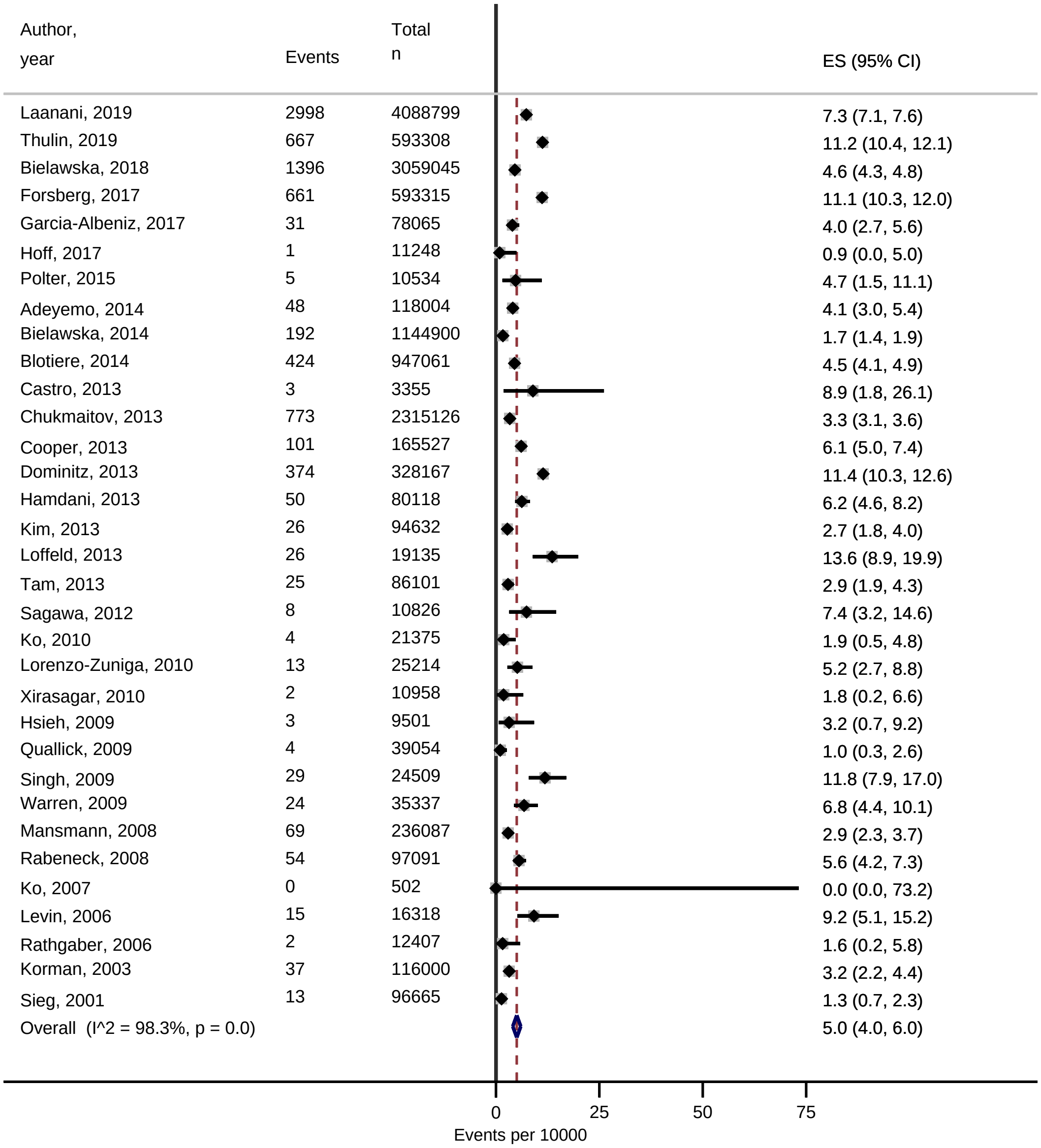
* Mixed are screening and symptomatic
Abbreviations: CI = confidence interval; ES = effect size; n = number

Figure 21. Key Question 3: Perforation Events From Screening Colonoscopies



Abbreviations: CI = confidence interval; ES = effect size; n = number

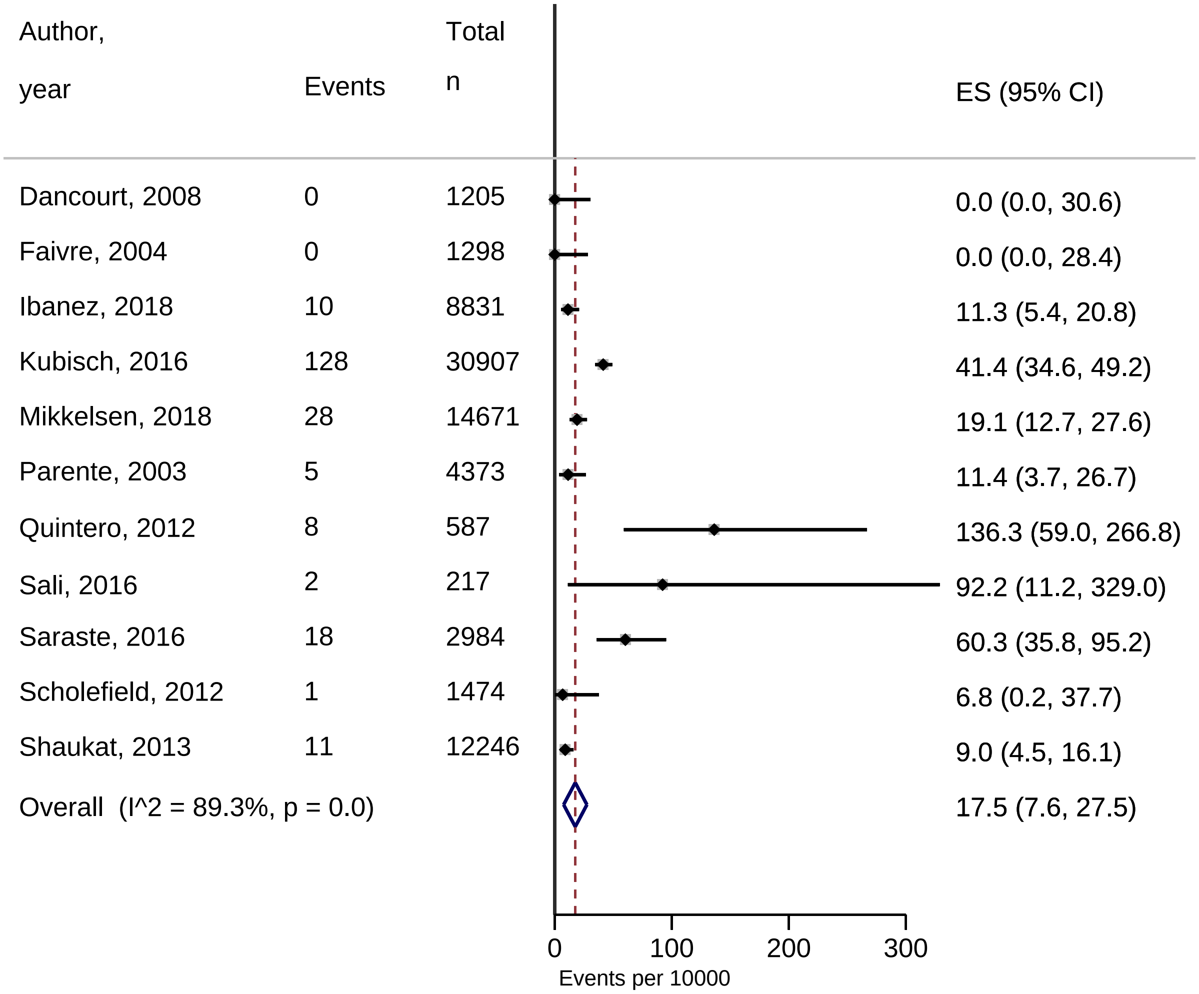
Figure 22. Key Question 3: Perforation Events From Mixed Colonoscopies*



* Mixed are screening and symptomatic

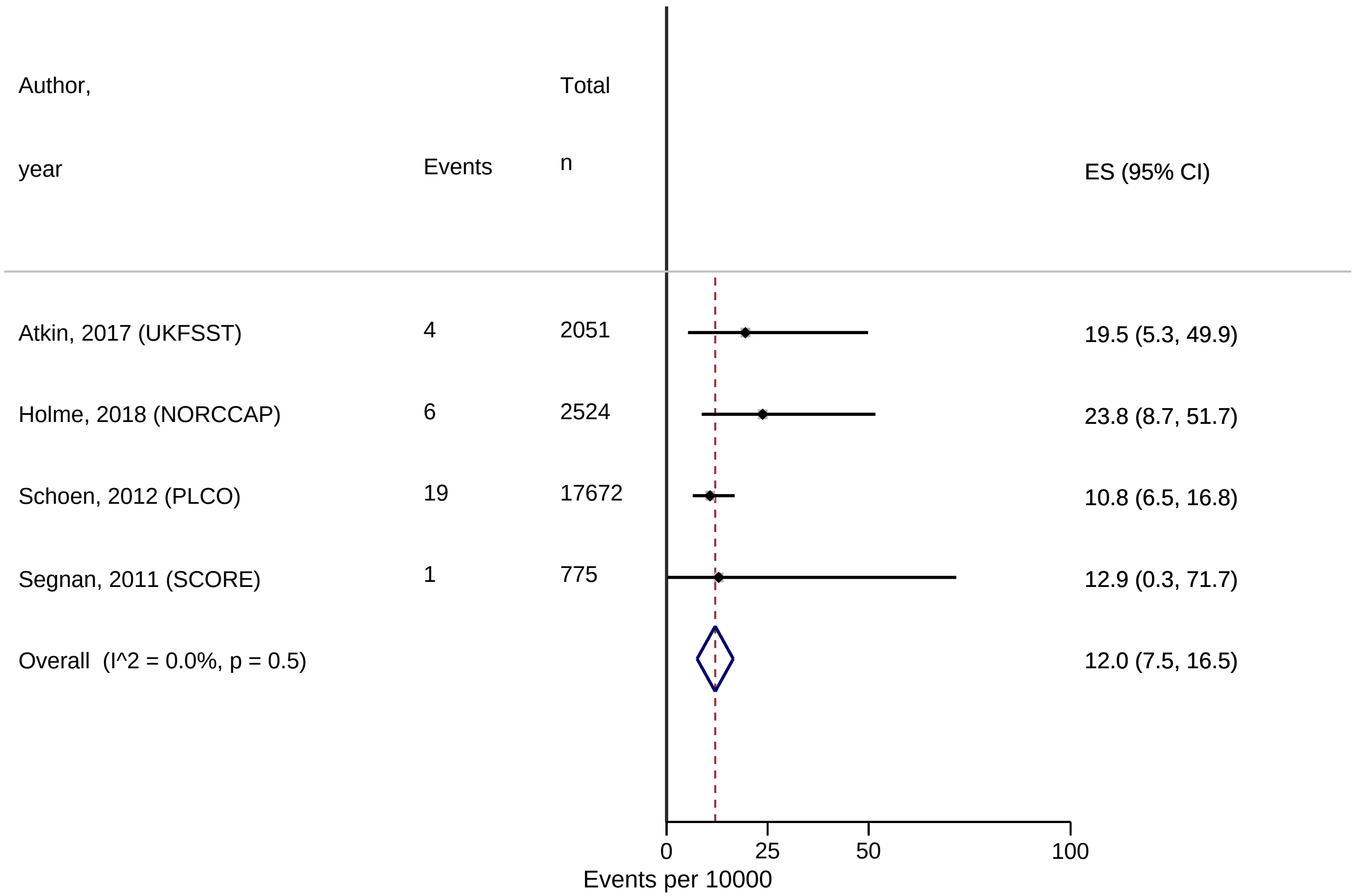
Abbreviations: CI = confidence interval; ES = effect size; n = number

Figure 23. Key Question 3: Serious Bleeding Events From Colonoscopy Following an Abnormal FOBT/FIT*



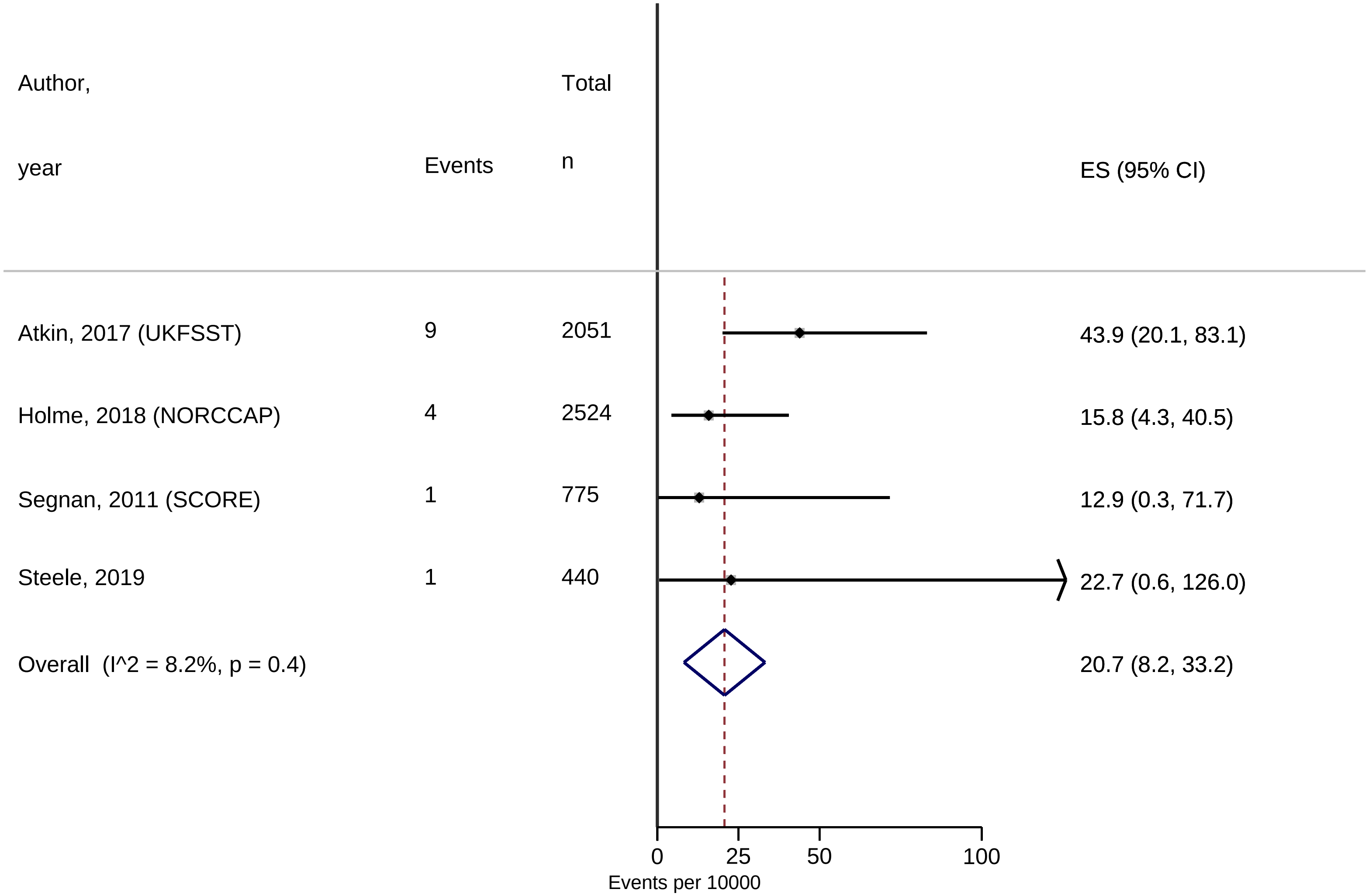
Abbreviations: CI = confidence interval; ES = effect size; n = number

Figure 24. Key Question 3: Perforations From Colonoscopy After an Abnormal FS



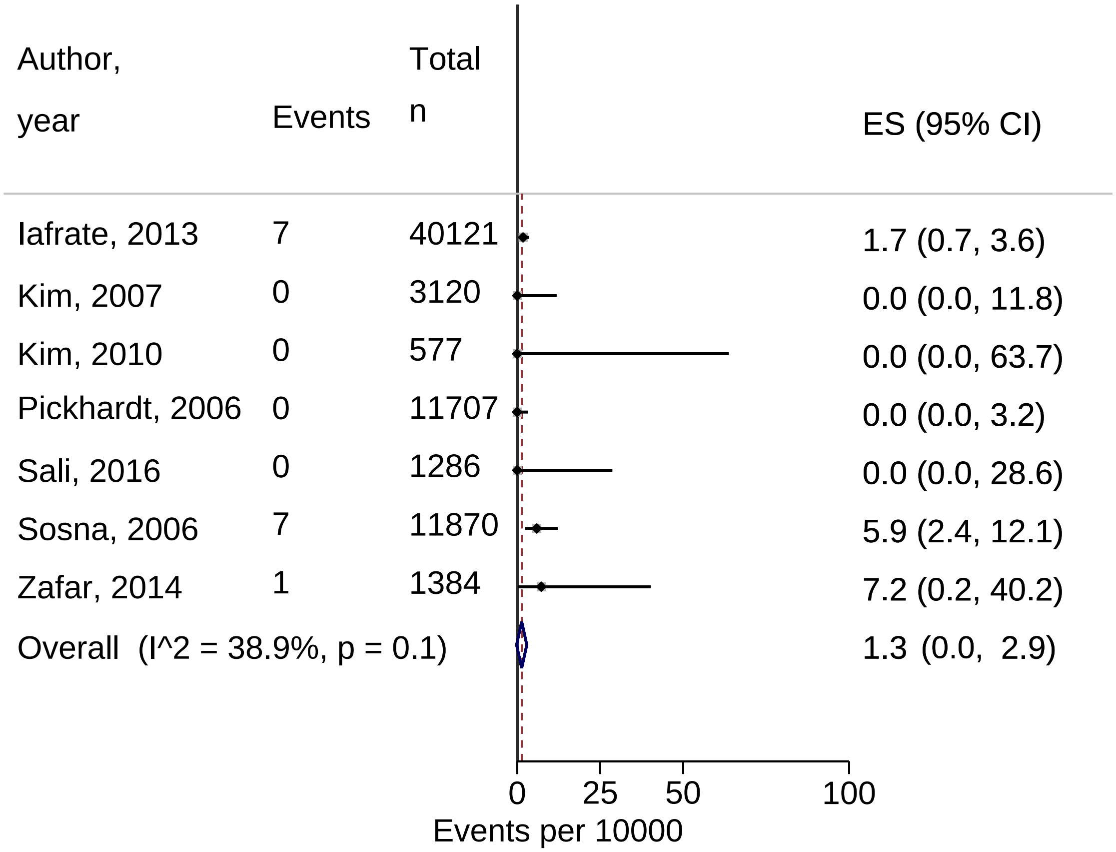
Abbreviations: CI = confidence interval; ES = effect size; n = number; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 25. Key Question 3: Serious Bleeding Events From Colonoscopy Following an Abnormal FS



Abbreviations: CI = confidence interval; ES = effect size; n = number; NORCCAP = Norwegian Colorectal Cancer Prevention; SCORE = Screening for COlon Rectum; UKFSST = United Kingdom Flexible Sigmoidoscopy Screening Trial

Figure 26. Key Question 3: Perforations From Screening or Mixed CTC



Abbreviations: CI = confidence interval; ES = effect size; n = number

Table 1. Definitions of Terms Describing Colorectal Cancer and Its Precursor Lesions

Term	**Definition**
Adenoma	Benign epithelial tumor or polyp
Advanced adenoma (AA)	Adenoma ≥1 cm in size, with tubulovillous/villous histology, or with high-grade dysplasia*
Sessile serrated lesion (adenoma or polyp) (SSL)	Adenoma with specific morphology (sessile), histology (serrated), and characteristic molecular features (serrated polyp with at least one unequivocal aberrant crypt) with potential for malignant transformation
Carcinoma in situ	Severe dysplasia limited to the mucosa, Stage 0 colorectal cancer
Adenocarcinoma	Malignant tumor that invades the muscularis mucosa, Stage I-IV colorectal cancer
Advanced neoplasia (AN)	Advanced adenoma and all stages of colorectal cancers

* Exact definitions may vary slightly

Table 2. Available Screening Tests for Colorectal Cancer

Type of test	Screening test	Considerations on evidence and availability
Direct visualization	Flexible sigmoidoscopy	Original RCTs show effectiveness of reducing CRC mortality; modeling studies suggest that flex sig used with FIT performs better than flex sig alone; currently very limited availability in the United States.
	Colonoscopy	Prospective cohort study demonstrating association with reduction in CRC mortality; most commonly used screening test in the United States.
	CT colonography	Test performance similar to colonoscopy for larger adenomas; uncertain impact of the visualization of extra-colonic findings and radiation exposure.
	Capsule endoscopy	Currently used as a diagnostic test; evaluation as a screening test extremely limited with only one group recommending this as a lower tiered test. FDA approval is as an adjunctive test in patients with prior incomplete colonoscopy.
	MRC	Currently used as a diagnostic, not screening, test; evaluation as a screening test extremely limited.
	DCBE	No longer used in clinical practice for screening due to inferior test performance compared to other available direct visualization tests.
Stool-based*	gFOBT	Original RCTs show effectiveness of reducing CRC mortality conducted using older guaiac-based FOBT; currently used gFOBT (HSgFOBT) have superior test performance compared with older versions.
	FIT	Immunochemical FOBT, or FITs, are not a homogeneous class of tests, and multiple manufacturers produce different FITs with differing test performance; many available FITs have superior test performance and greater feasibility (no dietary restriction and single specimen) compared to gFOBT
	sDNA	Stool-based DNA testing has evolved over time from single target to multi-targeted DNA tests paired with FIT (sDNA-FIT); currently only one sDNA-FIT stool test is FDA approved for CRC screening
Serum-based	mSEPT9	Currently only one serum-based test, testing for methylated septin 9 gene, is available for use with inferior test performance to stool-based testing; FDA approval is for screening only in persons unwilling or unable to be screened by gFOBT, FIT, FS, or colonoscopy.
Urine-based	Metabolomic-based test	Only one urine-based test, testing for various metabolites in the urine and clinical risk factors, is available for use by CLIA-certified laboratories. Limited evidence on test accuracy.

* Stool testing should be performed on spontaneously voided stool samples, as opposed to in-office stool samples obtained by digital rectal examination, because of the less sensitive or unclear test performance of the latter.[460, 461]

Abbreviations: CRC = colorectal cancer; CT = computed tomography; DCBE = double-contrast barium enema; DNA = deoxyribonucleic acid; FDA = Food and Drug Administration; FIT = fecal immunochemical test; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; HS = high-sensitivity; MRC = magnetic resonance colonography; RCT = randomized controlled trial; sDNA = stool-based deoxyribonucleic acid

Table 3. Recommended Screening Tests for Colorectal Cancer by Selected Society or Professional Organization Since 2008

Society or Professional Organization, Year	Age to begin screening	Age to stop screening	Screening test (recommended interval, years)							
			Colonoscopy	FS*	gFOBT†	FIT	CTC	FIT-DNA	m*SEPT9*	Capsule
ACP, 2019[462]	50	76	Y (10)	Y (10)	Y (2)	Y	--	--	--	--
BMJ International Panel, 2019‡	50†† (if 15-year CRC risk >3%)	79	Y (15)	Y (15)	--	Y (1-2)	--	--	--	--
ACR, 2018[463]	50	--	--	--	--	--	Y (5)	--	--	--
ACS, 2018[464]	45	85	Y (10)	Y (5)	Y (1)	Y (1)	Y (5)	Y (3)	N	N
USMSTF,*** 2017[465]	50 (45 for AA)	85	Y (10)	Y** (5-10)	N	Y (1)	Y** (5)	Y** (3)	N	Y** (5)
CTFPHC, 2016[466]	50	74	N	Y (10)	Y (2)	Y (2)	--	--	--	--
SIGN, 2016[467]	--	--	--	--	Y	Y	--	--	--	--
USPSTF, 2016[1]	50	85	Y (10)	Y (5-10)	Y (1)	Y (1)	Y (5)	Y (1-3)	N	N
AAFP, 2015[468]	50	75	Y (10)	Y	Y	Y	N	N	--	--
NCCN, 2015[469]	50	--	Y§ (10)	Y§	Y (1)	Y	Y§ (5)	N	--	--
Council of the European Union, 2012[470]	--	--	N	N	Y (<2)	--	--	--	--	--
ICSI, 2012[471]	50 (45 for AA)	--	Y (10)	Y (5)	Y (1)	Y (1)	Y (5)	--	--	--

* With or without stool testing
† High sensitivity
‡ For individuals with an estimated 15-year risk above 3% (For individuals with an estimated 15-year colorectal cancer risk below 3%, BMJ suggests no screening)
** The USMSTF recommends tests in tiers. First tier is colonoscopy and FIT; second tier is CTC, FIT-DNA, and FS; and the third tier is capsule endoscopy.
§ NCNN encourages tests that are designed to detect both early cancer and adenomatous polyps.
*** USMSTF includes American Gastroenterological Association, American College of Gastroenterology, and American Society for Gastrointestinal Endoscopy
†† For those with a 15-year CRC risk below 3%, no screening was suggested

Abbreviations: AA = African American; AAFP = American Academy of Family Physicians; ACP = American College of Physicians; ACR = American College of Radiology; ACS = American Cancer Society; CTFPHC = Canadian Task Force on Preventive Health Care; CTC = computed tomography colonography; DCBE = double-contrast barium enema; DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; I = insufficient evidence to evaluate; ICSI = Institute for Clinical Systems Improvement; MRC = magnetic resonance colonography; N = no, not recommended; NCCN = National Comprehensive Cancer Network; SIGN = Scottish Intercollegiate Guidelines Network; USMSTF = US Multi-Society Task Force; USPSTF = US Preventive Services Task Force; Y = yes, recommended as an acceptable option; -- = not addressed in the guideline

Table 4. Evidence Landscape of Included Studies by Key Question and Screening Test

Key question		Total no. of Studies	Direct Visualization				Stool				Serum	Urine
			FS (+/- stool testing)	Colo	CTC	CE	gFOBT	HSgFOBT	FIT	sDNA	mSEPT9	Metab
1	**Screening effectiveness**	13	4*	2*	0	0	6*	0	1*	0	0	0
	Comparative effectiveness	21	11*	5*	3*	0	8	0	13*	0	0	0
2	**Colonoscopy reference standard‡**	40	0	4	9	2*	NA	2*	26*	4*	1	1*
	Differential verification†	19	0	0	0	0	NA	3	19*	0	0	0
3	**Serious adverse events**	110	19*	68* (S) 20* (F)	17*	1*	NA**	NA**	NA**	NA**	NA**	NA**
	Radiation	7	NA	NA	7	NA	NA	NA	NA	NA	NA	NA
	ECF	27	NA	NA	27*	NA	NA	NA	NA	NA	NA	NA

* Includes new data since the 2016 USPSTF recommendation
† Differential verification consisted of direct visualization for those with an abnormal screening test and cancer registry followup for all participants.
** No hypothesized harms for non-invasive screening tests beyond that of the followup testing.
‡ For colonoscopy and CTC studies, the reference standard could include colonoscopy plus CTC (segmental unblinding)

Abbreviations: CE = capsule endoscopy; Colo = colonoscopy; CTC = computed tomography colonography; ECF = extracolonic findings; F = followup colonoscopy due to an abnormal screening test; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; HS = high-sensitivity; Metab = metabolomic-based test; NA = not applicable or not addressed in this review; S = screening; sDNA = stool-based deoxyribonucleic acid

Table 5. Key Question 1: Overall Summary of Impact of Screening vs. No Screening on Colorectal Cancer Incidence and Mortality

Screening test (Sample n)	Round	Followup, years	Group	CRC incidence	CRC mortality
Colonoscopy k=2, cohort (n=436,927)[21, 125]	1	8-24†	*Total*	w/polypectomy HR, adj: 0.53 (95% CI, 0.40 to 0.71)* negative colo HR, adj: 0.47 (95% CI, 0.39 to 0.57)* Age 70-74 y: RD -0.42% (95% CI, -0.24 to -0.63)† Age 75-79 y: RD -0.14% (95% CI, -0.41 to -0.16)†	HR, adj: 0.32 (95% CI, 0.24 to 0.45)*
			Distal	w/polypectomy HR, adj: 0.37 (95% CI, 0.23 to 0.61)* negative colo HR, adj: 0.29 (95% CI, 0.21 to 0.39)*	HR, adj: 0.18 (95% CI, 0.10 to 0.31)*
			Proximal	w/polypectomy HR, adj: 0.79 (95% CI, 0.52 to 1.19)* negative colo HR, adj: 0.29 (95% CI, 0.21 to 0.39)*	HR, adj: 0.47 (95% CI, 0.29 to 0.76)†
FS k=4, RCT (n=458,002)[119, 127, 130, 140]	1-2 Q3-5y	11-17	*Total*	IRR 0.78 (95% CI, 0.74 to 0.83)	IRR 0.74 (0.68 to 0.80)
			Distal	IRR 0.67 (95% CI, 0.60 to 0.75)	IRR 0.61 (95% CI, 0.49 to 0.74)
			Proximal	IRR 0.93 (95% CI, 0.88 to 0.99)	IRR 0.90 (95% CI, 0.80 to 1.00)
Hemoccult II k=5, RCT (n=419,966) [124, 128, 129, 138, 143]	2-9 Q2y	11-30	*Total*	RR range from 0.90 (95% CI, 0.77 to 1.04) from 1.02 (95% CI, 0.93 to 1.12)	RR range from 0.78 (95% CI, 0.65, 0.93) to 0.91 (95% CI, 0.84, 0.98)‡
			Distal	NR	NR
			Proximal	NR	NR
FIT k=1, cohort (n=5.4 million)[122]	Q2y	Up to 6 y (mean 3y)	*Total*	NR	RR, adj: 0.90 (95% CI, 0.84, 0.95)

* 22 year followup for incidence; 24 year followup for mortality. Adjusted for: age, BMI, family history, smoking status, physical activity, diet, vitamin use, aspirin use, NSAID use, cholesterol-lowering drug use, hormone replacement therapy

‡ Annual RR from one trial only 0.68 (0.56, 0.82), 11 rounds, q1y, 30 y follow-up

† standardized 8 year risk

Abbreviations: adj = adjusted; CI = confidence interval; colo = colonoscopy; FIT = fecal immunochemical test; f/u = followup; HR = hazard ratio; IRR = incidence rate ratio; k = number of studies; n = number; NR = not reported; Q = interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; w/ = with; y = years.

Table 6. Key Question 1: Study and Population Characteristics of Screening Flexible Sigmoidoscopy RCTs

	NORCCAP	PLCO	SCORE	UKFSST
Author, year*	Holme, 2018[127]	Miller, 2019[130]	Segnan, 2011[140]	Atkin, 2017[119]
Country	Norway	US	Italy	UK
Targeted Age, years	50–64	55–74	55–64	55–64
Program n	IG: 20,572 CG: 78,220	IG: 77,445 CG: 77,455	IG: 17,136 CG: 17,136	IG: 57,099 CG: 112,939
Number of rounds	1	2	1	1
Median length of followup, years	14.8	16.8 12.1 (all-cause mortality)	10.5 (incidence) 11.4 (mortality)	17.1
Attendance to screening, %	63	1st Screen: 84 2nd Screen: 54	58	67
CRC yield at baseline, % (n/n)	0.3 (41/12,960)	0.3 (185/64,658)	0.5 (54/9,911)	0.3 (131/40,674)
CRC cumulative incidence, % (n/n)	2.2 (2,144/98,792)	2.1 (3222/154,887)	1.6 (557/34,272)	2.6 (4483/170,034)
Criteria for colonoscopy	Polyp ≥10 mm; adenoma; CRC; abnormal FOBT	Polyp or mass was detected	Advanced adenoma; CRC; ≥3 adenomas; ≥5 hyperplastic polyps above rectum; inadequate bowel prep with ≥1 polyp	Advanced adenoma; CRC; ≥3 adenomas; ≥20 hyperplastic polyps above rectum
Referred to Colonoscopy, %	20.4	32.9 (of participants screened 1 or 2 times); 20.7 (of FS exams)	8.6	5.2

* Most recent publication

Abbreviations: CG = control group; CRC = colorectal cancer; FOBT = fecal occult blood test; IG = intervention group; n = number of participants; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UK = United Kingdom; UKFSST = UK Flexible Sigmoidoscopy Screening Trial; US = United States

Table 7. Key Question 1: Results of Screening Flexible Sigmoidoscopy RCTs

Trial	Median followup, years	Randomized group	N	CRC incidence			CRC mortality			All-cause mortality		
				No. of CRC cases	Rate, per 100,000 p-y	RR (95% CI)	No. of CRC deaths	Rate, per 100,000 p-y	RR (95% CI)	No. of deaths	Rate, per 100,000 p-y	RR (95% CI)
NORCCAP[127]	14.8	IG	20,572	393	135.9	0.78* (0.70, 0.87)	122	41.9	0.79* (0.65, 0.96)	3,809	1309.1	0.98* (0.95, 1.02)
		CG	78,220	1,751	174.5		530	52.9		13,433	1333.3	
PLCO[130]	16.8 (12.1 for all-cause mortality)	IG	77,445	1,461	125.5	0.82 (0.76, 0.88)	417	33.7	0.75 (0.66, 0.85)	10,879	NR	NR
		CG	77,455	1,761	153.3		549	44.8		11,102	NR	
SCORE[140]	10.5 (11.4 for CRC mortality)	IG	17,136	251	144.11	0.82 (0.69, 0.96)	65	34.66	0.78 (0.56, 1.08)	1,202	640.96	NR
		CG	17,136	306	176.43		83	44.45		1,233	660.26	
UKFSST[119]	17.1	IG	57,099	1,230	137	0.74* (0.70, 0.80)	353	39	0.70* (0.62, 0.79)	13,279	1472	0.99* (0.97, 1.01)
		CG	112,939	3,253	184		996	56		26,409	1483	

* Hazard ratio

Abbreviations: CG = control group; CI = confidence interval; CRC = colorectal cancer; FOBT = fecal occult blood test; IG = intervention group; n = number of participants; NORCCAP = Norwegian Colorectal Cancer Prevention; p-y = person-years; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = relative risk; SCORE = Screening for COlon Rectum; UK = United Kingdom; UKFSST = UK Flexible Sigmoidoscopy Screening Trial; US = United States

Table 8. Key Question 1: Results of Screening Flexible Sigmoidoscopy RCTs, for Sex, Location, and Age Subgroups

Trial	Median followup, years	Subgroup	CRC incidence			CRC mortality			All-cause mortality		
			IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)	IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)	IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)
NORCCAP[127]	14.8	Male	131.4	196.9	0.66* (0.57, 0.78)	40	63.3	0.63* (0.47, 0.83)	1572	1638.1	0.96* (0.91, 1.0)
		Female	140.1	153.6	0.92* (0.79, 1.07)	43.7	43.3	1.01* (0.77, 1.33)	1056.4	1047.5	1.02* (0.96, 1.07)
		Distal	67.1	98.5	0.68* (0.58, 0.79)	23.4	27.8	0.83* (0.64, 1.09)	NA	NA	NA
		Proximal	66.1	72.0	0.92* (0.78, 1.08)	16.2	22.7	0.71* (0.52, 0.98)	NA	NA	NA
		50-54 years	81.5	110.2	0.67* (0.42, 1.07)	21.1	31.3	0.67* (0.42, 1.07)	NR	NR	1.02* (0.95, 1.08)
		55-64 years	162.4	206.0	0.79* (0.70, 0.89)	52.0	63.5	0.82* (0.66, 1.02)	NR	NR	1.02* (0.95, 1.08)
PLCO[130]	16.8 (12.1 for all-cause mortality)	Male	141.3	184.1	0.77 (0.70, 0.84)	38.8	57.3	0.68 (0.57, 0.80)	NR	NR	NR
		Female	110.5	123.9	0.89 (0.80, 0.99)	28.8	30.3	0.87 (0.71, 1.06)	NR	NR	NR
		Distal	53.2	74.6	0.71 (0.64, 0.79)	10.9	21.4	0.51 (0.41, 0.63)	NR	NR	NR
		Proximal	70.3	77.1	0.91 (0.83, 1.00)	18.8	19.7	0.95 (0.79, 1.14)	NR	NR	NR
		55-64 years	102.1	120.6	0.85 (0.77, 0.93)	28.1	32.0	0.88 (0.73, 1.05)	NR	NR	NR
		65-74 years	171.0	215.9	0.79 (0.72, 0.88)	44.4	69.6	0.64 (0.53, 0.77)	NR	NR	NR
SCORE[140]	10.5 (11.4 for CRC mortality)	Male	190.94	216.83	0.88 (0.71, 1.09)	NR	NR	NR	NR	NR	NR
		Female	98.54	136.05	0.72 (0.55, 0.96)	NR	NR	NR	NR	NR	NR
		Distal	87.27	114.16	0.76 (0.62, 0.94)	18.66	25.70	0.73 (0.47, 1.12)	NR	NR	NR
		Proximal	56.84	62.27	0.91 (0.69, 1.20)	16.00	18.74	0.85 (0.52, 1.39)	NR	NR	NR
		Age 60-64	157.49	199.56	0.79 (0.62, 1.00)	NR	NR	NR	NR	NR	NR
		Age 55-59	133.70	158.95	0.84 (0.67, 1.06)	NR	NR	NR	NR	NR	NR
UK	17.1	Male	166	236	0.70*	48	71	0.67*	1841	1835	1.00*

Table 8. Key Question 1: Results of Screening Flexible Sigmoidoscopy RCTs, for Sex, Location, and Age Subgroups

Trial	Median followup, years	Subgroup	CRC incidence			CRC mortality			All-cause mortality		
			IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)	IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)	IG rate, per 100,000 p-y	CG rate, per 100,000 p-y	RR (95% CI)
					(0.65, 0.77)			(0.57, 0.79)			(0.98, 1.03)
		Female	111	137	0.81* (0.73, 0.89)	31	42	0.74* (0.61, 0.90)	1136	1163	0.98* (0.95, 1.01)
		Distal	66	112	0.59* (0.54, 0.64)	Female: 11 Male: 23	Female: 18 Male: 45	Female: 0.61* (0.45, 0.83) Male: 0.51* (0.41, 0.64)	NA	NA	NA
		Proximal	68	71	0.96* (0.87, 1.06)	Female: 19 Male: 23	Female: 22 Male: 24	Female: 0.86* (0.67, 1.10) Male: 0.95* (0.75, 1.21)	NA	NA	NA
		55-59 years	114	154	0.74* (0.67, 0.82)	31	46	0.67* (0.55, 0.81)	1138	1138	1.00* (0.97, 1.03)
		60-64 years	162	216	0.75* (0.69, 0.82)	48	66	0.72* (0.62, 0.84)	1821	1849	0.98* (0.96, 1.01)

* Hazard ratio

Abbreviations: CG = control group; CI = confidence interval; CRC = colorectal cancer; FOBT = fecal occult blood test; IG = intervention group; n = number of participants; NORCCAP = Norwegian Colorectal Cancer Prevention; p-y = person-years; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = relative risk; SCORE = Screening for COlon Rectum; UK = United Kingdom; UKFSST = UK Flexible Sigmoidoscopy Screening Trial; US = United States

Table 9. Key Question 1: Study and Population Characteristics of Screening gFOBT Trials

Trial, year of publication	Start year	Country	Targeted age, years	Screen frequency	Program n	Rounds	Followup, years	Attendance, round 1	Attendance, at least 1 round	Test positivity, round 1, pct	Test positivity, all rounds, pct
Burgundy, 2004[124]	1988	FRA	45–74	Biennial	IG: 45,642 CG: 45,557	6	11	53	70	2.1	1.5
Funen, 2004[128]	1985	DNK	45–75	Biennial	IG: 30,967 CG: 30,966	9	17	67	67	1.0	1.5
Göteborg, 2008[129]	1982	SWE	60–64	Varied (1 to 9 years)	IG: 34,144 CG: 34,164	2-3	19	62	70	3.8‡	4.1
Finland, 2015[132]	2004	FIN	60–69	Biennial	IG: 180,210 CG: 180,282	4*	4.5	NR	69	NR	3.6
Nottingham, 2012[138]	1981	GBR	45–74	Biennial	IG: 76,056 CG: 75,919	3-5	28	53	60	2.1	NR
Minnesota Colon Cancer Control Study, 2013[143]	1975	US	50–80	Biennial	IG: 15,587 CG: 15,394	6	30 (18 for incidence)	NR	90	NR‡	NR†
				Annual	IG: 15,570 CG: 15,394	11	30 (18 for incidence)	NR	90	NR‡	NR†

* Estimated based on 8.5 years followup and biennial screening
† From 1976 through 1982, the positivity for rehydrated tests was 9.8% and for tests without rehydration was 2.4%.
‡ Study included rehydrated tests: Göteborg – 91.7% of all tests were rehydrated; Minnesota Colon Cancer Control Study – 82.5% of all tests were rehydrated

Abbreviations: CG = control group; CI = confidence interval; CRC = colorectal cancer; DNK = Denmark; FIN = Finland; FRA = France; GBR = Great Britain; IG = intervention group; n = number; NR = not reported; RR = relative risk; SWE = Sweden; US = United States

Table 10. Key Question 1: Results of Screening gFOBT Trials

Trial	Median followup, years	Screening frequency	IG n analyzed	CG n analyzed	CRC Incidence			CRC Mortality			All-cause Mortality		
					IG n	CG n	RR (95% CI)	IG n	CG n	RR (95% CI)	IG n	CG n	RR (95% CI)
Burgundy, 2004[124]	11	Biennial	45642	45557	699	696	1.01 (0.91, 1.12)	254	304	0.84 (0.71, 0.99)	NR	NR	NR
Funen, 2004[128]	17	Biennial	30967	30966	889	874	1.02 (0.93, 1.12)	362	431	0.84 (0.73, 0.96)	12,205	12,248	0.99 (0.97, 1.02)
Göteborg, 2008[129]	19	Variable*	34144	34164	721	754	0.96 (0.86, 1.06)	252	300	0.84 (0.71, 0.99)	10,591	10,432	1.02 (0.99, 1.06)
Finland, 2015[132]	4.5	Biennial	180210	180282	903	811	1.11** (1.01, 1.23)	170	164	1.04** (0.84, 1.28)	8000	7963	1.00 (0.97, 1.04)
Nottingham, 2012[138]	28	Biennial	76056	75919	2279	2354	0.97 (0.91, 1.03)	1176	1300	0.91 (0.84, 0.98)	40,681	40,550	1.00 (0.99, 1.02)
Minnesota Colon Cancer Control Study, 2013[143]	30‡	Biennial	15587	15394	435	507	0.85 (0.74, 0.96)†	237	295	0.78 (0.65, 0.93)	11,004	10,944	0.99 (0.98, 1.01)
	30‡	Annual	15570	15394	417	507	0.81 (0.71, 0.93)†	200	295	0.68 (0.56, 0.82)	11,072	10,944	1.00 (0.99, 1.01)

* 1-9 years
† Calculated in Stata using iri; exact confidence interval
** Rate ratio
‡ For CRC incidence, followup was 18 years and IG n analyzed=15550 and CG n analyzed=15363

Abbreviations: CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; n = number; NR = not reported; RR = relative risk.

Table 11. Key Question 1: Comparative Effectiveness Studies and Included Screening Tests

Author, year (Trial name)	n randomized	Colonoscopy	FS (+/- stool testing)	CTC	gFOBT	FIT
Grobbee, 2019[149] (COCOS and others††)	30,052	X	X			X
Holme, 2018[127] (NORCCAP)			X			
Steele, 2020[150]	51,769		X***		X	
Schreuders, 2019[139]	13,205					X†
Passamonti, 2018*[131]	48,888					X
Regge, 2017*[135] (Proteus 2)	5,412		X	X		
Sali, 2016*[136] (SAVE)	16,087	X		X		X
Santare, 2016*[137]	9,770					X
Zubero, 2014[148]	37,999					X
van Roon, 2013[145]	7,501					X‡
Faivre, 2012**[124]	85,149				X	X
Quintero, 2012[133] (COLONPREV)	53,302	X				X
Stoop, 2012[144] (COCOS)	8,844	X		X		
Hol, 2010[126]	15,011		X		X	X
van Rossum, 2008[146]	20,623				X	X
Segnan, 2007[142] (SCORE III)	18,114	X	X			X
Segnan, 2005[140] (SCORE II)	22,676		X			X
Rasmussen, 1999[134]	10,978		X		X	
Verne, 1998[147]	3,744		X		X	
Berry, 1997[120]	6,371		X		X	
Brevinge, 1997[121]	6,365		X		X	

* Newly identified study since the previous review
† Compares the number of samples
‡ Compares the interval of testing
** Cohort study
†† This study combines randomized arms from other included trials. The participants overlap with those in COCOS[144] and those in Hol, 2010[126]
*** FS with gFOBT for those with a normal FS or those who refused FS

Abbreviations: COCOS = Colonoscopy or Colonography for Screening; CTC = computed tomography colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; n = number; SCORE = Screening for COlon Rectum

Table 12. Key Question 2: Summary of Test Accuracy Results* for Direct Visualization Screening Tests

Screening test group	No. of studies	No. of participants	CRC	Adenomas ≥10 mm		Adenomas ≥6 mm	
			Sensitivity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
CTC†	7	5328	0.86-1.0 (0.21-1.0)	0.89 (0.83, 0.96)	0.94 (0.89, 1.0)	0.86 (0.78, 0.95)	0.88 (0.83, 0.95)
Colonoscopy	4	4821	0.18-1.0 (0.01, 1.0)	0.89-0.95 (0.70, 0.99)	0.89‡ (0.86, 0.91)	0.75-0.93 (0.63,0.96)	0.94‡ (0.92, 0.96)
FS	0	NA	NA	NA	NA	NA	NA
Capsule Endoscopy	2	920	1.0 (0.34, 1.0)	0.92-1.0 (0.70, 1.0)	0.95-0.98 (0.93, 0.99)	0.91 (0.85, 0.95)	0.83 (0.80, 0.86)

* Pooled estimates from meta-analysis when available; otherwise range of values and range of the 95% CI reported.
† CTC with bowel preparation. Two studies without bowel preparation were also included.
‡ Only one study reported specificity

Abbreviations: CI = confidence interval; CRC = colorectal cancer; CTC = computed tomography colonography; FS = flexible sigmoidoscopy; IG = intervention group; mm = millimeter; No = number; RR = relative risk

Table 13. Key Question 2: Summary of Test Accuracy Results* From Studies With Colonoscopy Follow-Up for Stool, Serum, and Urine Screening Tests

Screening test group	No. of studies	No. of participants	CRC		AN		AA	
			Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hemoccult Sensa	2	3,503	0.50-0.75 (0.09, 1.0)	0.96-0.98 (0.95, 0.99)	0.07-0.21 (0.02, 0.27)	0.96-0.99 (0.96, 0.99)	0.06-0.17 (0.02, 0.23)	0.96-0.99 (0.96, 0.99)
OC-Sensor	13†	44,887	0.74 (0.64, 0.83)	0.94 (0.93, 0.96)	0.25 (0.21, 0.31)	0.96 (0.95, 0.97)	0.23 (0.20, 0.25)	0.96 (0.95, 0.97)
OC-Light	4	32,424	0.81 (0.70, 0.91)	0.93 (0.91, 0.96)	0.27 (0.16, 0.38)	0.95 (0.92, 0.98)	0.28 (0.19, 0.37)	0.94 (0.91 to 0.97)
Other FITs	12†	53,527	0.50-0.97 (0.09, 1.00)	0.83-0.97 (0.82, 0.97)	0.02-0.66 (0.01, 0.99)	0.60-0.99 (0.58, 1.0)	0.18-0.50 (0.13 to 0.56)	0.85-0.98 (0.84 to 0.98)
Cologuard	4	12,424	0.93 (0.87,1.0)	0.85 (0.84, 0.86)	0.47 (0.44, 0.50)	0.89 (0.87, 0.92)	0.43 (0.40, 0.46)	0.89 (0.86, 0.92)
Epi proColon	1	6857	0.68 (0.53, 0.80)	0.79 (0.77, 0.81)	0.25 (0.22, 0.28)	0.79 (0.76, 0.82)	0.22 (0.18, 0.24)	0.79 (0.76, 0.82)
PolypDx	1	228	NR	NR	0.43 (0.30, 0.57)	0.91 (0.87, 0.96)	NR	NR

* Pooled estimates and 95% CI from meta-analysis when available; otherwise range of values and range of the 95% CIs reported.
† One nested case control study[171] is not represented in this table (n=516).
Abbreviations: AA = advanced adenoma; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal cancer; CTC = computed tomography colonography; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; No = number; NR = not reported

Table 14. Key Question 2: Study and Population Characteristics for CTC and Colonoscopy Test Accuracy Studies

Bowel prep	Author, year Quality	Country	Number screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history ††, %	CTC protocol	Colonoscopy Practitioners	Reference standard
With bowel prep	Lefere, 2013[184] Fair	PRT	496	CRC: 4 (0.8) AA: 28 (5.6) A10: NR A6: 49 (9.9)	60	60	NR	NR	Fecal tagging: Y Number of Readers: 1 Training: >5000 exams Reading strategy: 3D (with 2D)	n = 5 Experience: ≥15 years	Repeat colonoscopy if indicated
	Graser, 2009[172] Good	DEU	307	CRC: 1 (0.3) AA: 29 (9.4) A10: 24 (7.8) A6: 45 (14.6)	60	45	NR	0 (FDR diagnosed before 60 or 2 at any age)	Fecal tagging: N Number of Readers: 3 Training: >300 exams Reading strategy: 3D (with 2D)	n = 6 Experience: 1000 colonoscopies	Colonoscopy with segmental unblinding
	Johnson, 2008[177] Good	US	2531	CRC: 7 (0.3) AA: NR A10: 102 (4.0) A6: 203 (8.0)	58	52	White 83* Black: 13 AI/AN: 0.9 Asian/PI: 3 Hispanic: 4	9	Fecal tagging: Y Number of Readers: 15 Training: >500 exams† Reading strategy: 3D (with 2D)	n = NR Experience: Performed or supervised by experience GE or surgeon	Repeat colonoscopy if indicated‡
	Kim, 2008[181] Fair	KOR	241	CRC: 1 (0.4) AA: 16 (6.6) A10: 10 (4.1) § A6: 44 (18.2) ‖	58	49	NR	5	Fecal tagging: N Number of Readers: 2 Training: >100 exams Reading strategy: 2D (with 3D)	n = 5 Experience: NR	Single colonoscopy
	Johnson, 2007[178] Fair	US	452	CRC: 5 (1.1) AA: NR A10: 21 (4.6) A6: 51 (11.3)	65	44	White: 85 Asian/PI: 12 Hispanic: 3 Black: 1 AI/AN: 0.2	NR	Fecal tagging: N Number of Readers: 3 Training: >1000 exams Reading strategy: 3D (with 2D) ¶	n = NR Experience: Performed or supervised by experience GE or surgeon	Repeat colonoscopy if indicated ‡
	Macari, 2004[188] Fair	US	68	CRC: NR AA: NR A10: 3 (4.4)** A6: NR	55	0	NR	0	Fecal tagging: N Number of Readers: 1 Training: 5 years of experience Reading strategy: NR	n = 1 GE and trainees Experience: 5 years	Single colonoscopy
	Pickhardt, 2003[195] Good	US	1233	CRC: 2 (0.16) AA: NR A10: 46 (3.7) A6: 166 (13.5)	58	41	NR	2.6	Fecal tagging: Y Number of Readers: 6 Training: >25 exams Reading strategy: 3D (with 2D)	n = 17 Experience: NR	Colonoscopy with segmental unblinding‡

Table 14. Key Question 2: Study and Population Characteristics for CTC and Colonoscopy Test Accuracy Studies

Bowel prep	Author, year Quality	Country	Number screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history ††, %	CTC protocol	Colonoscopy Practitioners	Reference standard
Without bowel prep	Fletcher, 2013[169] Good	US	564	CRC: 1 (0.2) AA: 25 (4.4) A10: 15 (2.6) A6: 36 (6.4)	NR	58	White: 91 Asian/PI: 4 Black: 2 Hispanic: 2 AI/AN: 0.2	7	Fecal tagging: Y Number of Readers: 2 Training: >150 exams Reading strategy: 2D and 3D	n = NR Experience: NR – staff GE	Single colonoscopy
	Zalis, 2012[205] Good	US	605	CRC: 3 (0.5) AA: NR A10: 19 (3.1) A6: 71 (11.7)	60	47	White: 90 Asian/PI: 2 Black: 4 AI/AN: <1 Hispanic: 2	18	Fecal tagging: Y Number of Readers: 3 Training: >200 exams Reading strategy: 2D and 3D	n = NR Experience: NR – GE	Colonoscopy with segmental unblinding‡

* Participants could select more than one race/ethnicity category
† Or 1.5 day training session
‡ Test accuracy for colonoscopy in addition to CTC.
§ Any histology ≥10 mm
|| Any histology ≥6 mm;
¶ Study evaluated different reading strategies, data shown reflect primary 3D strategy
****** For polyps ≥10 mm
†† Family history variably defined: FDR diagnosed before 60 or 2 at any age (Graser), FDR with CRC (Kim, Macari, Johnson), family history of CRC (Pickhardt), family history of colorectal neoplasia (Fletcher), family history of CRC or polyps (Zalis).

Abbreviations: AA = advanced adenoma; A6 = adenoma ≥6 mm; A10 = adenoma ≥10 mm; Adenoma CRC = colorectal cancer; DEU = Germany; GE = gastroenterologist; KOR = Korea; n = number; N = no; NR = not reported; PRT = Portugal; US = United States; Y = yes; 2D = two dimensional; 3D = three dimensional.

Table 15. Key Question 2: Results for CT Colonography Test Accuracy

Bowel prep	Author, year	Number screened	Prevalence, n (%)	CRC	Advanced adenoma		Adenoma ≥10 mm		Adenoma ≥6 mm	
				Sensitivity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
With bowel prep	Lefere, 2013[184]	496	CRC: 4 (0.8) AA: 28 (5.6) A10: NR A6: 49 (9.9)	1.0 (0.51, 1.0)	1.0 (0.87, 1.0)	0.87 (0.84, 0.90)	NR	NR	0.98 (0.89, 1.0)	0.91 (0.88, 0.93)
	Graser, 2009[172]	307	CRC: 1 (0.33) AA: 29 (9.4) A10: 24 (7.8) A6: 45 (14.6)	1.0 (0.21, 1.0)	0.97 (0.83, 0.99)	0.39 (0.34, 0.45)	0.92 (0.74, 0.99)	0.98 (0.95, 0.99)	0.91 (0.79, 0.98)	0.93 (0.89, 0.96)
	Johnson, 2008[177]	2531	CRC: 7 (0.28) AA: NR A10: 102 (4.0) A6: 203 (8.0)	0.86 (0.49, 0.97)	NR	NR	0.90 (0.83, 0.95)	0.86 (0.85, 0.87)	0.78 (0.72, 0.83)	0.88 (0.87, 0.89)
	Kim, 2008 [181]	241	CRC: 1 (0.4) AA: 16 (6.6) A10: 10 (4.1) A6: 44 (18.3)	1.0 (0.21, 1.0)	0.88 (0.64, 0.96)	NR	0.87*† (0.62, 0.96)	0.97*† (0.94, 0.99)	0.68*† (0.55, 0.79)	0.88*† (0.84, 0.92)
	Johnson, 2007[178]	452	CRC: 5 (1.1) AA: NR* A10: 21 (4.6) A6: NR 51 (11.3)	1.0 (0.56, 1.0)	NR	NR	0.67 (0.45, 0.83)	0.98 (0.96, 0.99)	NR	NR
	Macari, 2004[188]	68	CRC: NR AA: NR A10: 3 (4.4)* A6: NR	NR	NR	NR	1.0* (0.44, 1.0)	0.98* (0.92, 1.0)	NR	NR
	Pickhardt, 2003[195]	1233	CRC: 2 (0.16) AA: NR* A10: 46 A6: 166	1.0 (0.34, 1.0)	NR	NR	0.94 (0.82, 0.98)	0.96 (0.95, 0.97)	0.89 (0.83, 0.93)	0.80 (0.77, 0.82)
Without bowel prep	Fletcher, 2013[169]	564	CRC: 1 (0.18) AA: 25 (4.4) A10: 15 (2.6) A6: 36 (6.4)	1.0 (0.03, 1.0)	0.64 (0.44, 0.80)	NR	0.67 (0.42, 0.85)	0.97 (0.96, 0.98)	0.75 (0.59, 0.86)	0.92 (0.90, 0.94)
	Zalis, 2012[205]	605	CRC: 3 (0.5) AA: NR A10: 19 (3.1) A6: 71 (11.7)	1.0 (0.44, 1.0)	NR	NR	0.90 (0.69, 0.97)	0.85 (0.82, 0.88)	0.58 (0.46, 0.69)	0.88 (0.85, 0.91)

* Any histology
† Sensitivity for adenomas ≥6 mm 0.73 (95% CI, 0.57 to 0.85); Sensitivity for adenomas ≥10 mm 0.9 (95% CI, 0.56 to 1.0)

Abbreviations: AA = advanced adenoma; A6 = adenoma ≥6 mm; A10 = adenoma ≥10 mm; CI = confidence interval; CRC = colorectal cancer; n = number; NR = not reported.

Table 16. Key Question 2: Results for Colonoscopy Test Accuracy

Author, year	Number screened	Prevalence, n (%)	CRC	Adenoma ≥10 mm		Adenoma ≥6 mm	
			Sensitivity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Zalis, 2012[205]	605	CRC: 3 (0.5) A10: 19 (3.1) A6: 71 (11.7)	1.0 (0.29, 1.0)	0.95 (0.74, 0.99)*	0.89 (0.86, 0.91)	0.75 (0.63, 0.84)†	0.94 (0.92, 0.96)
Johnson, 2008[177]	2531	CRC: 7 (0.28) A10: 102 (4.0) A6: 203 (8.0)	1.0 (0.59, 1.0)‡	0.98 (0.93, 1.0)‡	NR	NR	NR
Johnson, 2007[178]	452	CRC: 5 (1.1) A10: 21 (4.6) A6: NR	0.18 (0.01, 0.72)§	0.90 (0.70, 0.99)§	NR	NR	NR
Pickhardt, 2003[195]	1233	CRC: 2 (0.16) A10: 46 (3.7) A6: 166 (13.5)	0.50 (0.01, 0.99) §	0.89 (0.78, 0.96) §	NR	0.93 (0.88, 0.96)||	NR

* Per lesion = 0.96 (0.77, 1.0)
† Per lesion = 0.76 (0.66, 0.84)
‡ Per lesion
§ Same sensitivity per lesion
|| Per lesion = 0.90 (0.86, 0.94)

Abbreviations: AA = advanced adenoma; CI = confidence interval; CRC = colorectal cancer; n = number NR = not reported.

Table 17. Key Question 2: Study and Population Characteristics for Hemoccult Sensa

Reference standard	Author, year	Quality	Country	N screened	CRC prevalence, n (%)	AA prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %
Colonoscopy	Ahlquist, 2008[151]	Fair	US	2497	12 (0.5)	145 (5.8)	60	54	White: 92.7	0†
	Shapiro, 2017[200]	Fair	US	1006	2 (0.2)	53 (5.3)	NR	54.5	White: 87.0 Black: 10.6 Other: 2.4	13.2
Registry	Allison, 1996[152]	Fair	US	7904	35 (0.43)	NA	NR	59.3	White: 53.5 Black: 31.1 Asian: 12.0 Other: 3.3	NR
	Allison, 2007[153]	Fair	US	5799	14‡ (0.3)	NA	NR	52.5	White: 74.1 Black: 5.0 Asian: 11.8 Hispanic: 5.2 Other: 3.9	NR
	Levi, 2011[185]	Fair	ISR, GBR	2266	19 (0.55)	NA	NR	NR	NR	NR

* 1 or more FDR with CRC, unless otherwise noted.
† More than 2 FDR with colorectal neoplasia
‡ Distal CRC only

Abbreviations: GBR = Great Britain; ISR = Israel; n = number; US = United States

Table 18. Key Question 2: Results for Hemoccult Sensa Test Accuracy

Followup	Author, year	N analyzed	CRC sensitivity (95% CI)	CRC specificity (95% CI)	AN sensitivity (95% CI)	AN specificity (95% CI)	AA sensitivity (95% CI)	AA specificity (95% CI)
Colonoscopy	Ahlquist, 2008[151]	2497	0.75 (0.51, 1.0)	0.96 (0.95, 0.96)	0.21 (0.15, 0.27)	0.96 (0.96, 0.97)	0.17 (0.11, 0.23)	0.96 (0.96,0.97)
	Shapiro, 2017[200]	1006	0.50 (0.09, 0.91)	0.98 (0.97, 0.99)	0.07* (0.02, 0.17)	0.99* (0.98. 0.99)	0.06* (0.02, 0.15)	0.99* (0.98, 0.99)
Registry	Allison, 1996[152]	7904	0.79 (0.64, 0.94)	0.87 (0.86, 0.87)	NA	NA	NA	NA
	Allison, 2007[153]	5799	0.64† (0.36, 0.86)	0.90† (0.89, 0.91)	NA	NA	NA	NA
	Levi, 2011[185]	2266	0.62 (0.36, 0.82)	0.96 (0.96, 0.97)	NA	NA	NA	NA

* Includes SSL
† Distal CRC only

Abbreviations: AA = advanced adenoma; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal cancer; N = number; NA = not applicable.

Table 19. Key Question 2: Study and Population Characteristics for FITs

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %	FIT
Colonoscopy	Brenner, 2013[156]	Good	DEU	2235	CRC: 15 (0.67) AA: 207 (9.3)	62.7	50.8	NR	NR	OC-Sensor, RIDASCREEN Hemoglobin, RIDASCREEN Hemoglobin-Haptoglobin Complex
	Brenner, 2017[155]	Good	DEU	3494	CRC: 30 (0.86) AA: 359 (10.3)	62.1	50.3	NR	NR	FOB Gold
	Chang, 2017[158]	Good	TWN	6198	CRC: 0 (0) AA: 339 (5.5)	59.0	48.9	Asian: 100	0 (Family history of CRC)	OC-Sensor
	Chen, 2014[162]	Good	TWN	6096	CRC: 13 (0.2) AA: 241 (4.0)	54	44	NR	NR	OC-Light
	Cheng, 2002[163]	Fair	TWN	7411	CRC: 16 (0.22) AA: 77 (1.0)	47	44.8	NR	NR	OC-Light
	Chiu, 2013[165]	Good	TWN	18296	CRC: 28 (0.15) AA: 632 (3.5)	59.8	40.8	NR	NR	OC-Light
	Chiu, 2016[164]	Fair	AUS, BRN, CHN, HKG, JPN, MYS, PAK, PHL, SGP, KOR, TWN, THA	4434	CRC: 16 (0.4) AA: 158 (3.6)	58	49	NR	11.6	OC-Sensor, Combination
	Cooper, 2018[166]	Fair	US	760	CRC: 2 (0.26) AA: 49 (6.44)	56.7	60.2	White: 65.1 Black: 34.9	NR	OC FIT-CHEK

Table 19. Key Question 2: Study and Population Characteristics for FITs

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %	FIT
	de Wijkerslooth, 2012[167]	Good	NLD	1256	CRC: 8 (0.64) AA: 111 (8.8)		49	White: 96 Other: 4	16	OC-Sensor
	Gies, 2018[171]	Fair	DEU	516	CRC: 16 (3.1) AA: 200 (38.8)	63.2	44.4	NR	NR	CAREprime Hb, Eurolyser FOB test, Hb ELISA, ImmoCARE-C, OC-Sensor, QuantOn Hem, QuikRead go iFOBT, RIDASCREEN Hb, SENTiFIT-FOB Gold
	Hernandez, 2014[174]	Good	ESP	779	CRC: 5 (0.6) AA: 92 (11.8)	58	50	NR	0	OC-Sensor
	Imperiale, 2014[175]	Fair	US,CAN	9989	CRC: 65 (0.65) AA: 757 (7.6)	64.2	53.7	White: 84.0 Black: 10.7 Other: 5.2	0	OC FIT-CHEK
	Kim, 2017[180]	Fair	KOR	14912	CRC: 15 (0.1) AA: 363 (2.4)		30	NR	4.7	OC-Sensor
	Lee, 2014[183]	Good	KOR	1397	NR		52	NR	NR	Hemo Techt NS-Plus C system
	Levy, 2014[186]	Fair	US	621	NR	56.9	59.2	White: 94.1 Black: 2.3 Hispanic: 1.3	NR	A Clearview, I Clearview, OC-Light, QuickVue
	Liles, 2018[187]	Fair	US	2771	CRC: 2 (0.07) AA: 209 (7.5)		51	White: 89.1 Black: 2.2 Asian: 3.7 AI/AN: 0.5 Other: 2.4	5.2	OC-Auto

Table 19. Key Question 2: Study and Population Characteristics for FITs

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %	FIT
	Morikawa, 2005[190]	Fair	JPN	21805	CRC: 79 (0.4) AA: 648 (3.0)	48	28.0	NR	NR	Magstream 1000/Hem SP
	Nakama, 1999[192]	Fair	JPN	4611	CRC: 18 (0.39) AA: NR	NR	NR	NR	NR	Monohaem
	Ng, 2013[193]	Fair	HKG	4539	CRC: 22 (0.48) AA: 197 (4.3)	57.7	54.7	NR	12.6	Hemosure
	Park, 2010[194]	Fair	KOR	770	CRC: 13 (1.7) AA: 59 (7.7)	59	49	NR	NR	OC-Micro
	Redwood, 2016[197]	Fair	US	661	CRC: 10 (1.5) AA: 82 (12.4)		60	AI/AN: 100	NR	OC-Sensor
	Shapiro, 2017[200]	Fair	US	1006	CRC: 2 (0.2) AA: 53 (5.3)		54.5	White: 87.0 Black: 10.6 Other: 2.4	13.2	OC FIT-CHEK, InSure FIT
	Sohn, 2005[201]	Fair	KOR	3794	CRC: 12 (0.3) AA: 67 (1.8)	49	43.3	NR	NR	OC-Hemodia
	Wong, 2015[204]	Fair	HKG	5343	CRC: 22 (0.4) AA: 269 (5.0)	58	55	NR	12.3	Hemosure
	Graser, 2009[172]	Good	DEU	307	CRC: 307 (0.33) AA: 285 (0.084)	60.5	45	NR	0	FOB Gold
Registry	Allison, 1996[152]	Fair	US	7493	CRC: 35 (0.43)	NR	59.3	White: 53.5 Black: 31.1 Asian: 12.0 Other: 3.3	NR	HemeSelect

Table 19. Key Question 2: Study and Population Characteristics for FITs

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %	FIT
	Allison, 2007[153]	Fair	US	5356	CRC: 14 (0.3)	NA	52.5	White: 74.1 Black: 5.0 Asian: 11.8 Hispanic: 5.2 Other: 3.9	NR	FlexSure OBT
	Arana-Arri, 2017[154]	Fair	ESP	296378	CRC: 1168 (0.39)	NR	NR	NR	0 (hereditary or familial CRC)	OC-Sensor
	Castiglione, 2007[157]	Fair	ITA	24913	CRC: 83 (0.30)	NR	52.2	NR	NR	OC-Hemodia
	Chen, 2011[160]	Fair	TWN	46355	CRC: 150 (0.32)	52.1	63	NR	NR	OC-Sensor
	Chen, 2016[159]	Fair	TWN	512066	CRC: 921 (0.18)	NR	52	NR	3	OC-Sensor
	Chen, 2018[161]	Fair	TWN	723113	CRC: 2005 (0.3)	58	61.7	NR	NR	HM-Jack, OC-Sensor
	Garcia, 2015[170]	Fair	ESP	4618	CRC: 20 (0.43)	NR	NR	NR	0 (high risk family history)	OC-Auto
	Haug, 2017[173]	Fair	NLD	4523	CRC: 36 (0.8)	60.5	52	NR	NR	OC-Sensor Micro
	Itoh, 1996[176]	Fair	JPN	27860	CRC: 89 (0.32)	NR	14.0	NR	NR	OC-Hemodia
	Juul, 2018[179]	Fair	DNK	245299	CRC: 976 (0.4)		53.7	NR	NR	OC-Sensor
	Launoy, 2005[182]	Fair	FRA	7421	CRC: 28 (0.38)	NR	56.9	NR	NR	Magstream 1000
	Levi, 2011[185]	Fair	ISR,GBR	1204	CRC: 19 (0.55)	NR	NR	NR	NR	OC-Micro
	Mlakar, 2018[189]	Fair	SVN	251948	CRC: 572 (0.001)		50.3	NR	NR	OC-Sensor
	Nakama, 1996[191]	Fair	JPN	3365	CRC: 14 (0.42)	NR	51.4	NR	NR	Monohaem
	Selby, 2018[199]	Fair	US	640859	CRC: 1245 (0.19)		53	White: 55 Black: 7 Asian: 16 Hispanic: 18 Other: 3	NR	OC FIT-CHEK
	Stegeman, 2015[202]	Good	NLD	2871	CRC: 20 (0.7)	59	49	NR	NR	OC-Sensor

Table 19. Key Question 2: Study and Population Characteristics for FITs

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history*, %	FIT
	van der Vlugt, 2017[203]	Fair	NLD	18716	CRC: 152 (0.81)	NR	NR	NR	NR	OC-Sensor/FOB Gold

* 1 or more FDR with CRC, unless otherwise noted.

Abbreviations: AA = advanced adenoma; AUS = Australia; BRN = Brunei; CHN = China; CRC = colorectal cancer; DEU = Germany; DNK = Denmark; ESP = Spain; FIT = fecal immunochemical test; FOB = fecal occult blood; FRA = France; HKG = Hong Kong; ISR = Israel; ITA = Italy; JPN = Japan; KOR = Korea; MYS = Malaysia; n = number; NLD = Netherlands; NR = not reported; PAK = Pakistan; PHL = Philippines; SGP = Singapore; THA = Thailand; TWN = Taiwan; US = United States

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
Brenner, 2013[156]	RIDASCREEN Hemoglobin	2	All	2235	0.600 (0.353, 0.812)	0.954 (0.945, 0.962)	0.234 (0.182, 0.293)	0.971 (0.963, 0.977)	0.208 (0.157, 0.267)	0.971 (0.963, 0.977)
	OC-Sensor	20	All	2235	0.733 (0.483, 0.902)	0.955 (0.946, 0.963)	0.257 (0.203, 0.317)	0.974 (0.966, 0.980)	0.222 (0.170, 0.282)	0.974 (0.966, 0.980)
	RIDASCREEN Hemoglobin-Haptoglobin Complex	2	All	2235	0.533 (0.294, 0.761)	0.954 (0.945, 0.962)	0.203 (0.154, 0.259)	0.968 (0.959, 0.975)	0.179 (0.131, 0.235)	0.968 (0.959, 0.975)
Brenner, 2017[155]	FOB Gold	12	All	3466	0.97 (0.82, 1.00)	0.90 (NR)	0.44 (0.39, 0.49)	0.90 (NR)	NR	NR
			Recruited 2012-2014	1822	NR	NR	NR	NR	0.40 (0.35, 0.45)	0.90 (NR)
		17	All	3466	0.967 (0.828, 0.999)	NR	0.386 (0.337, 0.436)	0.928 (0.918, 0.936)	0.337 (0.288, 0.389)	0.928 (0.918, 0.936)
			Distal	3466	0.969 (0.796, 0.999)	NR	0.490 (0.428, 0.553)	NR	0.441 (0.376, 0.507)	NR
			Proximal	3466	1.00 (0.478, 1.00)	NR	0.226 (0.161, 0.303)	NR	0.199 (0.136, 0.274)	NR
		27	All	3466	0.97 (0.82, 1.00)	0.95 (NR)	0.33 (0.29, 0.38)	0.95 (NR)	0.28 (0.23, 0.33)	0.95 (NR)
		8	All	3466	0.97 (0.82, 1.00)	0.85 (NR)	0.54 (0.49, 0.59)	0.85 (NR)	0.50 (0.45, 0.56)	0.85 (NR)
		8.5	All	3466	0.967 (0.828, 0.999)	NR	0.511 (0.461, 0.562)	0.865 (0.853, 0.877)	0.474 (0.421, 0.527)	0.865 (0.853, 0.877)
			Distal	3466	0.969 (0.796, 0.999)	NR	0.598 (0.535, 0.658)	NR	0.559 (0.493, 0.624)	NR
			Proximal	3466	1.00 (0.478, 1.00)	NR	0.397 (0.317, 0.481)	NR	0.376 (0.296, 0.461)	NR

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
Chang, 2017[158]	OC-Sensor	10	All	6198	NR	NR	NR	NR	0.324 (0.275, 0.378)	NR
		15	All	6198	NR	NR	NR	NR	0.245 (0.201, 0.295)	NR
		20	All	6198	NR	NR	NR	NR	0.209 (0.168, 0.257)	NR
Chen, 2014[162]	OC-Light	10	All	6096	0.692 (0.441, 0.943)	0.964 (0.959, 0.969)	0.221 (0.170, 0.272)	0.97 (0.966, 0.975)	NR	NR
			≥50 years	3874	NR	NR	0.192 (0.137, 0.247)	NR	NR	NR
			>75 years	88	NR	NR	0.333 (0, 0.711)	NR	0.333 (0, 0.711)	NR
			40-49 years	2214	NR	NR	0.321 (0.199, 0.444)	NR	NR	NR
			50-75 years	3794	NR	NR	0.188 (0.132, 0.243)	NR	NR	NR
Cheng, 2002[163]	OC-Light	10	All	7411	NR	NR	NR	NR	NR	NR
Chiu, 2013[165]	OC-Light	10	All	18296	0.786 (0.585, 0.910)	0.928 (0.925, 0.932)	0.302 (0.267, 0.338)	0.936 (0.932, 0.939)	0.280 (0.246, 0.317)	0.935 (0.931, 0.938)
			Distal	18296	0.823 (0.558, 0.953)	NR	0.343 (0.292, 0.397)	NR	0.316 (0.265, 0.372)	NR
			Proximal	18296	0.727 (0.393, 0.927)	NR	0.241 (0.194, 0.294)	NR	0.225 (0.179, 0.278)	NR
Chiu, 2016[164]	Combination	combination	All	3873	NR	NR	NR	NR	NR	NR
			Low risk APCS	646	NR	NR	NR	NR	NR	NR
			Moderate risk APCS	3243	NR	NR	NR	NR	NR	NR
	OC-Sensor	20	All	2803	NR	NR	NR	NR	NR	NR

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
			Low risk APCS	416	NR	NR	NR	NR	NR	NR
			Moderate risk APCS	2387	NR	NR	NR	NR	NR	NR
Cooper, 2018*[166]	OC FIT-CHEK	20	All	760	NR	NR	0.32 (NR)	0.97 (NR)	NR	NR
			Black	265	NR	NR	0.35 (NR)	0.97 (NR)	NR	NR
			White	495	NR	NR	0.33 (NR)	0.97 (NR)	NR	NR
de Wijkerslooth, 2012[167]	OC-Sensor	10	All	1256	0.88 (0.47, 0.99)	0.91 (0.89, 0.92)	0.38 (0.29, 0.47)	0.93 (0.92, 0.95)	0.35 (0.27, 0.45)	0.93 (0.91, 0.94)
			Distal	1256	NR	NR	0.37 (NR)	NR	NR	NR
			Proximal	1256	NR	NR	0.38 (NR)	NR	NR	NR
			Female	618	NR	NR	0.35 (0.2, 0.49)	0.94 (0.92, 0.96)	NR	NR
			Male	638	NR	NR	0.40 (0.29, 0.52)	0.93 (0.90, 0.94)	NR	NR
		15	All	1256	0.75 (0.36, 0.96)	0.93 (0.92, 0.95)	0.33 (0.25, 0.42)	0.96 (0.94, 0.97)	0.31 (0.23, 0.40)	0.96 (0.94, 0.97)
			Distal	1256	NR	NR	0.31 (NR)	NR	NR	NR
			Proximal	1256	NR	NR	0.33 (NR)	NR	NR	NR
		20	All	1256	0.75 (0.36, 0.96)	0.95 (0.93, 0.96)	0.31 (0.23, 0.40)	0.97 (0.96, 0.98)	0.29 (0.21, 0.39)	0.97 (0.95, 0.98)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
			Distal	1256	NR	NR	0.29 (NR)	NR	NR	NR
			Proximal	1256	NR	NR	0.33 (NR)	NR	NR	NR
			Female	618	NR	NR	0.33 (0.22,0.47)	0.98 (0.96, 0.98)	NR	NR
			Male	638	NR	NR	0.29 (0.20, 0.41)	0.96 (0.95, 0.98)	NR	NR
		30	All	1256	NR	NR	0.28 (0.20, 0.36)*	0.98 (0.97, 0.99)*	NR	NR
			Female	618	NR	NR	0.26 (0.15, 0.39)	0.98 (0.38, 0.77)	NR	NR
			Male	638	NR	NR	0.29 (0.20, 0.41)	0.98 (0.96, 0.99)	NR	NR
		40	All	1256	NR	NR	0.24 (0.17, 0.32)*	0.99 (0.98, 0.99)*	NR	NR
			Female	618	NR	NR	0.22 (0.12, 0.35)	0.98 (0.97, 0.99)	NR	NR
			Male	638	NR	NR	0.25 (0.16, 0.38)	0.99 (0.97, 0.99)	NR	NR
Gies, 2018[171]	CAREprime Hb	12.35	All	516	0.688 (0.41, 0.89)	NR	0.236 (0.18, 0.30)	0.967 (0.94, 0.98)	0.20 (0.15, 0.26)	0.967 (0.94, 0.98)
		15	All	516	0.688 (0.41, 0.89)	NR	0.218 (0.16, 0.28)	0.97 (0.94, 0.99)	0.18 (0.13, 0.24)	0.97 (0.94, 0.99)
		26.22	All	516	NR	NR	0.162 (0.12, 0.22)	0.99 (0.97, 1.0)	0.13 (0.09, 0.18)	0.99 (0.97, 1.0)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
		26.22	All	516	NR	NR	0.162 (0.12, 0.22)	0.99 (0.97, 1.0)	0.563 (0.30, 0.80)	NR
		6.3	All	516	0.813 (0.54, 0.96)	NR	0.347 (0.28, 0.41)	0.913 (0.88, 0.94)	0.31 (0.25, 0.38)	0.913 (0.88, 0.94)
		6.65	All	516	0.813 (0.54, 0.96)	NR	0.333 (0.27, 0.40)	0.93 (0.90, 0.96)	0.295 (0.23, 0.36)	0.93 (0.90, 0.96)
	Eurolyser FOB test	15	All	516	0.563 (0.30, 0.80)	NR	0.167 (0.12, 0.22)	0.98 (0.96, 0.99)	0.135 (0.09, 0.19)	0.98 (0.96, 0.99)
		2.01	All	516	0.75 (0.48, 0.93)	NR	0.343 (0.28, 0.41)	0.93 (0.90, 0.96)	0.31 (0.25, 0.38)	0.93 (0.90, 0.96)
		21.15	All	516	0.563 (0.30, 0.80)	NR	0.144 (0.10, 0.20)	0.99 (0.97, 1.0)	0.11 (0.07, 0.16)	0.99 (0.97, 1.0)
		6.11	All	516	0.688 (0.41, 0.89)	NR	0.236 (0.18, 0.30)	0.967 (0.94, 0.98)	0.20 (0.15, 0.26)	0.967 (0.94, 0.98)
		8.04	All	516	0.625 (0.35, 0.85)	NR	0.227 (0.17, 0.29)	0.97 (0.94, 0.97)	0.195 (0.14, 0.26)	0.97 (0.94, 0.97)
	Hb ELISA	15	All	516	0.688 (0.41, 0.89)	NR	0.213 (0.16, 0.27)	0.963 (0.94, 0.98)	0.175 (0.13, 0.23)	0.963 (0.94, 0.98)
		15.32	All	516	0.688 (0.41, 0.89)	NR	0.213 (0.16, 0.27)	0.967 (0.94, 0.98)	0.175 (0.13, 0.23)	0.967 (0.94, 0.98)
		2	All	516	0.813 (0.54, 0.96)	NR	0.463 (0.40, 0.53)	0.857 (0.81, 0.89)	0.435 (0.37, 0.51)	0.857 (0.81, 0.89)
		29.16	All	516	0.625 (0.35, 0.85)	NR	0.157 (0.11, 0.21)	0.99 (0.97, 1.0)	0.12 (0.08, 0.17)	0.99 (0.97, 1.0)
		4.8	All	516	0.813 (0.54, 0.96)	NR	0.352 (0.29, 0.42)	0.93 (0.90, 0.96)	0.315 (0.25, 0.38)	0.93 (0.90, 0.96)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
	ImmoCare-C	15	All	515	0.75 (0.48, 0.93)	NR	0.27 (0.21, 0.33)	0.96 (0.93, 0.98)	0.231 (0.17, 0.30)	0.96 (0.93, 0.98)
		17.3	All	515	0.625 (0.35, 0.85)	NR	0.233 (0.18, 0.29)	0.967 (0.94, 0.98)	0.201 (0.15, 0.26)	0.967 (0.94, 0.98)
		36.8	All	515	0.563 (0.30, 0.80)	NR	0.163 (0.12, 0.22)	0.99 (0.97, 1.0)	0.131 (0.09, 0.19)	0.99 (0.97, 1.0)
		6.25	All	515	0.813 (0.54, 0.96)	NR	0.386 (0.32, 0.45)	0.90 (0.86, 0.93)	0.352 (0.29, 0.42)	0.90 (0.86, 0.93)
		9.2	All	515	0.813 (0.54, 0.96)	NR	0.335 (0.27, 0.40)	0.93 (0.90, 0.96)	0.297 (0.23, 0.37)	0.93 (0.90, 0.96)
	OC-Sensor	10	All	516	0.688 (0.41, 0.89)	NR	0.218 (0.16, 0.28)	0.977 (0.95, 0.99)	0.18 (0.13, 0.24)	0.977 (0.95, 0.99)
		15	All	516	0.563 (0.30, 0.80)	NR	0.162 (0.12, 0.22)	0.97 (0.94, 0.99)	0.130 (0.09, 0.18)	0.97 (0.94, 0.99)
		18.2	All	516	0.563 (0.30, 0.80)	NR	0.162 (0.12, 0.22)	0.99 (0.97, 1.0)	0.13 (0.09, 0.18)	0.99 (0.97, 1.0)
		3.6	All	516	0.75 (0.48, 0.93)	NR	0.301 (0.24, 0.36)	0.93 (0.90, 0.96)	0.265 (0.21, 0.33)	0.93 (0.90, 0.96)
		6.60	All	516	0.688 (0.41, 0.89)	NR	0.236 (0.18, 0.30)	0.967 (0.94, 0.98)	0.20 (0.15, 0.26)	0.967 (0.94, 0.98)
	QuantOn Hem	15	All	516	0.75 (0.48, 0.93)	NR	0.264 (0.21, 0.33)	0.95 (0.92, 0.97)	0.225 (0.17, 0.29)	0.95 (0.92, 0.97)
		17.73	All	516	0.75 (0.48, 0.93)	NR	0.227 (0.17, 0.29)	0.967 (0.94, 0.98)	0.185 (0.13, 0.25)	0.967 (0.94, 0.98)
		29.81	All	516	0.625 (0.35, 0.85)	NR	0.148 (0.10, 0.20)	0.99 (0.97, 1.0)	0.11 (0.07, 0.16)	0.99 (0.97, 1.0)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
		3.7	All	516	0.813 (0.54, 0.96)	NR	0.44 (0.38, 0.51)	0.857 (0.81, 0.89)	0.415 (0.35, 0.49)	0.857 (0.81, 0.89)
		9.59	All	516	0.75 (0.48, 0.93)	NR	0.315 (0.25, 0.38)	0.93 (0.90, 0.96)	0.28 (0.22, 0.35)	0.93 (0.90, 0.96)
	QuikRead go iFOBT	15	All	516	0.625 (0.35, 0.85)	NR	0.218 (0.16, 0.28)	0.967 (0.94, 0.98)	0.185 (0.13, 0.25)	0.967 (0.94, 0.98)
		23	All	516	0.563 (0.30, 0.80)	NR	0.185 (0.14, 0.24)	0.99 (0.97, 1.0)	0.155 (0.11, 0.21)	0.99 (0.97, 1.0)
	RIDASCREEN Hb	12.27	All	516	0.813 (0.54, 0.96)	NR	0.347 (0.28, 0.41)	0.93 (0.90, 0.96)	0.31 (0.25, 0.38)	0.93 (0.90, 0.96)
		15	All	516	0.813 (0.54, 0.96)	NR	0.343 (0.28, 0.41)	0.94 (0.91, 0.96)	0.305 (0.24, 0.37)	0.94 (0.91, 0.96)
		29.54	All	516	0.625 (0.35, 0.85)	NR	0.222 (0.17, 0.28)	0.967 (0.94, 0.98)	0.19 (0.14, 0.25)	0.967 (0.94, 0.98)
		8	All	516	0.813 (0.54, 0.96)	NR	0.333 (0.27, 0.40)	0.907 (0.87, 0.94)	0.360 (0.29, 0.43)	0.907 (0.87, 0.94)
	SENTiFIT-FOB Gold	1.7	All	516	0.688 (0.41, 0.89)	NR	0.315 (0.25, 0.38)	0.933 (0.90, 0.96)	0.285 (0.22, 0.35)	0.933 (0.90, 0.96)
		15	All	516	0.688 (0.41, 0.89)	NR	0.227 (0.17, 0.29)	0.96 (0.93, 0.98)	0.19 (0.14, 0.25)	0.96 (0.93, 0.98)
		17	All	516	0.688 (0.41, 0.89)	NR	0.218 (0.16, 0.28)	0.963 (0.94, 0.98)	0.18 (0.13, 0.24)	0.963 (0.94, 0.98)
		17.68	All	516	0.688 (0.41, 0.89)	NR	0.218 (0.16, 0.28)	0.967 (0.94, 0.98)	0.18 (0.13, 0.24)	0.967 (0.94, 0.98)
		53.38	All	516	0.563 (0.30, 0.80)	NR	0.144 (0.10, 0.20)	0.99 (0.97, 1.0)	0.11 (0.07, 0.16)	0.99 (0.97, 1.0)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
Graser, 2009[172]	FOB Gold	NR	All	285	1.00 (0.147, 1.00)	NR	0.320 (0.164, 0.515)	0.858 (0.811, 0.896)	0.292 (0.141, 0.489)	0.858 (0.811, 0.896)
Hernandez, 2014[174]	OC-Sensor	20	All	779	1.0 (0.90, 1.0)	0.94 (0.92, 0.95)	0.32 (0.22, 0.42)	0.96 (0.95, 0.98)	NR	NR
		23	All	779	NR	NR	NR	NR	NR	NR
		30	All	779	NR	NR	NR	NR	NR	NR
		40	All	779	NR	NR	NR	NR	NR	NR
		10	All	779	1.0 (0.9, 1.0)	0.92 (0.90, 0.94)	0.35 (0.25, 0.45)	0.95 (0.93, 0.97)	NR	NR
		15	All	779	NR	NR	NR	NR	NR	NR
Imperiale, 2014[175]	OC FIT-CHEK	20	All	9989	0.738 (0.615, 0.840)	NR	NR	NR	0.238 (0.208, 0.270)	0.949 (0.944, 0.953)
Kim, 2017[180]	OC-Sensor	20	All	14912	NR	NR	NR	NR	NR	NR
			≥50 years	4374	0.636 (0.308, 0.891)	0.963 (0.957, 0.968)	0.22 (0.163, 0.287)	0.969 (0.964, 0.974)	NR	0.969 (0.963, 0.974)
			40-49 years	10538	0.75 (0.194, 0.994)	0.970 (0.968, 0.974)	0.172 (0.121, 0.233)	0.974 (0.971, 0.977)	NR	0.974 (0.97, 0.977)
Lee, 2014[183]	Hemo Techt NS-Plus C system	19	All	1397	0.714 (0.419, 0.916)	0.955 (0.943, 0.965)	0.619 (0.384, 0.819)	0.963 (0.952, 0.972)	NR	NR
Liles, 2018[187]	OC-Auto	10	All	2771	NR	NR	0.23 (0.17, 0.28)	0.94 (0.93, 0.95)	NR	NR
		15	All	2771	NR	NR	0.16 (0.12, 0.22)	0.96 (0.95, 0.97)	NR	NR
		20	All	2771	NR	NR	0.14 (0.1, 0.19)	0.97 (0.96, 0.97)	NR	NR
		25	All	2771	NR	NR	0.14 (0.09, 0.18)	0.97 (0.97, 0.98)	NR	NR

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, μg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
		30	All	2771	NR	NR	0.12 (0.08, 0.17)	0.98 (0.97, 0.98)	NR	NR
Morikawa, 2005[190]	Magstream 1000/Hem SP	100-200	All	21805	0.658 (0.554, 0.763)	0.946 (0.943, 0.949)	0.271 (0.239, 0.303)	0.951 (0.948, 0.954)	NR	NR
			<50 years	NR	NR	NR	NR	NR	0.253 (NR)	NR
			≥60 years	NR	NR	NR	NR	NR	0.197 (NR)	NR
			50-59 years	NR	NR	NR	NR	NR	0.229 (NR)	NR
			Distal	21805	NR	NR	0.307 (0.267, 0.348)	NR	0.261 (NR)	NR
			Proximal	21805	NR	NR	0.163 (0.113, 0.213)	NR	0.112 (NR)	NR
			Female	NR	NR	NR	NR	NR	0.167 (NR)	NR
			Male	NR	NR	NR	NR	NR	0.239 (NR)	NR
Nakama, 1999[192]	Monohaem	NR	1-day collection	4611	0.556 (NR)	NR	NR	0.971 (NR)	0.301 (NR)	NR
			2-day collection	4611	0.833 (NR)	NR	NR	0.960 (NR)	0.507 (NR)	NR
			3-day collection	4611	0.889 (NR)	NR	NR	0.939 (NR)	0.548 (NR)	NR
Ng, 2013[193]	Hemosure	50	All	4539	0.545 (0.323, 0.737)	0.894 (0.884, 0.902)	0.388 (0.325, 0.454)	0.906 (0.897, 0.914)	0.371 (0.305, 0.439)	0.906 (0.897, 0.914)
Park, 2010[194]	OC-Micro	20	All	770	0.923 (0.640, 0.998)	0.901 (0.877, 0.921)	0.444 (0.327, 0.566)	0.921 (0.899, 0.940)	0.339 (0.228, 0.465)	0.921 (0.899, 0.940)
		25	All	770	0.846 (0.546, 0.981)	0.913 (0.890, 0.932)	0.389 (0.276, 0.511)	0.930 (0.908, 0.948)	0.288 (0.178, 0.421)	0.930 (0.908, 0.948)
		30	All	770	0.846 (0.546, 0.981)	0.919 (0.898, 0.938)	0.375 (0.264, 0.497)	0.936 (0.915, 0.953)	0.271 (0.164, 0.403)	0.936 (0.915, 0.953)

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
		10	All	770	0.923 (0.640, 0.998)	0.872 (0.846, 0.895)	0.528 (0.407, 0.647)	0.898 (0.873, 0.920)	0.441 (0.312, 0.576)	0.898 (0.873, 0.920)
		15	All	770	0.923 (0.640, 0.998)	0.890 (0.866, 0.912)	0.472 (0.353, 0.593)	0.913 (0.889, 0.932)	0.373 (0.250, 0.509)	0.913 (0.889, 0.932)
Redwood, 2016[197]	OC-Sensor	20	All	661	0.80 (0.44, 0.97)	NR	0.28 (0.19, 0.39)	0.94 (0.91, 0.95)	NR	NR
			Screening group	435	0.75 (0.20, 0.99)	NR	0.31 (0.20, 0.44)	NR	0.28 (0.17, 0.42)	NR
Ribbing Wilen, 2019[206]	OC-Sensor	10	All	806	NR	NR	0.20 (0.12, 0.30)	0.93 (0.90, 0.94)	NR	NR
		20	All	806	NR	NR	0.15 (0.08, 0.24)	0.97 (0.95, 0.98)	NR	NR
		40	All	806	NR	NR	0.10 (0.04, 0.18)	0.98 (0.97, 0.99)	NR	NR
		60	All	806	NR	NR	0.07 (0.03, 0.15)	0.99 (0.98, 1.0)	NR	NR
		80	All	806	NR	NR	0.07 (0.03, 0.15)	0.99 (0.98, 1.0)	NR	NR
Shapiro, 2017[200]	InSure FIT	50	All	987	NR	NR	0.263 (0.159, 0.407)	0.968 (0.955, 0.978)	NR	NR
	OC FIT-CHEK	20	All	947	NR	NR	0.151 (0.067, 0.261)	0.978 (0.966, 0.986)	NR	NR
Sohn, 2005[201]	OC-Hemodia	20	All	3794	0.250 (NR)	NR	0.024 (NR)	0.988 (NR)	0.024 (NR)	NR
			Female 40-49 years	582	NR	NR	0 (NR)	0.996 (NR)	NR	NR
			Female 50-59 years	514	NR	NR	0 (NR)	0.982 (NR)	NR	NR
			Female 60-69 years	233	NR	NR	0.02 (NR)	0.989 (NR)	NR	NR

Table 20. Key Question 2: Results for FIT Test Accuracy (All Colonoscopy Follow-Up)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
			Female 70+ years	14	NR	NR	0 (NR)	1.0 (NR)	NR	NR
			Male 40-49 years	760	NR	NR	0 (NR)	0.989 (NR)	NR	NR
			Male 50-59 years	617	NR	NR	0.028 (NR)	0.986 (NR)	NR	NR
			Male 60-69 years	317	NR	NR	0.037 (NR)	0.978 (NR)	NR	NR
			Male 70+ years	45	NR	NR	0.125 (NR)	1.0 (NR)	NR	NR
Wong, 2015[204]	Hemosure	10	All	5343	0.545 (0.327, 0.749)	0.905 (0.897, 0.913)	0.347 (0.293, 0.405)	0.917 (0.909, 0.925)	0.331 (0.276, 0.391)	0.915 (0.907, 0.922)
			Distal	5343	0.429 (0.188, 0.704)	NR	0.40 (0.325, 0.479)	NR	0.397 (0.320, 0.480)	NR
			Proximal	5343	0.714 (0.303, 0.949)	NR	0.279 (0.20, 0.374)	NR	0.250 (0.173, 0.346)	NR

* Calculated sensitivity, specificity, and/or confidence interval

Abbreviations: AA = advanced adenoma; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal cancer; N = number; NR = not reported; sens = sensitivity; spec = specificity; µg Hb/g = micrograms hemoglobin per gram feces

Table 21. Key Question 2: Study and Population Characteristics for sDNA

Reference standard	Author, year	Quality	Country	N screened	Prevalence, n (%)	Age, mean	Female, %	Race/ Ethnicity, %	Family history, %
Colonoscopy	Cooper, 2018*[166]	Fair	US	760	CRC: 2 (0.3) AA: 49 (6.4)	56.7	60.2	White: 65.1 Black: 34.9	NR
	Bosch, 2019[209]	Good	NLD	1014	CRC: 7 (0.7) AA: 119 (11.7)	60	49	White: 96	16 (1+ FDR)
	Redwood, 2016*[197]	Fair	US	661	CRC: 10 (1.5) AA: 82 (12.4)	55 (median)	60	AN: 100	NR
	Imperiale, 2014[175]	Fair	US, CAN	9,989	CRC: 65 (0.6) AA: 757 (7.6)	64.2	53.7	White: 84.0 Black: 10.7 Other: 5.2	0 (no specific definition reported)

* Newly identified study since the previous review

Abbreviations: AA = advanced adenoma; CAN = CAN; CRC = colorectal cancer; FDR = first-degree relative; n = number; NLD = the Netherlands; US = United States

Table 22. Key Question 2: Results for sDNA Test Accuracy

Author, year	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
Cooper, 2018*[166]	All	760	NR	NR	0.43 (0.31, 0.57)	0.91 (0.88, 0.95)	NR	NR
	Black	265	NR	NR	0.50 (0.29, 0.71)	0.92 (0.88, 0.95)	NR	NR
	White	495	NR	NR	0.39 (0.25, 0.56)	0.91 (0.89, 0.93)	NR	NR
Bosch, 2019[209]	All	1014	0.86 (0.42, 1.0)	0.85 (0.84, 0.86)	0.48 (0.40, 0.57)	0.89 (0.87, 0.92)	0.46 (0.37, 0.56)	0.89 (0.87, 0.91)
Redwood, 2016*[197]	All	661	1.0 (0.69, 1.0)	0.87 (0.84, 0.89)	0.49 (0.38, 0.60)	0.91 (0.88, 0.93)	0.43 (0.33, 0.53)	0.91 (0.88, 0.93)
Imperiale, 2014[175]	All	9989	0.92 (0.83, 0.98)	0.84 (0.84,0.85)	0.46 (0.43, 0.50)	0.87 (0.86, 0.87)	0.42 (0.39, 0.46)	0.87 (0.86, 0.87)
	Female	5408	0.84 (0.67, 0.93)	0.85 (0.83, 0.86)	NR	NR	0.39 (0.34, 0.45)	0.87 (0.85, 0.89)
	Male	4645	1.00 (0.90,1.00)	0.85 (0.84, 0.86)	NR	NR	0.45 (0.40, 0.49)	0.87 (0.86, 0.88)
	White	8422	0.96 (0.88, 0.99)	0.84 (0.83, 0.85)	NR	NR	0.42 (0.39, 0.46)	0.86 (0.85, 0.87)
	Black	1071	0.63 (0.31, 0.86)	0.87 (0.85, 0.89)	NR	NR	0.42 (0.32, 0.53)	0.90 (0.88, 0.92)
	Asian	259	1.00 (0.21, 1.00)	0.92 (0.88, 0.95)	NR	NR	0.31 (0.13, 0.58)	0.94 (0.90, 0.96)
	AI/AN	36	NA	0.69 (0.53, 0.82)	NR	NR	0.75 (0.30, 0.95)	0.75 (0.58, 0.87)
	Hawaiian/PI	23	NA	0.91 (0.73, 0.98	NR	NR	NA	0.91 (0.73, 0.98)
	Other race	206	1.00 (0.21, 1.00)	0.88 (0.83, 0.92)	NR	NR	0.44 (0.23, 0.67)	0.90 (0.85, 0.94)
	Hispanic	991	0.89 (0.57, 0.98)	0.89 (0.87, 0.91)	NR	NR	0.39 (0.28, 0.52)	0.91 (0.89, 0.92)
	Non-Hispanic	9028	0.93 (0.83, 0.97)	0.84 (0.83, 0.85)	NR	NR	0.43 (0.39, 0.46)	0.86 (0.85, 0.87)
	<60 years	2881	1.00 (0.65, 1.00)	0.90 (0.89, 0.91)	NR	NR	0.38 (0.31, 0.45)	0.92 (0.91, 0.93
	60-64 yeas	826	0.75 (0.30, 0.95)	0.87 (0.84, 0.89)	NR	NR	0.42 (0.30, 0.55)	0.89 (0.87, 0.91)
	65-69 years	3673	0.95 (0.76, 0.99)	0.83 (0.82, 0.85)	NR	NR	0.41 (0.36, 0.47)	0.86 (0.84, 0.87)
	70-74 years	1738	0.89 (0.67, 0.97)	0.80 (0.78, 0.82)	NR	NR	0.47 (0.39, 0.55)	0.82 (0.81, 0.84)
	75-79 years	685	1.00 (0.61, 1.00)	0.76 (0.72, 0.79)	NR	NR	0.47 (0.35, 0.59)	0.78 (0.74, 0.81)

Table 22. Key Question 2: Results for sDNA Test Accuracy

Author, year	Screened group	N analyzed	CRC sens (95% CI)	CRC spec (95% CI)	AN sens (95% CI)	AN spec (95% CI)	AA sens (95% CI)	AA spec (95% CI)
	>79 years	220	0.90 (0.60, 0.98)	0.76 (0.70, 0.81)	NR	NR	0.47 (0.25, 0.70)	0.78 (0.72, 0.83)

* Newly identified study since the previous review

Abbreviations: AA = advanced adenoma; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal cancer; N = number; NR = not reported; sens = sensitivity; spec = specificity

Table 23. Key Question 3: Harms of Flexible Sigmoidoscopy Screening

Author, year	Country	Female, %	Mean age, years	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Miller, 2019[130]	US	51	NR	Not specified	Total	107236	NR	3	NR
Steele, 2020[150]	GBR	50	NR	Not specified	Total	25851	NR	NR	SAE: 0
Holme, 2018[127]	NOR	50	56	Not specified	Total*	12960	NR	0	NR
					55-64 years*	13653	NR	NR	SAE: 0
Atkin, 2017[119]	GBR	51	60	30 days	Total	40332	12#	1	MI - non-fatal: 2
									Pulmonary embolism: 1
									Glutaraldehyde-induced colitis: 5
									Mortality - possibly from screening: 6
Kim, 2013[255]	KOR	63	68†	Not specified	Total	20653	NR	1	NR
Tam, 2013[297]	US	46	67	Not specified	Total	46158	NR	1	NR
Segnan, 2011[140]	ITA	50	60	30 days	Total	9911	0	1	Seizures: 2
									Glutaraldehyde-induced colitis: 2
Segnan, 2007[142]	ITA	51	NR	30 days	Total	1197	NR	NR	Total hospitalizations: 16
									Hospitalization - due to cardiovascular event: 3
									Hospitalization - due to rectal prolapse: 1
									Hospitalization - due to other GI event: 2
Viiala, 2007[300]	AUS	41	60	Not specified	Total	3402	0	0	NR
MACS Group, 2006[272]	AUS	49	NR	4 weeks	Total	52	0	0	SAE: 0
Segnan, 2005[141]	ITA	53	NR	Not specified	Total	4466	0	NR	Cardiac event: 1

Table 23. Key Question 3: Harms of Flexible Sigmoidoscopy Screening

Author, year	Country	Female, %	Mean age, years	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Jain, 2002[249]	US	NR	NR	Not specified	Total	5017	0	0	Mortality: 0
Levin, 2002[264]	US	49	61	4 weeks	Total	109534	2	2	MI: 33‡ Other serious GI AEs: 3 Mortality: 10
Hoff, 2001[245]	NOR	NR	NR	Not specified	Total	775	0	0	Hospitalization: 1§ SAE: 0
Wallace, 1999[301]	US	50	59	Not specified	Total	3701	0	0	Mortality: 0
Atkin, 1998[213]	GBR	NR	NR	Not specified	Total	1285	0	NR	Mortality - screening-related: 1 MI: 1 Hospitalization: 1
Verne, 1998[147]	GBR	50	NR	0	Total	1116	NR	NR	SAE: 0
Brevinge, 1997[121]	SWE	49	NR	0	Total	1431	1	NR	Diverticulitis: 1
Lindholm, 2008**[129]	SWE	NR	NR	Not specified	Total	2108	0	3	NR

* The Norwegian Colorectal Cancer Prevention (NORCCAP) study reported no serious complications from flexible sigmoidoscopy in an analysis (n=12960) published in 2003[342] as well as in a later analysis in participants age 55-64 (n=13653) published in 2009.[343]
† Refers to participants with perforations only
# Hospitalization due to bleeding
‡ Study reports that 478 MIs occurred within one year after FS
§ Unclear if this hospitalization is from the bowel prep for FS or colonoscopy
** FS following an abnormal FOBT/FIT

Abbreviations: AUS = Australia; GBR = Great Britain; ITA = Italy; KOR = Republic of Korea; MI = myocardial infarction; n = number; NOR = Norway; NR = not reported; SAE = serious adverse event; SWE = Sweden; US = United States

Table 24. Key Question 3: Harms of Screening Colonoscopy

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Penz, 2020[311] (Newly identified)	AUT	51	65	Not specified	Total	218193	207*	29	Cardiopulmonary complication: 169 Other events (not specified): 59
Grossberg, 2019[310] (Newly identified)	US	49	60 (median)	7 days	Total	30409†	45†	NR	Hospitalization: 54† ED visit: 188† ED visit – cardiopulmonary 35† ED visit - syncope, loss of consciousness, altered mental status: 5† ED visit - abdominal CT (splenic injury): 2†
Kobiela, 2019[309] (Newly identified)	POL	54	59	30 days	Total - intention to screen	338477 (IG); 338557 (CG)	NR	NR	Hospitalization - directly or potentially related to colonoscopy: 827 (IG); 748 (CG); p=0.046 Mortality: 327 (IG); 312 (CG); p=0.551
					Total - as screened	54743 (IG); 54743 (CG)	NR	NR	Hospitalization - directly or potentially related to colonoscopy: 172 (IG); 76 (CG); p<0.001 Mortality: 11 (IG); 49 (CG); p<0.001
Basson, 2018[308] (Newly identified)	US	NR	NR	7 days	Total	392485	NR	NR	Appendicitis: 26 Appendectomy: 19
Wang, 2018[303] (Newly identified)	US	57	NR	7 days	Total	462068	NR	NR	Hospitalizations (all cause): 5366
									Hospitalization - due to infection: 521
									GI infections: 74
									Infection - non-GI: 447
									Infection - respiratory: 242
									Infection - genitourinary: 21
									Septicemia: 88
				30 days	Total	462068	NR	NR	Hospitalization: 14637
									Hospitalization - due to infection: 1841
Wang, 2018[302] (Newly identified)	US	51	60	30 days	Total	1580318	3745*†	772†	Upper GI bleeding: 232†
									Diverticulitis - colonic: 3703†
									Diverticulitis - small bowel: 28†
									Cardiac event: 11499†
									Cerebrovascular event: 2696†
									Pulmonary event: 4901†
									Infectious event: 1376†
									Mortality: 512†

Table 24. Key Question 3: Harms of Screening Colonoscopy

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Zwink, 2017[307] (Newly identified)	DEU	52	61‡	4 weeks	Total	5252	5§	2§	NR
				3 months	Total	5252	NR	NR	Mortality - from screening: 0
Bretthauer, 2016[221] (Newly identified)	NLD, NOR, POL, SWE	50	60‡	30 days	Total	12574	18	1	Mortality - from screening: 0
Kubisch, 2016[260] (Newly identified)	DEU	55	NR	0	Total	250776	430*	54	Cardiopulmonary event: 83
Sali, 2016 [136] (Newly identified)	ITA	54	59	0	Total	153	0*	0	Post-polypectomy syndrome: 1
Layton, 2014[263]	US	55	59	6 months	Total	550696	NR	NR	Acute kidney injury: 1595
Zafar, 2014[306] ‖¶	US	55	74	30 days	Total	54039	371	46	Ileus: 76
									Any cardiovascular event: 610
									MI or angina: 176
									Arrhythmia: 329
									Congestive heart failure: 94
									Cardiac or respiratory arrest: 43
									Syncope, hypotension/shock: 149
Stock, 2013[294]	DEU	55	66	30 days	Total	8658 (IG); 8658 (CG)	4 (IG); 1 (CG)	7 (IG); 0 (CG)	MI: 2 (IG); 5 (CG)
									Stroke: 3 (IG); 9 (CG)
									Splenic injury: 0 (IG); 0 (CG)
									Other SAE: 5 (IG); 4 (CG)
									Mortality - any: 5 (IG); 21 (CG)
									Mortality - in hospital: 5 (IG); 14 (CG)
Pox, 2012[283] #	DEU	56	65	Not specified	Total	2821392	573	439	Cardiopulmonary event: 83
									Mortality - from screening: 2
									Other SAE: 45
Quintero, 2012[133]	ESP	54	59	0	Total	4953	12	1	Hypotension or bradycardia: 10
	US	52	NR	30 days	Total	38472	103*†	15†	Diverticulitis: 71†

Table 24. Key Question 3: Harms of Screening Colonoscopy

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Rutter, 2012[288]									Hospitalization: 428† ED visit: 869† Mortality: 12†
Suissa, 2012[296]	ISR	NR	58	Not specified	Total	839	0	0	NR
Ferlitsch, 2011[235] **	AUT	51	61	Not specified	Total	44350	54*	3	Cardiopulmonary event: 46†† Other SAE: 8 Mortality - from screening: 0
Arora, 2009[212]	US	NR	NR	7 days	Total	58457	NR	39	NR
Bair, 2009[214]	CAN	52	57	Not specified	Total	3741	2	1	NR
Berhane, 2009[215]	US	NR	NR	Not specified	Total	11808	5	2	Hemodynamically unstable: 8 MI: 1 Mortality - from screening: 0
Bokemeyer, 2009[220]	DEU	56	NR	Not specified	Total	269144	442	55	Cardiopulmonary event: 222 Surgery - due to bleeding: 19
Crispin, 2009[229]	DEU	56	64‡	Not specified	Total	55993	10	22	Cardiopulmonary event: 39
Warren, 2009[304]	US	62	NR	30 days	Total	5349 (IG); 5349 (CG)	11 (IG); 7 (CG)†	3 (IG); 1 (CG)†	Any cardiovascular event: 53 (IG); 80 (CG)† MI or angina: 13 (IG); 18 (CG)† Arrhythmia: 30 (IG); 37 (CG)† Congestive heart failure: 8 (IG); 30 (CG)† Syncope, hypotension/shock: 8 (IG); 14 (CG)† Cardiac or respiratory arrest: 8 (IG); 8 (CG)†
Kim, 2007[254]	US	56	58	Not specified	Total	3163	NR	7	NR
MACS Group, 2006[272]	AUS	49	NR	4 weeks	Total	63	0	0	Other SAE: 0
Strul, 2006[295]	ISR	53	60	Not specified	Total	1177	0	0	Severe abdominal pain requiring hospitalization: 1 Mortality - from screening: 0
Cotterill, 2005[228]	CAN	44	NR	Not specified	Total	324	0	0	NR

Table 24. Key Question 3: Harms of Screening Colonoscopy

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Nelson, 2002[273]	US	3	63	30 days	Total	3196	7	0	Arrhythmia: 1
									MI or cerebrovascular accident: 4
									Mortality: 1
									Other SAE: 4

* Unspecified bleeding
† Number of procedures or events (rather than number of people)
‡ Median age
§ Physician confirmed hospitalizations due to bleeding and/or perforation
∥ Increasing risk of bleeding, perforation, and other GI events with older ages (only odds ratios presented; not statistically significant; also includes 1384 people total who received CT colonography)
¶ Increasing risk of cardiovascular events with older ages (only odds ratios presented; statistically significant; also includes 1384 people total who received CT colonography)
# Increasing major and minor complications with increasing age. Statistically significant for both males and females with 55-59 years (by sex) as the reference group
** Bleeding events were unchanged by age (p=0.23)
†† Cardiopulmonary adverse events increased with age, from 0.05% in patients age 50-60 years to 0.25% in patients age 70-80 years (p<0.001)

Abbreviations: AUS = Australia; CAN = Canada; CG = control (no screening) group; DEU = Germany; ESP = Spain; GI = gastrointestinal; IG = intervention (screening) group; ISR = Israel; ITA = Italy; MI = myocardial infarction; NLD = Netherlands; NOR = Norway; NR = not reported; POL = Poland; SAE = serious adverse events; SWE = Sweden; AUT = Austria

Table 25. Key Question 3: Harms of Mixed Colonoscopies

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Chukmaitov, 2019[312] (Newly identified)	US	54	NR	30 days	Total	1020372	NR	NR	Hospitalization due to perforations and GI bleeding: 1199
Laanani, 2019[261] (Newly identified)	FRA	55	NR	5 days	Total	4088799	2655 (minimum); 9459 (maximum)*	1436 (minimum); 2998 (maximum)*	Splenic injury: 83 (minimum); 139 (maximum)*
									Mortality - due to splenic injury: 0 (minimum); 0 (maximum)*
									Mortality - due to serious bleed: 1 (minimum); 8 (maximum)*
									Mortality - due to perforations: 9 (minimum); 34 (maximum)*
				30 days	Total	4088799	NR	NR	Mortality - due to splenic injury: 3 (minimum); 4 (maximum)*
									Mortality - due to serious bleed: 35 (minimum); 66 (maximum)*
									Mortality - due to perforations: 42 (minimum); 124 (maximum)*
Thulin, 2019[313] (Newly identified)	SWE	54	63	30 days	Total	593308	983‖	667	NR
Bielawska, 2018[217] (Newly identified)	CAN	51	NR	7 days	Total	3059045	NR	1396	Splenic injury: 138
				14 days	Total	3059045	NR	NR	Aspiration pneumonia: 186
					Anesthesia	862817	NR	NR	Aspiration pneumonia: 74
					No anesthesia	2196228	NR	NR	Aspiration pneumonia: 112
Grossberg, 2018[240] (Newly identified)	US	53	59†	2 days	Total	50319	NR	NR	ED visit - related to colonoscopy - cardiopulmonary: 33
									ED visit - related to colonoscopy - loss of consciousness: 9
				7 days	Total	50319	77‡	NR	Any ED visit - related to colonoscopy: 260
									ED visit - related to colonoscopy - cerebrovascular: 1
Forsberg, 2017[237] ¶ (Newly identified)	SWE	56	63	30 days	Total	593315§	972‖	661	Splenic injury: 31
									Mortality: 80

Table 25. Key Question 3: Harms of Mixed Colonoscopies

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Garcia-Albeniz, 2017[125] (Newly identified)	US	50	NR	30 days	Total	78065	34	31	Other GI events: 463 Cardiovascular event: 1011††
Hoff, 2017[244] (Newly identified)	NOR	NR	NR	1 days	Total	11248	2#	1	Hospitalization: 18 Syncope: 6 Stroke: 1 Bradycardia: 2 Hypoxia: 1 Technical failure: 1
Johnson, 2017[250] (Newly identified)	US	46	NR	30 days	Total**	480688	NR	NR	Cardiac event: 4053 Pulmonary event: 710 Neurovascular: 963
Chukmaitov, 2016[226] (Newly identified)	US	54	NR	30 days	Total	4234084	NR	NR	SAE‡‡: 1471
Polter, 2015[281] (Newly identified)	US	NR	NR	30 days	Total	10534	NR	5	NR
Adeyemo, 2014[210]	US	54	61	Not specified	Total	118004	NR	48	NR
Bielawska, 2014[216]	US	48	NR	Not specified	Total	1144900	NR	192	NR
Blotiere, 2014[219] §§	FRA	56	NR	3 days	Total	947061	182	424	NR
Castro, 2013[223]	US	74	56	30 days	Total	3355	1#	3	Post-polypectomy syndrome: 0 Excessive abdominal pain: 1 Cardiopulmonary complication: 3 Surgery - due to perforations: 3 Mortality - from screening: 0

Table 25. Key Question 3: Harms of Mixed Colonoscopies

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Chukmaitov, 2013[225] ##	US	54	NR	30 days	Total	2315126	3822# ‖‖	773¶¶ ‖‖	NR
Cooper, 2013[227] ***	US	55	76	30 days	Total	100359	NR	101‖‖	Splenic injury: 12‖‖ Aspiration pneumonia: 173‖‖ Mortality: 291
					Anesthesia	35128‖‖	NR	NR	Aspiration pneumonia: 48‖‖
					No anesthesia	130399‖‖	NR	NR	Aspiration pneumonia: 125‖‖
Dominitz, 2013[232]	US	58	NR	30 days	Total	328167	2299	374	ED visit: 14278 Hospitalization: 10478
Hamdani, 2013[241]	US	51	NR	7 days	Total	80118	NR	50	NR
Kim, 2013[255]	KOR	63	68†††	Not specified	Total	94632	NR	26	NR
Loffeld, 2013[266]	NLD	65†††	75†††	Not specified	Total	19135	NR	26	NR
Tam, 2013[297]	US	46	67	Not specified	Total	86101	NR	25	NR
Ho, 2012[243]	CAN	52	73†	7 days	Total‡‡‡	50660	NR	NR	Hospitalization: 534 Mortality - from screening: 13 Other SAEs§§§: 1218 ED visit: 682
Sagawa, 2012[289]	JPN	38	67	Not specified	Total	10826	NR	8	NR
Ko, 2010[257]	US	45	NR	30 days	Total	21375	34#	4¶¶	Diverticulitis: 18‖‖‖ Post-polypectomy syndrome: 2 Hospitalization - due to MI or angina: 12 Hospitalization - due to stroke or TIA: 7 Mortality: 3
Lorenzo-Zuniga, 2010[267]	ESP	NR	57	Not specified	Total	25214	59	13	NR
Xirasagar, 2010[305]	US	52	58	Not specified	Total	10958	1	2	Aspiration: 1 Post-polypectomy syndrome: 1 Renal failure: 1
Hsieh, 2009[246]	TWN	42	51	Not specified	Total	9501	NR	3	NR
Kamath, 2009[251]	US	71††††	54††††	22 months****	Total	296248	NR	NR	Splenic injury during colonoscopy: 7

Table 25. Key Question 3: Harms of Mixed Colonoscopies

Author, year	Country	Female, pct	Age, mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Quallick, 2009[284]	US	50†††	65†††	Not specified	Total	39054	NR	4	NR
Singh, 2009[292]	CAN	56	59	30 days	Total	24509	21‡‡‡‡	29	Diverticulitis - acute: 2 Intestinal obstruction: 3 MI - acute: 3 Pneumonia: 1 Post-polypectomy syndrome: 9 Acute renal failure: 1
Mansmann, 2008[269]	DEU	57	59	Not specified	Total	236087	10	69	Cardiopulmonary event: 152 Mortality from cardiopulmonary event: 3
Rabeneck, 2008[285] §§§§	CAN	54	61	30 days	Total	97091	137	54	Mortality: 51 Mortality - from screening: 3
Ko, 2007[258]	US	51	NR	30 days	Total	502	3	0	ED visit: 2 Hospitalization: 2 Unplanned physician visit: 1
Levin, 2006[265] ‖‖‖‖	US	40	62	30 days	Total	16318	15	15	Post-polypectomy syndrome: 6 MI: 9 Mortality - from screening: 1
Rathgaber, 2006[286]	US	52	60	30 days	Total	12407	25¶¶¶¶	2	Cerebrovascular event: 1 Mortality: 0
Korman, 2003[259]	US	73	69	Not specified	Total	116000	NR	37	NR
Sieg, 2001[291]	DEU	NR	NR	Not specified	Total	96665	17	13	AE - due to medication: 12 Cardiopulmonary event: 12 Mortality - from screening: 2

* Study estimated a minimum and a maximum rate estimated respectively by stringent and broad definition for each SAE. Stringent definitions included specific ICD-10 codes of colonoscopy SAEs, while broad definitions included less specific ICD-10 codes and procedures that could identify SAEs not captured by stringent definitions.
† Median age
‡ ED visit for GI bleeding
§ N=593315 colonoscopies performed on 426560 individuals
‖ Unspecified bleeding
¶ Study presents risk ratios for risk of bleeding and perforation by sex. Male sex was associated with a higher risk of bleeding compared with female sex; no significant differences by sex were found for perforations
\# Hospitalizations due to bleeding
** Study also reports AEs in subgroups who: are taking antithrombotic medications; have pulmonary risk factors; or have neither of these preconditions
†† Includes cardiac events, pulmonary events, and neurovascular events
‡‡ Hospitalizations due to colonic perforation and GI bleeding
§§ Study reports odds ratios for risk of bleeding and perforation by age subgroups with 0-39 as reference group. Older age groups (e.g., age >=70) were associated with higher risks of bleeding and perforation

Table 25. Key Question 3: Harms of Mixed Colonoscopies

‖ Number of events (rather than number of people)
¶¶ Hospitalization due to perforation
Study reports odds ratios for risk of bleeding and perforation by age, sex, and race/ethnicity subgroups. Older age groups (e.g., age >=65) were associated with higher risks of bleeding and perforation compared with age 19-49, and Hispanic ethnicity and Black or African American race were associated with higher risks of bleeding compared with white race. No significant differences were found for perforation by race/ethnicity, and no significant differences were found for bleeding or perforation by sex
*** Study reports odds ratios for risk of complications (defined as perforation, splenic injury, or aspiration pneumonia) by age subgroups. Older age groups (e.g., age >=70 years) were associated with higher risks of complications compared with age 66-69 years
††† Refers to patients with perforations only
‡‡‡ Study also reports AEs by subgroups receiving either polyethylene glycol or sodium picosulfate bowel preparation
§§§ Includes electrolyte disturbances, congestive heart failure, syncope, dehydration, and falls
‖‖ N=5 required hospitalization
**** Median followup; range 1-164 months
†††† Refers to patients with splenic injury only
‡‡‡‡ N=21 post-polypectomy bleeding; n=1 bleeding after biopsy
§§§§ Study reports odds ratios for risk of bleeding and perforation by age and sex groups. Older age groups (e.g., age 60-75) were associated with higher risk of bleeding and perforation compared with age 50-59 years. Male sex was associated with a higher risk of bleeding compared with female sex; the study found no significant differences in perforations by sex.
‖‖‖‖ Study reports rate ratios for risk of perforation, bleeding with transfusion, and diverticulitis requiring surgery by age and sex groups. Older age groups (e.g., age >= 60 years) were associated with higher risk of these complications compared with age 40-59 years. No significant differences were found by sex
¶¶¶¶ 23 were postpolypectomy bleedings
Abbreviations: CAN = Canada; CG = control (no screening) group; DEU = Germany; ED = emergency department; ESP = Spain; GI = gastrointestinal; FRA = France; IG = intervention (screening) group; JPN = Japan; KOR = Republic of Korea; MI = myocardial infarction; NLD = Netherland; NOR = Norway; NR = not reported; SAE = serious adverse events; SWE = Sweden; TWN = Taiwan; US = United States

Table 26. Key Question 3: Harms From Other Screening Procedures

	Author, year	Country	Female pct	Age mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Colonoscopy, post CTC	Sali, 2016[136] (Newly identified)	ITA	54*	59	Time of procedure	Total	126	0†	0	NR
Colonoscopy, post FOBT/FIT	Derbyshire, 2018[231] (Newly identified)	GBR	39	66	30 days	Total	263129	NR	147	Mortality - due to perforation: 1
						Female	103934	NR	53	NR
						Male	159193	NR	92	NR
						North East region	11564	NR	NR	Mortality - due to post-polypectomy bleeding: 0
	Ibanez, 2018[248] (Newly identified)	ESP	42	NR	30 days	Total	8831	10	13	Hospitalization: 142
										Mortality: 0
										Peritonitis: 0
						Male	5126	NR	NR	Any SAE: 15
										SAE - immediate: 8
										SAE - late: 7
						Female	3705	NR	NR	Any SAE: 8
										SAE - immediate: 6
										SAE - late: 2
						≤59 years	3541	NR	NR	Any SAE: 7
										SAE - immediate: 6
										SAE - late: 1
						≥60 years	5290	NR	NR	Any SAE: 16
										SAE - immediate: 8
										SAE - late: 8
	Mikkelsen, 2018[270] (Newly identified)	DNK	44	64	30 days	Total	14671	28	15‡	Post-polypectomy syndrome: 24
										Mortality: 11
										Mortality, screening-related: 0
Colonoscopy, post FOBT/FIT	Rim, 2017[287] (Newly identified)	KOR	NR	NR	3 months	Total	473960	393†	294	Infectious event: 76
										Other SAE: 22
						Female	NR	122†	81	Infectious event: 25
										Other SAE: 7
						Male	NR	271†	213	Infectious event: 51
										Other SAE: 15
						Female 50-59 years	NR	47†	30	Infectious event: 13
										Other SAE: 4

Table 26. Key Question 3: Harms From Other Screening Procedures

	Author, year	Country	Female pct	Age mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
						Female 60-69 years	NR	54†	32	Infectious event: 8
										Other SAE: 2
						Female ≥70 years	NR	21†	19	Infectious event: 4
										Other SAE: 1
						Male 50-59 years	NR	107†	68	Infectious event: 27
										Other SAE: 5
						Male 60-69 years	NR	97†	86	Infectious event: 13
										Other SAE: 7
						Male ≥70 years	NR	67†	59	Infectious event: 11
										Other SAE: 3
	Kubisch, 2016[260] (Newly identified)	DEU	55	NR	Not specified	Total	30907	128†	10	Cardiopulmonary complication: 23
	Sali, 2016[136] (Newly identified)	ITA	54*	59	Time of procedure	Total	217	2§	0	NR
	Saraste, 2016[290] (Newly identified)	SWE	NR	NR	30 days	Total	2984	18§	3	Infectious event: 3
										Thromboembolic event: 6
										Re-operations post-colonoscopy: 6
										Re-admissions, miscellaneous: 11
										Mortality: 1
	Binefa, 2015[218] (Newly identified)	ESP	NR	NR	30 days	1st round‖	63880	NR	NR	SAE¶: 3
						2nd round‖	66534	NR	NR	SAE¶: 0
						3rd round‖	65142	NR	NR	SAE¶: 2
						4th round‖	62934	NR	NR	SAE¶: 4
						5th round‖	64117	NR	NR	SAE¶: 10
	Parente, 2013[275]	ITA	NR	NR	Not specified	Total	4373	5	2	Other SAEs: 0
	Shaukat, 2013[143]	US	52	62*	Not specified	Total	12246	11	4	NR
	Quintero, 2012[133]	ESP	54	59	Not specified	Total	587	8	0	Hypotension or bradycardia: 2

Table 26. Key Question 3: Harms From Other Screening Procedures

	Author, year	Country	Female pct	Age mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
Colonoscopy, post FS	Scholefield, 2012[138]	GBR	NR	NR	Not specified	Total	1474	1	5	NR
	Dancourt, 2008[230]	FRA	54	NR	Not specified	Total	1205	0	0	NR
	Faivre, 2004[124]	FRA	53	NR	Not specified	Total	1298	0	0	NR
	Miller, 2019[130]	US	51	NR	Not specified	Total	17672	NR	19	NR
	Steele, 2020[150]	GBR	50	NR	Not specified	Total	440	1	NR	NR
	Holme, 2018[127]	NOR	50	56	Not specified	Total	2524	4#	6	Post-polypectomy syndrome: 24
	Atkin, 2017[119]	GBR	51	60	30 days	Total	2051	9#	4	Mortality - possibly from screening: 1
	Segnan, 2011[140]	ITA	50	60	30 days	Total	775	1	1	NR
	Lindholm, 2008[129]	SWE	NR	NR	Not specified	Total	190	1	2	NR
Colonoscopy, post FS or FOBT	Segnan, 2005[141]	ITA	53	NR	Not specified	Total	332	1#	NR	NR
Colonoscopy or FS, screening or mixed	Kang, 2008[252]	KOR	36	60	Not specified	Total	44534	NR	53	NR
						Followup colonoscopy	37762	NR	26	NR
						Therapeutic colonoscopy	6772	NR	27	NR
CTC, screening or mixed	Sali, 2016[136] (Newly identified)	ITA	54*	59	Time of procedure	Total	1286	0†	0	NR
	Zafar, 2014[306]	US	64	77	30 days	Total	1384	4	1	Ileus: 0
										Any cardiovascular event: 26
										MI or angina: 4
										Arrhythmia: 14
										Cardiac or respiratory arrest: 1
										Congestive heart failure: 5

Table 26. Key Question 3: Harms From Other Screening Procedures

	Author, year	Country	Female pct	Age mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
										Syncope, hypotension/shock: 9
	Iafrate, 2013[247]	ITA	NR	NR	Not specified	Total	40121	NR	7	Mortality - screening-related: 0
	Cash, 2012[222]	US	42	75	Not specified	Total	1410	NR	NR	CTC-related complications: 0
	Zalis, 2012[205]	US	47	60	Not specified	Total	605	NR	NR	Events that required treatment: 0
	Kim, 2010[253]	US	48	69	Not specified	Total	577	0	0	NR
	Pickhardt, 2010[279]	US	48	60	Not specified	Total	10286	NR	NR	Mortality: 3
	Graser, 2009[172]	DEU	45	61	Not specified	Total	309	NR	NR	SAE: 0
	An, 2008[211]	KOR	40	51	Not specified	Total	1015	NR	NR	SAE: 0
	Johnson, 2008[177]	US	52	58	Not specified	Total	2534	NR	NR	Hospitalization due to e. coli bacteremia: 1
	Kim, 2008[256]	KOR	40	58	Not specified	Total	2230	NR	NR	Severe reaction to contrast media: 0
	Kim, 2008[181]	KOR	49	58	Not specified	Total	241	NR	NR	Urticaria (contrast medium induced): 2
										Clinically important complication: 0
	Kim, 2007[254]	US	56	57	Not specified	Total	3120	NR	0	NR
	MACS Group, 2006[272]	AUS	49	NR	4 weeks	Total	38	0	0	SAE: 0
	Pickhardt, 2006[276]	US, BEL, IRL, ITA, NLD	NR	NR	Not specified	Total	11707	NR	0	NR
	Sosna, 2006[293]	ISR	42	60	Not specified	Total	11870	NR	7	Mortality - screening-related: 0
	Edwards, 2004[234]	AUS	46	NR	Not specified	Total	340	NR	NR	SAE: 0
FOBT/FIT, screening	Segnan, 2007[142]	ITA	51	NR	30 days	Total	1363	NR	NR	Hospitalization: 12
										Hospitalization - due to rectal prolapse: 0

Table 26. Key Question 3: Harms From Other Screening Procedures

	Author, year	Country	Female pct	Age mean	Followup	Group	n	n with serious bleeding events	n with perforation events	n with other SAEs
										Hospitalization - due to cardiovascular event: 1
										Hospitalization - due to other GI event: 0
	MACS Group, 2006[272]	AUS	49	NR	4 weeks	Total	125	0	0	SAE: 0
	Rasmussen, 1999[134]	DNK	NR	NR	0	Total	2235	0	0	Mortality - from screening: 0
Capsule endoscopy	Rex, 2015[198] (Newly identified)	US, ISR	56	57	Not specified	Total	689	NR	NR	SAE: 0
										Non-serious AE related to the capsule procedure: 3

* Refers to participants at randomization
† Unspecified bleeding
‡ Perforation or lesion
§ Post-polypectomy bleeding
‖ The screening program included 5 rounds of screening with an approximately 2-year interval between screening rounds
¶ Defined as severe complications requiring hospitalization, including serious bleeding, perforation, vagal syndrome, peritonitis-like syndrome
# Hospitalization due to bleeding

Abbreviations: AUS = Australia; AE = adverse event; BEL = Belgium; CTC = Computed tomographic colonography; DEU = Denmark; DNK = Denmark; ESP = Spain; FRA = France; GI = gastrointestinal; IRL = Ireland; ISR = Israel; ITA = Italy; IV = intravenous; KOR = Republic of Korea; MI = myocardial infarction; NLD = Netherlands; NOR = Norway; NR = not reported; SAE = serious adverse event; SWE = Sweden; US = United States

Table 27. Key Question 3: CTC Radiation Exposure

Author, year	Radiation exposure (Effective Dose)
Fletcher, 2013[169]	6-7 mGy*
Lefere, 2013[184]	10.56 mGy*
Zalis, 2012[205]	5.3 mSv
Graser, 2009[172]	4.5 mSv
An, 2008[211]	0.8-1.0 mSv
MACS Group, 2006[272]	<5 mSv
Edwards, 2004[234]	5 mSv

* Radiation output from the CT scanner (volume CT dose index)
Relevant definitions[472]:
Volume CT dose index ($CTDI_{vol}$) = A measure of radiation output from the CT scanner (units mGy). Linear relationship with radiation exposure, but independent of patient size and size of scanned body region. Useful for comparing different CT scanners, but not a measure of patient dose.
Absorbed dose = Amount of ionizing radiation deposited in tissues; energy absorbed per unit mass (unit mGy). Dependendent on $CTDI_{vol}$, length of body region scanned, and patient size.
Effective dose = Uniform whole-body dose (units mSv). Useful to compare different radiologic exposures (from other medical procedures or other forms of radiation). Applicable to a population, not an individual.

Abbreviations: mSv = millisievert; mGy = milligrays

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Taya, 2019[298] Fair	Screening only	2.8 yrs (mean)	C-RADS	Total	262	E3: 9 persons (9 findings) E3 - indeterminate renal lesion: 3 findings E3 - lung opacity: 2 findings E3 - lymphadenopathy: 2 findings E3 - liver mass: 1 event E3 - pericardial effusion: 1 event	Follow-up imaging of E3 findings: 6 persons	Benign disease: 6 (none required an invasive procedure for diagnosis of a benign condition)	NR
						E4: 20 persons (24 findings) E4 - lung nodule: 7 findings E4 - abdominal aortic aneurysm: 2 findings E4 - common iliac aneurysm: 3 findings E4 - other vascular aneurysm: 3 findings E4 - renal mass: 3 findings E4 - urolithiasis or hydronephrosis: 2 findings E4 - liver mass: 1 event E4 - mediastinal mass:1 event E4 - lung opacity: 1 finding E4 - avascular necrosis of hip: 1 event	Follow-up imaging of E4 findings: 18 persons	Clinically significant pathology on followup: 12 persons	NR
								Benign disease: 6 persons (All 6 had imaging; none required an invasive procedure for diagnosis of a benign condition)	NR
								Malignant tumor: 2 persons (1 non-small cell lung cancer, 1 renal cell carcinoma)	NR
Larson, 2018[262] Fair	Screening only	NR	C-RADS	Cancer hx	349	E3: 50 persons E4: 9 persons	NR	NR	NR
				Cancer hx, female	234	E3: 33 persons E4: 8 persons			
				Cancer hx, male	115	E3: 17 persons E4: 1 person			
				No cancer hx	8859	E3: 965 persons E4: 166 persons			

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
				No cancer hx, female	4725	E3: 560 persons E4: 89 persons			
				No cancer hx, male	4134	E3: 405 persons E4: 77 persons			
				Non-melanoma skin cancer hx	271	E3: 39 persons E5: 9 persons			
Moreno, 2018[271] Fair	Screening only	NR	C-RADS	45-49 yrs	249	E3: 8 persons E4: 4 persons	NR	NR	NR
				50-75 yrs	2404	E3: 151 persons E4: 94 persons			
				50-80 yrs	2490	E3: 163 persons E4: 100 persons E4 - Lung nodule: 5 persons E4 - lytic or sclerotic bone lesions: 4 persons E4 - renal mass: 4 persons E4 - liver mass: 2 persons E4 - adrenal mass: 2 persons			
				65-80 yrs	606	E3: 50 persons E4: 37 persons			
Regge, 2017[135] Fair	Screening only	0	C-RADS	Total	2595	E4 and aortic aneurysms ≥4cm: 35 persons*	NR	NR	NR
Pooler, 2016[282]	Screening only	>2 yrs	C-RADS	Total	7952	E3: 725 persons	Evaluation with imaging: 608 persons	Clinically significant pathology on followup: 55 persons	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Good								Malignancy: 8 persons (3 renal cell carcinoma, 3 lymphoma,1 ovarian adenocarcinoma, 1 metastatic breast cancer)	NR
								Benign/borderline neoplasms: 17 persons (7 ovarian dermoid, 3 ovarian mucinous cystadenoma, 1 pancreatic mucinous cystadenoma, 1 benign gastrointestinal stromal tumor, ovarian borderline serous tumor, 1 renal oncocytoma, 1 ovarian Brenner tumor, peripheral)	NR
								Benign disease: 605 persons	NR
								Other significant pathology: 30 persons (9 endometriosis, 4 complicated urolithiasis, 3 porcelain gallbladder, 2 inflammatory bowel disease, 2 asbestos-related pleural plaques, 2 pneumonia, and 2 obstructing ureterocele	NR
						E4: 202 persons E4 - abdominal aortic aneurysm: 35 persons	Evaluation with imaging: 113 persons	Clinically significant pathology on followup: 123 persons	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
						E4 - liver mass: 26 persons E4 - renal mass: 20 persons E4 - lung nodule: 19 persons E4 - visceral abdominal/other aneurysm: 18 persons E4 - adnexal mass: 14 persons E4 - other gastrointestinal: 12 persons E4 - gastrointestinal mass: 8 persons E4 - lymphadenopathy: 8 persons E4 - urolithiasis or hydronephrosis: 8 persons E4 - other genitourinary: 8 persons E4 - pancreas mass: 5 persons E4 - other liver: 4 persons E4 - adrenal mass: 2 persons E4 - breast mass: 2 persons		Malignant tumor: 32 persons (7 lymphoma, 5 non-small cell lung cancer, 4 renal cell carcinoma, 1 transitional cell carcinoma, 1 ovarian adenocarcinoma, 1 appendiceal adenocarcinoma, 1 islet cell tumor, 1 pheochromocytoma, 1 adrenal cortical carcinoma, 1 nerve sheath tumor, 2 breast invasive ductal carcinoma, 7 other metastatic cancer)	
								Other tumors: 10 persons (4 mucinous tumor, 3 mature teratoma, 3 renal oncocytoma)	NR
								Vascular aneurysms: 46 persons (22 abdominal aortic aneurysms, 11 common iliac aneurysms, 13 visceral abdominal/other aneurysms)	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
								Other significant pathology: 35 persons (8 obstructing/staghorn urolithiasis, 7 intestinal malrotation, 5 polycystic kidney disease, 4 cirrhosis, 3 sarcoidosis, 2 endometriosis, 2 renal agenesis or dysgenesis, 1 IBD, 1 early acute appendicitis, 1 colovesical fistula, 1 hydrosalpinx)	NR
								Benign disease: 57 persons (2 ovarian serous cystadenoma, 1 adenofibroma, 1 pancreatic serous cystadenoma, pancreas tissue with lymphoepithelial cells, 1 small bowel benign papillary choristoma, 1 small bowel lymphectasia, 1 mesenteric lipoma, 1 appendiceal diverticulum,1 hamartomas of the lung and 1 pelvis. At confirmatory imaging, all liver masses in absence of cirrhosis or 18 other primary malignancy were found to be benign cavernous hemangiomas	NR
						Other ECF: 13 persons	NR	NR	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Sali, 2016[136] Fair	Screening only	0	C-RADS	Total	1286	E3-E4: 65 persons	NR	NR	NR
Cash, 2012[222] Fair	Screening only	NR	C-RADS	Total	1410	E3: 196 persons (214 findings) E3 - pulmonary: 68 findings E3 - retroperitoneal and genitourinary: 68 findings E3 - gastrointestinal: 45 findings E3 - Vascular: 33 persons findings E4: 41 persons (42 findings) E4 - pulmonary: 10 findings E4 - retroperitoneal and genitourinary: 18 findings E4 - gastrointestinal: 4 findings E4 - vascular: 10 findings	NR	NR	NR
Durbin, 2012[233] Fair	Screening only	NR	Major, moderate, minor†	Total	490	Major genitourinary findings: 10 persons Moderate genitourinary findings: 86 persons Minor genitourinary findings: 100 persons	Diagnostic workup: 25 persons‡	Renal cell cancer: 2 persons (required surgery)	NR
Stoop, 2012[144] Fair	Screening only	0	C-RADS	Total	982	E3-E4: 107 persons	Diagnostic followup: 94 persons	Extra-colonic cancer: 5 persons (4 renal-cell carcinoma, 1 duodenal carcinoma)	NR
								Abdominal aortic aneurysms: 7 persons	NR
								Aneurysms of a smaller vessel: 3 persons (3 underwent surgical treatment)	NR
								Low-risk myelofibrosis: 1 person	NR
								Paget's disease: 1 person	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
								Glandular papilloma: 1 person	NR
								Benign lesions: 76 persons (19 kidney, 12 gynecological, 7 liver, 7 lung, 5 adrenal, 26 in other organs)	NR
Zalis, 2012[205] Good	Screening only	NR	C-RADS	All	605	E3: 97 persons E4: 16 persons	Diagnostic workup: 33 persons	NR	NR
Macari, 2011[268] Fair	Mixed (including symptomatic)	NR	C-RADS	Total	454	E1-E4: 298 persons E3-E4: 24 persons	Diagnostic workup: 10 persons	NR	NR
				Age <65	204	E1-E4: 113 persons E3-E4: 9 persons	Diagnostic workup: 4 persons		
				Age ≥65	250	E1-E4: 185 persons E3-E4: 15 persons	Diagnostic workup: 6 persons		
O'Connor, 2011[274]§ Fair	Screening only	3 yrs	Benign, intermediate‖	Total	3001	Benign renal mass: 376 persons Indeterminate renal mass: 57 persons	Diagnostic workup: 41 persons	Renal cell cancer: 4 persons (2 additional patients who had benign index masses were found to have renal cell carcinoma 3 yrs later, but did not originate from the index mass or any other identifiable mass on the CTC)	NR
Pickhardt, 2011[277]§ Fair	Screening only	NR	Small, moderate, large#	Total	3126	Small hiatal hernia: 1281 persons Moderate hiatal hernia: 194 persons Large hiatal hernia: 20 persons	NR	NR	NR
Kim, 2010[253]§ Fair	Screening only	62 mos (1863 days)	C-RADS	Total	577	E3-E4: 89 persons	Diagnostic workup: 45 persons	Substantial but unsuspected diagnosis: 21 persons	NR
								Vascular aneurysms: 18 persons	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
								Lung cancer: 1 person	NR
								Malrotation: 1 person	NR
								Femoral hernia: 1 person	NR
Pickhardt, 2010[279]§ Fair	Screening only	56 mos	C-RADS	Total	10286	NR	Any surgical or medical treatment: 33 persons Surgery: 24 persons Chemotherapy: 12 persons Radiation treatment: 5 persons Percutaneous ablation: 2 persons Palliative: 1 person Hormonal therapy; 1 person	Malignancy after diagnostic workup: 36 persons	Alive (13-56 mos): 33 persons Died (21-31 mos): 3 persons (2 of the deaths related to ECF; one death from unrelated cerebrovascular cause)
								Adrenal cancer: 3 persons	All alive at followup (21-55 mos)
								Appendix cancer: 1 person	Alive at followup (30 mos)
								Hepatocellular cancer: 1 person	Alive at followup (17 mos)
								Stomach cancer: 1 person	Alive at followup (34 mos)
								Lung cancer: 8 persons	Alive at followup: 6 persons (14-43 mos) Died of lung cancer: 2 persons (21, 31 mos)
								Breast cancer: 1 person	Alive at followup (28 mos)
								Endometrial cancer: 1 person	Alive at followup (47 mos)
								Skin cancer: 1 person	Alive at followup (18 mos)
								Non-Hodgkin lymphoma: 6 persons	All alive at followup (26-56 mos)

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
								Prostate cancer: 2 persons	All alive at followup (25-43 mos)
								Renal cell cancer: 11 persons	Alive: 10 persons (13-40 mos) Died (of unrelated cerebrovascular cause after 27 mos): 1 persons
Veerappan, 2010[299] Fair	Screening only	6 mos – 4 yrs	C-RADS	Total	2277	E2-E4: 1037 persons E2: 787 persons E3: 211 persons E4: 39 persons	Diagnostic workup: 199 persons Surgical or medical treatment: 19	Cancer: 6 persons	"Curative resection": 4 persons Chemotherapy: 2 persons Status at followup: NR
								Abdominal aortic aneurysms: 1 person	"Repaired successfully": 1 person
Flicker, 2008[236] Fair	Screening only	1-76 mos	C-RADS	Total	210	E3: 30 persons E3 - nephrolithiasis: 13 persons E3 - renal complex cyst: 3 persons E3 - pancreatic calcifications: 2 persons E3 - fatty liver: 6 persons E3 - large hiatal hernias: 2 persons E3 - ovarian cyst ≥3cm: 2 persons E3 - Abdominal aortic aneurysm ≥3cm: 2 persons	Evaluation with imaging: 6 persons	NR	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
						E4: 6 persons E4 - abdominal aortic aneurysm ≥3cm: 3 persons E4 - renal solid mass: 2 persons E4 - liver solid mass: 1 person	Evaluation with imaging: 5		NR
Johnson, 2008[177] Good	Screening only	NR	NR**	All	2531	E2-E4: 1665 persons E3-E4††: 428 persons E4 (requiring urgent care): 30 persons	NR	NR	NR
				50-64 yrs	2054	E3-E4††: 104 persons E4 (requiring urgent care): 26 persons			
				≥65 yrs	477	E3-E4††: 324 persons E4 (requiring urgent care): 4 persons			
Kim, 2008[256] Fair	Screening only	1-3 yrs	C-RADS	Total	2230	E2-E4: 1484 persons (2186 findings) E2: 1707 findings E3: 358 findings E4: 115 persons (115 findings)	Diagnostic workup: 100 persons Surgical or medical treatment: 45 persons	Renal cell cancer: 5 persons Hepatocellular cancer: 3 persons Pancreatic cancer: 1 person Lung cancer: 1 person Cervical cancer: 1 person Stomach cancer: 1 person Malignancy after diagnostic workup: 12 persons	Of 12 persons with malignancies after diagnostic workup: "Curative surgery": 11 persons Treated with radiation therapy: 1 person
				Male	1338	E4: 70 findings Any extracolonic findings: 944 persons		Malignancy after diagnostic workup: 8 persons	
				Female	892	E4: 45 findings Any extracolonic findings: 540 persons		Malignancy after diagnostic workup: 4 persons	

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Pickhardt, 2008[278]§ Fair	Screening only	1.6 (18 mos)	C-RADS	Total	2195	E4: 204 persons	Diagnostic workup recommended: 157 persons Diagnostic workup: 133 persons Surgical or medical treatment: 22 persons	Diagnosis of an unsuspected condition of at least moderate importance: 55 persons	NR
								Benign ovarian tumor: 13 persons	NR
								Malignant tumor: 9 persons (3 non-Hodgkin lymphoma, 3 renal cell carcinoma, 2 abdominal metastatic disease, 1 bronchogenic carcinoma)	NR
								Aortoiliac aneurysm: 12 persons	NR
								Congenital renal anomaly: 4 persons	NR
								Obstructing urolithiasis: 3 persons	NR
Kim, 2007[254]§ Fair	Screening only	NR	C-RADS	Total	3120	E2: 1490 persons E3: 265 persons E4: 70 persons	Diagnostic workup: 241 persons	Extra-colonic cancer: 8 persons (Treatment NR; 3 renal cancers, 2 bronchogenic cancers, 1 non-Hodgkin's lymphoma, 1 endometrial cancer, 1 GI stromal tumor)	NR
Pickhardt, 2007[280]§ ‡‡ Fair	Mixed (including symptomatic)	NR	NR	Total	2014	Gastrointestinal: 10 persons	Diagnostic workup: 10 persons Surgical resection: 7 persons Endoscopic resection: 1 person	NR	NR
	Screening only	2 yrs		Total	432	E2-E4: 118 persons‖‖ E3-E4††: 32 persons		Renal cell cancer: 1 person	All patients with relevant ECFs

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Chin, 2005[224] Fair			Clinically relevant §§**				Diagnostic evaluation: 32 persons	Abdominal aortic aneurysms: 6 persons	"have been followed up clinically and radiologically for a minimum of 2 years, however, none have progressed to require intervention." 1 person with renal cell cancer "is likely to have benefited in terms of mortality from participation in CTC screening program"
								Benign lesions: 24 persons	
								Splenic artery aneurysm: 1 person	
				Female	202	E3-E4: 14 persons		NR	
				Male	230	E3-E4: 18 persons		NR	
Ginnerup Pedersen, 2003[238] Fair	Screened positive (FIT+, FOBT+)	6 mos	NR**	Total	75	E2-E4: 49 persons E3-E4††: 9 persons	Diagnostic workup: 8 persons Underwent surgery¶¶: 2 persons	Lung cancer: 1 person	Lung resection. Recurrent disease, died 1 year after surgery
								Fatty sparing hepatic mass: 1 person	NR
								Renal cyst: 1 person	NR
								Adrenal incidentaloma: 2 persons	NR
								Endometrioma: 1 person	Experienced surgical draining of infection after exam
								Ovarian cyst ≥4cm: 1 person	NR
								Fibromatous uterus: 1 person	NR
				Female	35	E2-E4: 23 persons E3-E4: 5 persons		NR	NR
				Male	40	E2-E4: 26 persons E3-E4: 4 persons		NR	NR

Table 28. Key Question 3: Extracolonic Findings

Author, year Quality	Population	Follow up	Category of ECF findings	Group	N	Prevalence of extracolonic findings	Further evaluation or medical / surgical treatment	Findings of diagnostic evaluation	Longer-term clinical followup
Gluecker, 2003[239] Fair	Mixed (including symptomatic)	≥12 mos	High, moderate, low importance##	Total	681	E2-E4: 469 persons (858 findings) E2: 341 persons (574 findings) E3: 183 persons (196 findings) E4: 71 persons (88 findings)	Diagnostic workup: 109 procedures*** Surgical or medical treatment: 9 persons†††	NR	NR
Pickhardt, 2003[195]‡‡‡ Good	Screening only	NR	High, moderate, low importance##	All	1233	E4: 56 persons	Required diagnostic imaging: NR Underwent successful repair of unsuspected abdominal aortic aneurysms: 2 persons	Extra-colonic malignancy: 5 persons (1 lymphoma, 2 bronchogenic carcinoma, 1 ovarian cancer, 1 renal cancer)	Underwent "successful repair" of unsuspected abdominal aortic aneurysms: 2 persons
Hara, 2000[242] Fair	Screening only	7-22 mos	High, moderate, low importance##	Total	264	E2-E4: 109 persons E2: 55 persons E3: 46 persons E4: 30 persons	Diagnostic workup: 18 persons Required ongoing followup: 4 persons Surgical or medical treatment: 6 persons	Renal cell cancer: 2 persons (required surgery)	Both patients "underwent nephrectomy and had no metastases"
								Abdominal aortic aneurysms: 2 persons	NR
								Pneumothorax: 1 person (required surgery)	NR
								Intermediate lesions: 4 persons (2 pulmonary nodules, 2 probable adrenal adenomas)	NR
								Benign lesions: 9 persons (Renal cysts 4, pulmonary granuloma 1, liver with focal fat 1, 4.2 cm AAA 1, hepatic cyst 1, splenic cyst 1)	NR

* New diagnoses were: 16 (0.54%) masses (including 3 gastrointestinal extracolonic tumors, 4 urinary tract masses, 4 ovarian masses or complex cysts, 1 adrenal mass, 2 pancreatic masses, 1 adenopathy, and 1 liver mass) and 9 (0.3%) aneurysms (including 8 aortic aneurysms).

Table 28. Key Question 3: Extracolonic Findings

†Evaluated genitourinary findings only. Major: high clinical importance, required definitive management; Moderate: Potential moderate clinical significance; Minor: no or little clinical importance
‡ Consists of 16 persons with adrenal masses on CTC and 9 with renal masses on CTC
§ Overlapping populations from the University of Wisconsin screening program
‖ Evaluated renal masses only. Benign renal mass defined as masses containing fat or with attenuation less than 20 HU or greater than 70 HU without thickened walls or septations, three or more septations, mural nodules, or thick calcifications. Indeterminate renal mass defined as attenuation between 20 and 70 HU or any with without thickened walls or septations, three or more septations, mural nodules, or thick calcifications.
Evaluated hiatal hernias only
** Definitions for extracolonic findings in the publication are similar to C-RADS E1-E4 definitions and have been labeled as such
†† Likely includes a portion of extracolonic findings corresponding to C-RADS E3
‡‡ Only evaluated extracolonic GI tumors
§§ Required medical or surgical attention, or further hematological, biochemical, and/or radiological investigation after reviewing patient's medical history
‖‖ All patients followed for ≥2 yrs; none progressed to require intervention
¶¶ Underwent surgery because of the workup or because of complications of the workup
High importance: findings requiring surgical treatment, medical intervention, and/or further investigation during that patient care visit [similar to C-RADS E4], Moderate importance: benign findings that may eventually require medical or surgical intervention [similar to C-RADS E3], Low importance: unlikely to require any future treatment [similar to C-RADS E2]
*** 94 procedures in patients with high clinical importance, 15 procedures in patients with moderate clinical importance
††† 1 abdominal aortic aneurysm, 1 squamous cell carcinoma of the lung, 1 thyroid metastases to the lung, 1 renal adenocarcinoma, 1 renal oncocytoma, 3 serous cystadenoma of the ovary, 1 ileal ascariasis
‡‡‡ From University of Wisconsin screening program but in a non-overlapping time frame.
Abbreviations: Cat = Categorization; C-RADS = CT Colonography Reporting and Data System; E1 = normal examination or anatomic variant; E2 = clinically unimportant finding; E3 = findings unlikely to be clinically significant; E4 = potentially clinically important findings; ECF = Extracolonic findings; F/U = Followup; Hx = History; Mos = Months; NR = not reported; Yrs = Years

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1 FS	k=4 RCT n=458,002	One- or two-time FS decreased CRC mortality compared to no screening at 11-17 years follow-up (IRR 0.74 [95% CI 0.68 to 0.80]).	Consistent Precise	Only PLCO evaluated more than 1 round of screening. Variation in referral criteria led to differing rates of followup colonoscopy.	High	No longer widely used in the US. No studies included people under age 50 years.
KQ1 Colonoscopy	k=2 Cohort n=436,927	One study found CRC mortality was lower in people with at least one screening colonoscopy versus those who never had a screening colonoscopy after 24 years follow-up (adj HR 0.32 [95% CI, 0.24 to 0.45]). Another study in people age 70-74 years found CRC incidence was lower in people who had a screening colonoscopy versus those who did not after 8 years (standardized risk 0.42% [95% CI, 0.24 to 0.63]).	Consistent Imprecise	Variation in underlying risk for CRC, length of followup and outcomes reported (only one study reported CRC mortality).	Low	Studies limited to health professionals and older adults. Based on subgroup analyses, findings not applicable to people with FDR of CRC or adults age 75-79. One study included people under age 50 years.
KQ1 CTC	k=0	NA (see comparative effectiveness)	NA	NA	Insufficient	NA
KQ1 Capsule endoscopy	k=0	NA	NA	NA	Insufficient	NA
KQ1 gFOBT	k=6 RCT n=780,458	Biennial screening with Hemoccult II decreased CRC-specific mortality compared to no screening after 2-9 rounds of screening at 11-30 years of followup (range: RR 0.91 [95% CI 0.84, 0.98] at 19.5 years; RR 0.78 [95% CI 0.65, 0.93] at 30 years). One trial in Finland (n=360,492) has only interim findings, with a followup of 4.5 years.	Consistent Precise	Variation in number of screening rounds, use of rehydrated samples, definition of test positive and recommended followup testing.	High	Hemoccult II no longer widely used. Three trials included people younger than age 50 years.
KQ1 FIT	k=1 Cohort n=5,417,699	One to three rounds of biennial FIT were associated with lower CRC mortality compared to no screening at up to 6 years follow-up (adj RR 0.90 [95%CI 0.84, 0.95]).	NA	Limited follow-up (mean 3 years).	Low	Study conducted in TWN. FITs used include OC Sensor and HM JACK. Did not include participants younger than age 50 years.

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1 sDNA	k=0	NA	NA	NA	Insufficient	NA
KQ1 Serum	k=0	NA	NA	NA	Insufficient	NA
KQ1 Urine	k=0	NA	NA	NA	Insufficient	NA
KQ1 Comparative effectiveness	k=20 RCT n=386,711 k=1 Cohort n=85,149	Trials comparing different screening tests do not provide evidence of comparative benefit on CRC incidence or mortality outcomes† Limited data suggests: 4 rounds of FIT detects a similar number of cancers as one-time colonoscopy or FS; FIT can detect more cancers than Hemoccult II; 2-sample FIT does not appear superior to 1-sample FIT; and no statistically significant differences in cancer detection after 1-2 rounds of testing between FITs despite differences in test positivity.	Inconsistent Imprecise	Few trials powered to detect screening impact on mortality; limited to a single round of screening. Overall low number of cancers detected, and few interval cancers reported.	Insufficient	No studies evaluating comparative effectiveness of capsule endoscopy, sDNA, serum, or urine tests. No studies included people younger than age 50 years.
KQ2 FS	0	NA	NA	NA	Insufficient	NA
KQ2 Colonoscopy	K=4 Colo+CTC reference standard N=4821	CRC: Sensitivity ranged from 0.18 to 1.0 (95% CI range, 0.01 to 1.0) Adenoma ≥10mm: Sensitivity ranged from 0.89 to 0.95 (95% CI range 0.74, 1.0) Specificity = 0.89 (95% CI, 0.86 to 0.91) Adenoma ≥6mm: Sensitivity ranged from 0.75 to 0.93 (95% CI range, 0.63 to 0.96) Specificity = 0.94 (95% CI, 0.92 to 0.96)	Consistent Imprecise	Studies not designed to assess diagnostic accuracy to detect cancers. Specificity could only be calculated from 1 study.	Moderate	Colonoscopies were conducted or supervised by ‘experienced’ specialists. Two studies included people younger than age 50 years (one only if they had a family history).

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ2 CTC	k=9 Colo+CTC reference standard n=6,497	CRC:‡ Sensitivity ranged from 0.86 to 1.0 (95% CI range, 0.21 to 1.0) Adenoma ≥10 mm:‡ Sensitivity 0.89 (95% CI, 0.83 to 0.96; I^2=41.7%) Specificity 0.94 (95% CI, 0.89 to 1.0; I^2=98.3%) Adenoma ≥6 mm:‡ Sensitivity 0.86 (95% CI, 0.78 to 0.95; I^2=87.4%) Specificity 0.88 (95% CI, 0.83 to 0.95; I^2=94.9%)	CRC: Consistent Imprecise Adenomas: Consistent Precise	Studies not designed to assess diagnostic accuracy to detect cancers. Unclear if variation in test performance Is due to differences in study design, population, CTC imaging or reader experience or reading protocols.	Moderate	Estimates apply to CTC with full bowel prep. Mostly single center studies using limited number of highly trained radiologists; current practice may use lower doses of radiation (and therefore different technology/protocols). Four studies included people younger than age 50 years (two only if they had a family history).
KQ2 Capsule endoscopy	k=2 Colo reference standard n=920	CRC: No estimate Adenoma ≥10 mm: Sensitivity ranged from 0.92 to 1.0 (95% CI, 0.70 to 1.0) Specificity ranged from 0.95 to 0.98 (95% CI, 0.93 to 0.99) Adenoma ≥6 mm: Sensitivity = 0.91 (95% CI, 0.85 to 0.95) Specificity = 0.83 (95% CI, 0.80 to 0.86)	NA	Two small studies. Not designed to assess test accuracy to detect cancers. High proportion of incomplete or inadequate exams.	Insufficient for CRC Low for adenomas	Estimates apply to second generation capsule endoscopy, PillCam COLON 2. Currently only FDA approved for people with a prior incomplete colonoscopy. Did not include people younger than age 50 years.

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ2 High sensitivity gFOBT	k=2 Colo reference standard n=3503 k=3 Registry reference standard n=15,969	CRC: Sensitivity ranged from 0.50 to 0.75 (95% CI range 0.09, 1.0) Specificity ranged from 0.96 to 0.98 (95% CI range (0.95, 0.99) AA: Sensitivity ranged from 0.06 to 0.17 (95% CI range 0.02, 0.23) Specificity ranged from 0.96 to 0.99 (95% CI range 0.96, 0.99) Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry followup).	Inconsistent Imprecise	Only 2 studies without verification bias, with varying estimates.	Low	Estimates apply to Hemoccult SENSA, and test is no longer widely used in the US, requires 3 stool samples and dietary restrictions. Did not include people younger than age 50 years.
KQ2 FIT	k=25 Colo reference standard n=122,370 k=18 Registry reference standard n=2,824,358	CRC:§ Sensitivity = 0.74 (95% CI, 0.64 to 0.83; I^2=31.6%) Specificity = 0.94 (95% CI, 0.93 to 0.96; I^2=96.6%) AA:§ Sensitivity = 0.23 (95% CI, 0.20 to 0.25; I^2=47.4%) Specificity = 0.96 (95% CI, 0.95 to 0.97; I^2=94.8) Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry followup).	Consistent Precise	Other than OC-Sensor and OC-Light, FITs were not evaluated in more than a single study using colonoscopy reference standards.	High	Estimates apply to OC-Sensor family of FITs using manufacturer recommended cutoff.‖ OC-Light has similar sensitivity and specificity to OC-Sensor. Ten studies included people younger than age 50 years. No differences in test accuracy by age.

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ2 sDNA	k=4 Colo reference standard n=12,424	CRC: Sensitivity=0.93 (95% CI, 0.87 to 1.0; I^2=0%) Specificity=0.85 (95% CI, 0.84 to 0.86; I^2=37.7%) AA: Sensitivity=0.43 (95% CI, 0.40 to 0.46; I^2=0%) Specificity=0.89 (95% CI, 0.86 to 0.92; I^2=87.8%)	Consistent Precise	Only one study adequately powered to detect cancers.	Moderate	Estimates apply to Cologuard (sDNA-FIT). In the largest study 6% of people had inadequate stool samples. Two studies included people younger than age 50 years.
KQ2 Serum	k=1 Colo reference standard n=6857	CRC: Sensitivity = 0.68 (95% CI, 0.53 to 0.80) Specificity = 0.79 (95% CI, 0.77 to 0.81) AA: Sensitivity = 0.22 (95% CI, 0.18 to 0.24) Specificity = 0.79 (95% CI, 0.76 to 0.82)	NA (for consistency) Precise	Single nested case-control study.	Low	Estimates apply to Epi proColon, evaluating the mSEPT9 marker. Currently only FDA approved for people unwilling or unable to be screened by gFOBT, FIT, FS or colonoscopy. Did not include people younger than age 50 years.
KQ2 Urine	k=1 Colo reference standard n=228	CRC: No estimate AA: Sensitivity = 0.22 (95% CI, 0.18 to 0.24) Specificity = 0.79 (95% CI, 0.76 to 0.82)	NA	Single study with estimates derived using split-sample validation.	Insufficient	Estimates apply to PolypDx a metabolomic-based urine test. Majority of included people in study had a personal or family history of CRC or polyps. Included people younger than 50 years with a personal or family history.

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ3 FS	k=18 Observational n=395,077	Major bleeding: 0.5 bleeds per 10,000 procedures (95% CI, 0 to 1.3) Perforation: 0.2 perforations per 10,000 procedures (95% CI, 0.1, 0.4) Other serious harms: not routinely reported but cannot be attributed to FS procedure	Consistent Precise	No studies with control group (no FS). Possible reporting bias of harms other than bleeding and perforation.	Moderate	Reflects community practice, but FS no longer widely used in US practice. No studies included people younger than age 50 years.
KQ3 Screening colonoscopy	k=67 Observational n=27,746,669	Major bleeding: 14.6 (95% CI 9.4, 19.9) per 10,000 procedures Perforation: 3.1 (95% CI 2.3, 4.0) per 10,000 procedures Other serious harms: in 4 studies with comparator arms, similar or less frequent AEs in screened versus unscreened group	Consistent Precise	Limited (k=4) studies with unscreened comparison	Moderate	Reflects community practice. 21 studies included people younger than age 50 years. Risk of serious harms appears to increase with age.
KQ3 Followup colonoscopy	k=21 Observational n=903,872	Following abnormal stool testing Major bleeding: 17.5 (95% CI 7.6, 27.5) per 10,000 procedures Perforation: 5.7 (95% CI 2.8, 8.7) per 10,000 procedures Other serious harms: No estimate. Following abnormal FS Major bleeding: 20.7 (95% CI 8.2, 33.2) per 10,000 procedures Perforation: 12.0 (95% CI 7.5, 16.5) per 10,000 procedures Other serious harms: No estimate.	Consistent Precise	No studies with unscreened comparison	Moderate	Reflects community practice. Two studies following abnormal stool testing included people younger than age 50 years.

Table 29. Summary of Evidence

Key Question Instrument or Treatment	Studies (k) Study Designs, Observations (n)	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ3 CTC (harms)	k=19 Observational n=90,133	Serious harms from CTC in asymptomatic people are uncommon. The effective dose of radiation per exam ranged from 0.8 to 5.3 mSv.	Consistent Imprecise	No studies with control group (no CTC). More limited evidence in true average risk screening populations. Possible reporting bias of harms other than perforation.	Moderate	Reflects community practice. No studies included people younger than age 50 years.
KQ3 CTC (ECF)	k=27 Observational n=48,235	ECFs requiring workup of potentially important findings (E4) occurred in 1.3% to 11.4% of examinations. A minority of findings (≤3%) required definitive medical or surgical treatment, and extracolonic cancers were rarely detected (0.35%).	Consistent Imprecise	No studies able to quantify net benefit or harm. Studies with varying levels of followup, few studies with final disposition of ECF.	Low	ECF can be a benefit or a harm. Prevalence of ECF appears to increase with age. One study included people younger than age 50 years.
KQ3 Capsule endoscopy	k=1 Observational n=689	No serious harms reported.¶	NA	Single small study	Insufficient	NA
KQ3 Stool, serum and urine tests	k=0	No hypothesized serious harms from non-invasive testing other than diagnostic inaccuracy and follow-up testing (see followup colonoscopy).	NA	NA	NA	NA

† Several adequately powered comparative effectiveness studies are currently underway will evaluate the comparative effectiveness of direct visualization versus stool-based screening programs.
‡ CTC with bowel prep results, k=7, n=5328
§ FN: OC-Sensor results, k=13, n=44,597
‖ At lower cutoffs (15 and 10 µg Hb/g feces), the sensitivity for CRC increased (0.92 and 0.99, respectively) and the corresponding specificities decreased (0.92 and 0.90, respectively).
¶ Hypothesized harms based on studies in symptomatic persons include aspiration and capsule retention.

Abbreviations: AA = advanced adenoma; CI = confidence interval; Colo = colonoscopy; CTC = computed tomography colonography; ECF = extracolonic finding; FDA = Food and Drug Administration; FDR = first degree relative; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; HR = hazard ratio; IRR = incidence rate ratio; k = number of studies; kq = key question; n = number of observations; NA = not applicable; mSv = millisievert; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT = randomized controlled trial; RR = relative risk; sDNA = stool-based deoxyribonucleic acid.

Appendix A. Detailed Methods

Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
ab = word in abstract
ae = adverse effects
adj# = adjacent within x number of words
kf=keyword heading [word not phrase indexed]
kw=keyword
mo=mortality
pt = publication type
st=standards
ti = word in title

Cochrane Central Register of Controlled Clinical Trials
Issue 12 of 12, December 2019

#1 (colorectal or colon or colonic or rectal or rectum or rectosigmoid or adenomat*):ti,ab,kw near/3 (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplas* or polyp*):ti,ab,kw
#2 screen*:ti,ab,kw or detect*:ti,ab,kw
#3 #1 and #2
#4 colonoscop*:ti,ab,kw
#5 colonograph*:ti,ab,kw
#6 sigmoidoscop*:ti,ab,kw
#7 capsule:ti,ab,kw near/2 endoscop*:ti,ab,kw
#8 "pill camera":ti,ab,kw
#9 "pill cam":ti,ab,kw
#10 "pillcam":ti,ab,kw
#11 (fecal or faecal or stool):ti,ab,kw near/5 molecular*:ti,ab,kw
#12 (fecal or faecal or stool):ti,ab,kw near/5 (DNA or "deoxyribonucleic acid"):ti,ab,kw
#13 (f-dna or fdna):ti,ab,kw
#14 (s-dna or sdna):ti,ab,kw
#15 (fecal or faecal or stool):ti,ab,kw near/5 test*:ti,ab,kw
#16 (fecal or faecal or stool):ti,ab,kw near/5 (immunochemical or immunoassay):ti,ab,kw
#17 (fecal or faecal or stool):ti,ab,kw next occult:ti,ab,kw
#18 "occult blood":ti,ab,kw
#19 guaiac:ti,ab,kw
#20 (FOBT or IFOBT):ti,ab,kw
#21 ("SEPTIN 9" or SEPT9 or mSEPT9):ti,ab,kw
#22 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 with Publication Year from 2015 to 2019, in Trials

MEDLINE search strategy

KQ1:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 16, 2019>, Ovid MEDLINE(R) Epub Ahead of Print < December 16, 2019>, Ovid MEDLINE(R) Daily Update < December 4, 2019>
Search Strategy:
----
1 Colonoscopy/
2 colonoscop$.ti,ab,kf.
3 Sigmoidoscopy/
4 sigmoidoscop$.ti,ab,kf.
5 Colonography, Computed Tomographic/
6 colonograph$.ti,ab,kf.
7 Occult Blood/
8 occult blood.ti,ab,kf.
9 ((fecal or faecal or stool) adj occult).ti,ab,kf.
10 (fobt or ifobt or gfobt).ti,ab,kf.
11 guaiac.ti,ab,kf.

12 ((fecal or faecal or stool) adj5 test$).ti,ab,kf.
13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab,kf.
14 Capsule Endoscopy/
15 Capsule Endoscopes/
16 (capsule adj2 endoscop*).ti,ab,kf.
17 pill cam*.ti,ab,kf.
18 pillcam.ti,ab,kf.
19 DNA/
20 DNA Methylation/
21 DNA Mutational Analysis/
22 DNA, neoplasm/
23 19 or 20 or 21 or 22
24 Feces/
25 23 and 24
26 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab,kf.
27 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab,kf.
28 ((fecal or faecal or stool) adj5 molecular).ti,ab,kf.
29 (f-dna or fdna or s-dna or sdna).ti,ab,kf.
30 "SEPT9 protein, human".nm.
31 Septins/
32 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab,kf.
33 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 Mass screening/ or "Early Detection of Cancer"/
35 (screen$ or detect$).ti,ab,kf.
36 34 or 35
37 33 and 36
38 Colorectal Neoplasms/
39 Adenomatous Polyposis Coli/
40 Colonic Neoplasms/
41 Sigmoid Neoplasms/
42 Colorectal Neoplasms, Hereditary Nonpolyposis/
43 Rectal Neoplasms/
44 Anus Neoplasms/
45 Anal Gland Neoplasms/
46 Colonic Polyps/
47 Adenomatous Polyps/
48 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab,kf.
50 limit 49 to ("in data review" or in process or "pubmed not medline")
51 48 or 50
52 (screen$ or detect$).ti.
53 51 and (34 or 52)
54 37 or 53
55 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
56 meta-analysis as topic/
57 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.
58 control groups/ or double-blind method/ or single-blind method/
59 Random$.ti,ab,kf.
60 clinical trial$.ti,ab,kf.
61 controlled trial$.ti,ab,kf.
62 meta analy$.ti,ab,kf.
63 Cohort Studies/
64 cohort*.ti,ab,kf.
65 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66 54 and 65
67 Mortality/
68 mortality.fs.
69 Survival rate/
70 Survival analysis/

71 Life Expectancy/
72 "Cause of Death"/
73 mortality.ti,ab,kf.
74 (death or deaths).ti,ab,kf.
75 survival.ti,ab,kf.
76 (registry or registries).ti,ab,kf.
77 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78 54 and 77
79 66 or 78
80 limit 79 to humans
81 limit 79 to animals
82 81 not 80
83 79 not 82
84 limit 83 to english language
85 limit 84 to yr="2015 -Current"
86 remove duplicates from 85

KQ2:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 16, 2019>, Ovid MEDLINE(R) Epub Ahead of Print < December 16, 2019>, Ovid MEDLINE(R) Daily Update < December 4, 2019>

Search Strategy:
----
1 Colonoscopy/
2 colonoscop$.ti,ab,kf.
3 Sigmoidoscopy/
4 sigmoidoscop$.ti,ab,kf.
5 Colonography, Computed Tomographic/
6 colonograph$.ti,ab,kf.
7 Occult Blood/
8 occult blood.ti,ab,kf.
9 ((fecal or faecal or stool) adj occult).ti,ab,kf.
10 (fobt or ifobt or gfobt).ti,ab,kf.
11 guaiac.ti,ab,kf.
12 ((fecal or faecal or stool) adj5 test$).ti,ab,kf.
13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab,kf.
14 Capsule Endoscopy/
15 Capsule Endoscopes/
16 (capsule adj2 endoscop*).ti,ab,kf.
17 pill cam*.ti,ab,kf.
18 pillcam.ti,ab,kf.
19 DNA/
20 DNA Methylation/
21 DNA Mutational Analysis/
22 DNA, neoplasm/
23 19 or 20 or 21 or 22
24 Feces/
25 23 and 24
26 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab,kf.
27 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab,kf.
28 ((fecal or faecal or stool) adj5 molecular).ti,ab,kf.
29 (f-dna or fdna or s-dna or sdna).ti,ab,kf.
30 "SEPT9 protein, human".nm.
31 Septins/
32 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab,kf.
33 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 "Sensitivity and Specificity"/
35 "Predictive Value of Tests"/
36 ROC Curve/
37 False Negative Reactions/
38 False Positive Reactions/

39 Diagnostic Errors/
40 "Reproducibility of Results"/
41 Reference Values/
42 Reference Standards/
43 Observer Variation/
44 Receiver operat$.ti,ab,kf.
45 ROC curve$.ti,ab,kf.
46 sensitivit$.ti,ab,kf.
47 specificit$.ti,ab,kf.
48 predictive value.ti,ab,kf.
49 accuracy.ti,ab,kf.
50 false positive$.ti,ab,kf.
51 false negative$.ti,ab,kf.
52 miss rate$.ti,ab,kf.
53 error rate$.ti,ab,kf.
54 detection rate$.ti,ab,kf.
55 diagnostic yield$.ti,ab,kf.
56 likelihood ratio$.ti,ab,kf.
57 diagnostic odds ratio$.ti,ab,kf.
58 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59 33 and 58
60 Colonoscopy/st
61 Sigmoidoscopy/st
62 Colonography, Computed Tomographic/st
63 Capsule Endoscopy/st
64 60 or 61 or 62 or 63
65 59 or 64
66 Mass screening/ or "Early Detection of Cancer"/
67 (screen$ or detect$).ti,ab,kf.
68 66 or 67
69 65 and 68
70 limit 69 to humans
71 limit 69 to animals
72 71 not 70
73 69 not 72
74 limit 73 to english language
75 limit 74 to yr="2015 -Current"
76 remove duplicates from 75

KQ3

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 16, 2019>, Ovid MEDLINE(R) Epub Ahead of Print < December 16, 2019>, Ovid MEDLINE(R) Daily Update < December 4, 2019>

Search Strategy:

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1 Colonoscopy/ae, mo [Adverse Effects, Mortality] (2016)
2 Sigmoidoscopy/ae, mo
3 Colonography, Computed Tomographic/ae, mo
4 Capsule Endoscopy/ae, mo
5 Capsule Endoscopes/ae, mo
6 1 or 2 or 3 or 4 or 5
7 Colonoscopy/
8 Sigmoidoscopy/
9 Colonography, Computed Tomographic/
10 Occult Blood/
11 Capsule Endoscopy/
12 Capsule Endoscopes/
13 DNA/
14 DNA Methylation/
15 DNA Mutational Analysis/
16 DNA, neoplasm/

17 13 or 14 or 15 or 16
18 Feces/
19 17 and 18
20 "SEPT9 protein, human".nm.
21 Septins/
22 7 or 8 or 9 or 10 or 11 or 12 or 19 or 20 or 21
23 Colorectal Neoplasms/
24 Adenomatous Polyposis Coli/
25 Colonic Neoplasms/
26 Sigmoid Neoplasms/
27 Colorectal Neoplasms, Hereditary Nonpolyposis/
28 Rectal Neoplasms/
29 Anus Neoplasms/
30 Anal Gland Neoplasms/
31 Colonic Polyps/
32 Adenomatous Polyps/
33 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 Mass screening/ or "Early Detection of Cancer"/
35 (screen$ or detect$).ti.
36 33 and (34 or 35)
37 Mortality/
38 Morbidity/
39 Death/
40 Hemorrhage/
41 Gastrointestinal hemorrhage/
42 Postoperative hemorrhage/
43 Intraoperative complications/
44 Postoperative complications/
45 incidental findings/
46 (harm or harms or harmful or harmed).ti.
47 (adverse adj (effect$ or event$ or outcome$)).ti.
48 safety.ti.
49 complication$.ti.
50 (death or deaths).ti.
51 (hemorrhag$ or haemorrhag$).ti.
52 bleed$.ti.
53 (death or deaths).ti.
54 ((incidental or extracolonic) adj finding$).ti.
55 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 (964911)
56 (22 or 36) and 55
57 6 or 56
58 limit 57 to humans
59 limit 57 to animals
60 59 not 58
61 57 not 60
62 limit 61 to (english language and yr="2015 -Current")
63 colonoscop$.ti,ab,kf.
64 sigmoidoscop$.ti,ab,kf.
65 colonograph$.ti,ab,kf.
66 occult blood.ti,ab,kf.
67 ((fecal or faecal) adj occult).ti,ab,kf.
68 (fobt or ifobt or gfobt).ti,ab,kf.
69 guaiac.ti,ab,kf.
70 (capsule adj2 endoscop*).ti,ab,kf.
71 pill cam*.ti,ab,kf.
72 pillcam.ti,ab,kf.
73 ((fecal or faecal or stool) adj5 test$).ti,ab,kf.
74 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab,kf.
75 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab,kf.
76 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab,kf.
77 ((fecal or faecal or stool) adj5 molecular).ti,ab,kf.
78 (f-dna or fdna or s-dna or sdna).ti,ab,kf.

79 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab,kf.
80 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab,kf.
82 (screen$ or detect$).ti.
83 81 and 82
84 80 or 83
85 (harm or harms or harmful or harmed).ti,ab,kf.
86 (adverse adj (effect$ or event$ or outcome$)).ti,ab,kf.
87 safety.ti,ab,kf.
88 complication$.ti,ab,kf.
89 (death or deaths).ti,ab,kf.
90 (hemorrhag$ or haemorrhag$).ti,ab,kf.
91 bleed$.ti,ab,kf.
92 perforat$.ti,ab,kf.
93 ((incidental or extracolonic) adj finding$).ti,ab,kf.
94 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93
95 84 and 94
96 limit 95 to ("in data review" or in process or "pubmed not medline")
97 limit 96 to (english language and yr="2015 -Current")
98 62 or 97
99 remove duplicates from 98

PubMed search strategy [publisher-supplied references only]

#17 Search #13 AND #14 Filters: Publication date from 2015/01/01 to 2019/12/31; English

#16 Search #13 AND #14 Filters: Publication date from 2015/01/01 to 2019/12/31

#15 Search #13 AND #14

#14 Search publisher[sb]

#13 Search #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#12 Search ("septin 9"[ti] OR septin9[ti] OR sept9[ti])

#11 Search ("fecal occult"[ti] OR "faecal occult"[ti] OR “stool occult”[ti] OR "occult blood"[ti] OR FOBT[ti] OR IFOBT[ti])

#10 Search (fecal[ti] OR faecal[ti] OR stool[ti]) AND (immunochemical[ti] OR immunoassay[ti])

#9 Search (fdna[ti] OR f-dna[ti] OR sdna[ti] OR s-dna[ti])

#8 Search (fecal[ti] OR faecal[ti] OR stool[ti]) AND (molecular[ti] OR genetic[ti] OR genetics[ti])

#7 Search (fecal[ti] OR faecal[ti] OR stool[ti]) AND (DNA[ti] OR "deoxyribonucleic acid"[ti])

#6 Search "pill cam"[ti] OR pillcam[ti]

#5 Search capsule[ti] AND endoscop*[ti]

#4 Search (colonoscop*[ti] OR colonograph*[ti] OR sigmoidoscop*[ti])

#3 Search #1 AND #2

#2 Search (screen*[ti] OR detect*[ti] OR surveillance[ti])

#1 Search (colorectal[ti] OR colon[ti] OR colonic[ti] OR rectal[ti] OR rectum[ti] OR rectosigmoid*[ti] OR adenoma*[ti]) AND (cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR malignan*[ti] OR tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti] OR neoplas*[ti] OR polyp[ti] OR polyps[ti] OR polyposis[ti])

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Populations	Adults age ≥40 years in average-risk or unselected populations; screening populations (i.e., no symptoms)	Populations selected for personal or family history of colorectal cancer (e.g., one or more first-degree relatives with colorectal cancer diagnosed before age 60 years or two or more first-degree relatives diagnosed at any age), known genetic susceptibility syndromes (e.g., Lynch Syndrome, familial adenomatous polyposis), or personal history of inflammatory bowel disease; nonscreening populations (e.g., persons who have symptoms, test positive on screening, have iron deficiency anemia, or are under surveillance for a previous colorectal lesion)
Settings	Settings representative of community practice for flexible sigmoidoscopy and colonoscopy studies; studies conducted in developed countries (categorized as "very high" on the 2017 Human Development Index,[a] as defined by the United Nations Development Programme)	Primarily research-based settings for endoscopy studies (e.g., small studies aimed at evaluating new endoscopy technologies, studies with operator or resource characteristics that are not applicable to community practice); developing countries
Screening tests	**KQ 1:** Any program of colorectal cancer screening, including endoscopy, imaging, urine, stool or blood testing **KQs 2, 3:** *Direct visualization tests:* • Colonoscopy • Flexible sigmoidoscopy • Computed tomography colonography • Capsule endoscopy[b] *Stool-based tests:* • High-sensitivity guaiac fecal occult blood test • Fecal immunochemical test (quantitative and qualitative testing) • Stool DNA test (with or without fecal immunochemical testing) *Serum-based test:* • Circulating methylated septin 9 gene DNA test (m*SEPT9*)[b] *Urine-based test*	**KQs 2, 3:** New technologic enhancements to colonoscopy or computed tomography colonography; Hemoccult II (review of test performance and harms limited to high-sensitivity guaiac fecal occult blood test); stool testing using in-office digital rectal examination; double-contrast barium enema; magnetic resonance colonography
Comparisons	**KQ 1:** No screening or alternate screening strategy **KQ 2:** Diagnostic accuracy studies that use colonoscopy as a reference standard **KQ 3:** No comparator necessary	

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Outcomes	**KQ 1:** Colorectal cancer incidence (by stage and location) or interval colorectal cancer; colorectal cancer–specific or all-cause mortality **KQ 2:** Test accuracy, including: sensitivity and specificity (per person for all tests and per lesion for direct visualization tests), positive and negative predictive value (per person for all tests and per lesion for direct visualization tests), and false-positive and false-negative rates; for colorectal cancer, advanced adenoma (high-grade dysplasia, villous histology, and/or size ≥10 mm), or adenomatous or sessile serrated polyps by size (i.e., ≤5 mm, 6 to 9 mm, ≥10 mm) or by location (e.g., proximal or distal colon, rectum) **KQ 3:** Serious harms requiring unexpected or unwanted medical attention (e.g., requiring hospitalization) and/or resulting in death, including but not limited to perforation, major bleeding, severe abdominal symptoms, and cardiovascular events; extracolonic findings and subsequent diagnostic workup, and adverse events from diagnostic testing for incidental findings on computed tomography colonography; radiation exposure per each computed tomography colonography examination	**KQ 1:** Incidence of adenomas or advanced neoplasia (composite outcome of advanced adenomas and colorectal cancer) **KQ 3:** Minor harms, defined as those not necessarily needing or resulting in medical attention (e.g., patient dissatisfaction, anxiety or worry, minor gastrointestinal complaints)
Study design	**All KQs:** Fair- to good-quality studies **KQ 1:** Randomized, controlled trials; controlled clinical trials; prospective cohort studies **KQ 2:** Randomized, controlled trials; controlled clinical trials; cohort studies, nested case-control diagnostic accuracy studies, and screening registry studies **KQ 3:** Randomized, controlled trials; controlled clinical trials; large screening registry or database observational studies, cohort studies, or systematically selected case series	**All KQs:** Poor-quality studies **KQ 1:** Decision analyses[c] **KQ 2:** Diagnostic accuracy studies without a reference standard or without representation of a full spectrum of disease (e.g., case-control studies, studies that excluded indeterminate results) **KQ 3:** Case studies

[a] Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Montenegro, Netherlands, New Zealand, Norway, Oman, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK, United Arab Emirates, Uruguay, US. Taiwan is not incorporated into HDI calculations for the People's Republic of China and will be considered very high HDI based on calculations from Taiwan's government.
[b] Technologies with conditional approval by the U.S. Food and Drug Administration for screening for colorectal cancer.
[c] This review will be accompanied by commissioned collaborative microsimulation decision analyses by CISNET.

Abbreviations: CCT = controlled clinical trial; CRC = colorectal cancer; CTC = computed tomography colonography; DRE = digital rectal exam; FIT = fecal immunochemical test; FIT-DNA = fecal immunochemical test plus deoxyribonucleic acid; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GI = gastrointestinal; mm = millimeter; MRC = magnetic resonance colonography; NPV = negative predictive value; PPV = positive predictive value; RCT = randomized controlled trial

Appendix A Table 2. Quality Assessment Criteria*

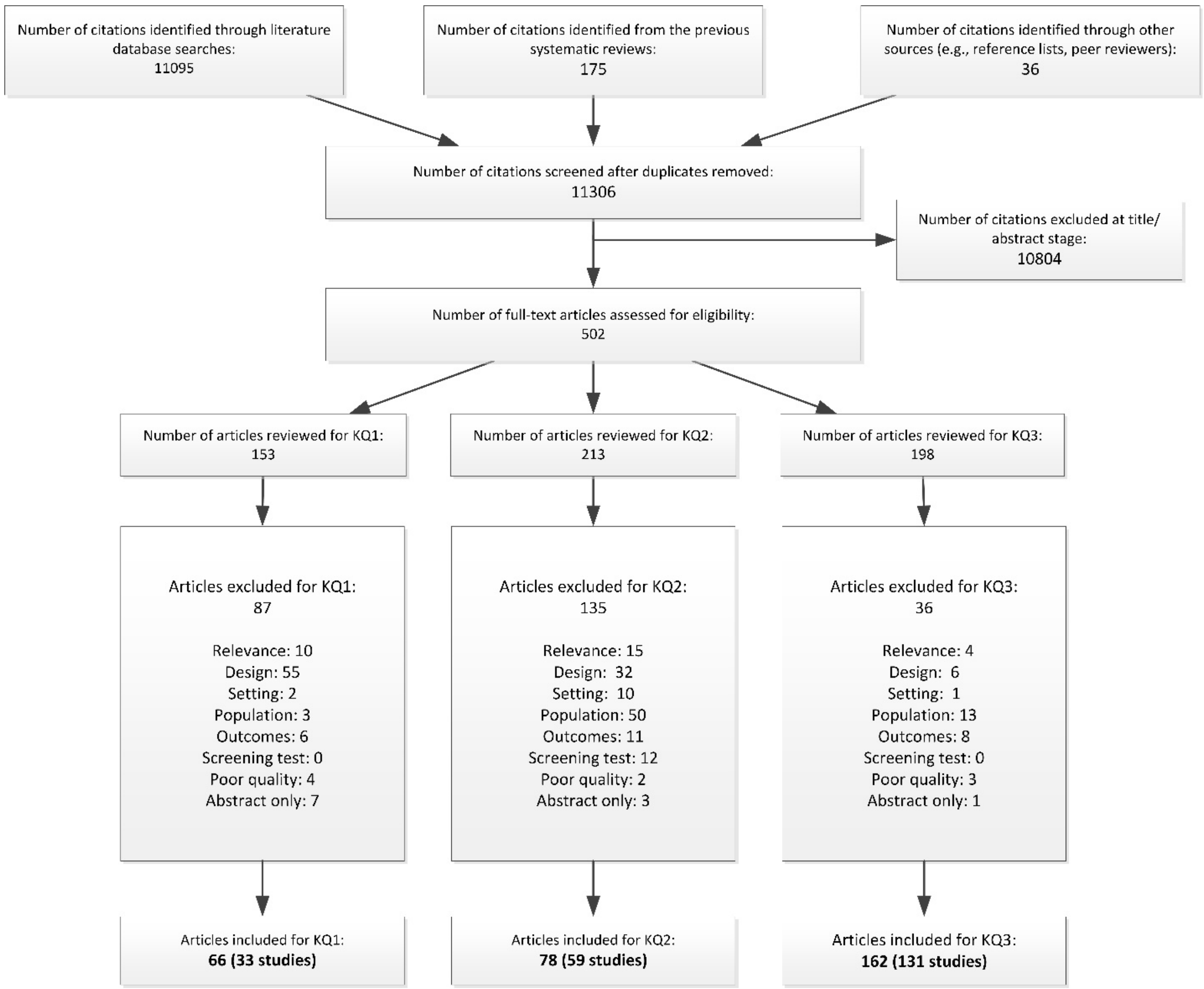
Study Design	Adapted Quality Criteria
Cohort studies, adapted from Newcastle-Ottawa Scale[1]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported
Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II[2] instrument	**Patient Selection** • Was a consecutive or random sample of patients enrolled? • Did the study avoid inappropriate exclusions? **Index Test** • Were the index test results interpreted without knowledge of the reference standard results? • If a threshold was used, was it prespecified or was a range of values presented? **Reference Standard** • Is the reference standard likely to correctly classify the target condition? • Were the reference standard results interpreted without knowledge of the index test? • Were staff trained in the use of the reference standard? • Was fidelity of the reference standard monitored or reported? **Flow and Timing** • Was there an appropriate interval between the index test and reference standard? • Did all patients receive a reference standard? • Did all patients receive the same reference standard? o Were all patients included in the analysis?

Appendix A Table 2. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized clinical trials, adapted from U.S. Preventive Services Task Force Manual[3]	**Bias arising in the randomization process or due to confounding** Valid random assignment/random sequence generation method used Allocation concealed Balance in baseline characteristics **Bias in selecting participants into the study** CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** Fidelity to the intervention protocol Low risk of contamination between groups Participants were analyzed as originally allocated **Bias from missing data** No, or minimal, post-randomization exclusions Outcome data are reasonably complete and comparable between groups Reasons for missing data are similar across groups Missing data are unlikely to bias results **Bias in measurement of outcomes** Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* All randomized clinical trials were classified as good, fair, or poor according to the USPSTF Procedure Manual[3]

Appendix A Figure 1. Literature Flow Diagram



Below is a list of included studies and their ancillary publications (indented below main results publication):

Key Question 1

1. Atkin WS, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet*. 2017;389(10076):1624-33. PMID: 28236467. https://dx.doi.org/10.1016/S0140-6736(17)30396-3
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    b. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375(9726):1624-33. https://dx.doi.org/10.1016/S0140-6736(10)60551-X
    c. Miles A, Wardle J, McCaffery K, et al. The effects of colorectal cancer screening on health attitudes and practices. *Cancer Epidemiol Biomarkers Prev*. 2003;12(7):651-5. PMID: 12869406.

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7. Garcia-Albeniz X, Hsu J, Bretthauer M, et al. Effectiveness of screening colonoscopy to prevent colorectal cancer among Medicare beneficiaries aged 70 to 79 years: a prospective observational study. *Ann Intern Med*. 2017;166(1):18-26. PMID: 27669524.

https://dx.doi.org/10.7326/M16-0758

8. Grobbee EJ, van der Vlugt M, van Vuuren AJ, et al. Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2019;13:13. https://dx.doi.org/10.1016/j.cgh.2019.08.015

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    c. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *Ann Intern Med.* 2014;312(6):606-15. PMID: 29710125
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PLCO cancer screening trial. *Lancet Gastroenterol Hepatol*. 2019;4(2):101-10. PMID: 30502933. https://dx.doi.org/10.1016/S2468-1253(18)30358-3

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b. Laiyemo AO, Doubeni C, Pinsky PF, et al. Occurrence of distal colorectal neoplasia among whites and blacks following negative flexible sigmoidoscopy: an analysis of PLCO Trial. *J Gen Intern Med*. 2015;30(10):1447-53. PMID: 25835747. https://dx.doi.org/10.1007/s11606-015-3297-3
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Key Question 2

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Key Question 3

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Appendix B. Excluded Studies

Code	Exclusion Criteria
E1	Study relevance
E1a	Study relevance: Primary aim technology improvements
E2	Study design: Not an included study design (e.g., non-nested case-control)
E2a	Study design: No reference standard
E2b	Study design: Case report
E3	Setting (e.g., not a very high HDI country)
E4	Population
E4a	Population: High-risk or symptomatic
E5	Outcomes: No relevant outcomes or incomplete outcomes
E5a	Outcomes: No additional relevant data (primary article included)
E6	Screening Test: Not one of the specified screening tests (including outdated technology)
E7	Study quality (including a reference standard not applied to any screen negatives or a random subset of screen negatives)
E8	Key existing SER with out of date MA
E9	Abstract only
KQ	Key Question

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Adler, A, Wegscheider, K, et al. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3). *Gut*. 62(2):236-241. 2013. PMID: 22442161.	KQ3E5
Adrian-de-Ganzo, Z, Alarcon-Fernandez, O, et al. Uptake of colon capsule endoscopy vs colonoscopy for screening relatives of patients with colorectal cancer. *Clin Gastroenterol Hepatol*. 13(13):2293-301.e1. 2015. PMID: 26133904. https://dx.doi.org/10.1016/j.cgh.2015.06.032	KQ2E4a
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Amitay, EL, Cuk, K, et al. Factors associated with false-positive fecal immunochemical tests in a large German colorectal cancer screening study. *Int J Cancer*. 144:2419-242. 2018. PMID: 30411799. https://dx.doi.org/10.1002/ijc.31972	KQ1E1
Amitay, EL, Gies, A, et al. Fecal immunochemical tests for colorectal cancer screening: is fecal sampling from multiple sites necessary? *Cancers (Basel)*. 11(3):21. 2019. PMID: 30901946. https://dx.doi.org/10.3390/cancers11030400	KQ2E7
Aniwan, S, Ratanachu-Ek, T, et al. Impact of fecal Hb levels on advanced neoplasia detection and the diagnostic miss rate for colorectal cancer screening in high-risk vs. average-risk subjects: a multi-center study. *Clin Transl Gastroenterol*. 8(8):e113. 2017. PMID: 28796231. https://dx.doi.org/10.1038/ctg.2017.40	KQ2E3
Aniwan, S, Rerknimitr, R, et al. A combination of clinical risk stratification and fecal immunochemical test results to prioritize colonoscopy screening in asymptomatic participants. *Gastrointest Endosc*. 81(3):719-27. 2015. PMID: 25708760. https://dx.doi.org/10.1016/j.gie.2014.11.035	KQ2E3
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Baiocchi, GL, Mazzarri, G, et al. CT colonography for the detection of nonpolypoid colorectal lesions: a prospective series. *Ann Ital Chir*. 86:532-8. 2015. PMID: 26899231.	KQ2E1a
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Bjerrum, A, Andersen, O, et al. Colorectal cancer mortality 10 years after a single round of guaiac faecal occult blood test (gFOBT) screening: experiences from a Danish screening cohort. *BMJ Open Gastroenterol*. 3(1):e000120. 2016. PMID: 28074150. https://dx.doi.org/10.1136/bmjgast-2016-000120	KQ1E1
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Caron, M, Lamarre, G, et al. The fecal immunochemical test (fit): Selected aspects regarding its effectiveness for colorectal cancer screening in Quebec City. *Prev Med Rep*. 12:6-11. 2018. PMID: 30116704. https://dx.doi.org/10.1016/j.pmedr.2018.08.003	KQ2E4a
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Cock, C, Anwar, S, et al. Low sensitivity of fecal immunochemical tests and blood-based markers of DNA hypermethylation for detection of sessile serrated adenomas/polyps. *Dig Dis Sci*. 64(9):2555-2562. 2019. PMID: 30835026. https://dx.doi.org/10.1007/s10620-019-05569-8	KQ2E4a
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Cubiella, J, Castro, I, et al. Diagnostic accuracy of fecal immunochemical test in average- and familial-risk colorectal cancer screening. *United European Gastroenterol J*. 2(6):522-9. 2014. PMID: 25452848. https://dx.doi.org/10.1177/2050640614553285	KQ2E4
de Klerk, CM, Wieten, E, et al. Performance of two faecal immunochemical tests for the detection of advanced neoplasia at different positivity thresholds: a cross-sectional study of the Dutch national colorectal cancer screening programme. *Lancet Gastroenterol Hepatol*. 4(2):111-118. 2019. PMID: 30497962. https://dx.doi.org/10.1016/S2468-1253(18)30319-4	KQ2E2b
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Decker, KM, Nugent, Z, et al. Interval colorectal cancer rates after Hemoccult Sensa and survival by detection mode for individuals diagnosed with colorectal cancer in Winnipeg, Manitoba. *PLoS One*. 13(9):e0203321. 2018. PMID: 30180176. https://dx.doi.org/10.1371/journal.pone.0203321	KQ1E2a
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Garcia, M, Mila, N, et al. Fecal hemoglobin concentration as a measure of risk to tailor colorectal cancer screening: are we there yet?. *Eur J Cancer Prev*. 24(4):321-7. 2015. PMID: 25370684. https://dx.doi.org/10.1097/CEJ.0000000000000090	KQ2E1
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Appendix D Table 1. Included FIT Tests Grouped by FIT "Family"

Test Family	Test Names	Type of Test	Test Principle	Cutoff, ng Hb/mL buffer	Cutoff, µg Hb/g feces	Manufacturer
Hemosure	Hemosure	Qualitative	Immunochromatographic	50†	50*	W.H.P.M., Inc., Irwindale, CA
Hemoccult ICT	Hemoccult ICT, FlexSure OBT	Qualitative	Immunochromatographic	--	300*	Beckman Coulter, Inc
immoCARE-C	immoCARE-C, Hemocare	Qualitative	Immunochromatographic	50*	30*	CAREdiagnostica, Voerde, Germany
MonoHaem	MonoHaem	Qualitative	Immunochromatographic	--	1,050***	Silenus Laboratories Proprietary Ltd. , Wilmington, DE (distributor for Chemicon International, Inc)
QuickVue	QuickVue iFOB	Qualitative	Immunochromatographic	50*	50*	Quidel, San Diego, CA
OC-Light	OC-L FIT-CHEK (manual), OC-Light	Qualitative	Immunochromatographic	50*	10**	Eiken Chemical Co., Tokyo, Japan, distributed in the US by Polymedco, Inc., Cortlandt Manor, NY
OC-Sensor	OC FIT-CHEK (using the OC-Auto Micro 80 Analyzer) OC-Auto, OC-Micro (using OC-Auto reagents), OC-Diana, OC-Sensor (using OC-Sensor Diana reagents), OC-Auto Micro	Quantitative‡	Latex agglutination, measured as optical change	100*	20†	Eiken Chemical Co., Tokyo, Japan, distributed in the US by Polymedco, Inc., Cortlandt Manor, NY
OC-Hemodia	OC-Hemodia (manual) , OC-Hemodia (automated, since 2000), OC-Sensor micro (when using OC-Hemodia reagents)	Qualitative	Visual particle agglutination		40**	Eiken Chemical Co., Tokyo, Japan
Clearview (casette)	Clearview iFOB Complete (casette)	Qualitative	Immunochromatographic	50†	6 ug Hb†	Alere Inc., Waltham, MA
Clearview (test strip)	Clearview ULTRA iFOB (test strip)	Qualitative	Immunochromatographic	50[1]	50[1]	Inverness Medical Innovation, Inc., now Alere, Inc., Waltham, MA
FOB advanced	FOB advanced	Qualitative	Immunochromatographic	50†	--	ulti med, Ahrensburg, Germany
PreventID CC	PreventID CC	Qualitative	Immunochromatographic	10**	--	Preventis, Bensheim, Germany
Bionexia (Hb)	Bionexia FOBplus	Qualitative	Immunochromatographic	40†	--	Biomerieux, Marcy l'Etoile, France [originally supplied by Dima Diagnostika]
Bionexia (Hb-Hp)	Bionexia Hb-Hp Complex	Qualitative	Immunochromatographic	25†	--	Biomerieux, Marcy l'Etoile, France [originally supplied by Dima Diagnostika]

Appendix D Table 1. Included FIT Tests Grouped by FIT "Family"

Test Family	Test Names	Type of Test	Test Principle	Cutoff, ng Hb/mL buffer	Cutoff, µg Hb/g feces	Manufacturer
Magstream/ Hemselect	HemeSelect, Immudia HemSp	Qualitative	Reverse passive hemagglutination	Samples diluted 1:8 showing erythrocyte agglutinat-ion	100-200†	Fujirebio, Tokyo, Japan, distributed by Beckman-Coulter, Inc., Brea, CA
	Magstream 1000/Hem SP	Quantitative‡	Magnetic particle agglutination	20**	67**	Fujirebio, Tokyo, Japan
RIDASCREEN (Hb)	RIDASCREEN Hemoglobin	Quantitative‡	Enzyme immunoassay	--	2†	R-Biopharm AG, Darmstadt, Germany
RIDASCREEN (Hb-Hp)	RIDASCREEN Hemoglobin-Haptoglobin Complex	Quantitative‡	Enzyme immunoassay	--	2†	R-Biopharm AG, Darmstadt, Germany
FOB Gold	FOB Gold	Quantitative‡	Latex agglutination, measured as optical change	100 ** [CE marked for user-defined cutoff]	17**	Sentinel Diagnostics, Milan, Italy
Hemo Techt	Hemo Techt NS-Plus C system	Quantitative‡	Colloidal gold agglutination measured as optical change	--	19	Alfresa Pharma Co., Osaka, Japan
HM-JACK	HM-JACK	Quantitative‡	Latex agglutination, measured as optical change	8	20	Kyowa Medex Co., Ltd., Tokyo, Japan

[1] per Levy 2014[5]
* from FDA summary
† from manufacturer website or calculated from information provided
‡Quantitative results may be transformed into qualitative results using the manufacturer's or a user-defined cutoff. In the US, quantitative FITs have been FDA-cleared only for qualitative use.
** from published literature

Appendix D Table 2. Key Question 1: Direct Visualization Comparative Effectiveness Studies

Author, year (Trial name)	Round	Test	Test pos, %	Group analyzed	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Grobbee, 2019 (COCOS and others)[6]	1	Colonoscopy	NR	Total	9/1426	(0.63)	NR	NR
				Distal	4/1426	(0.28)	NR	NR
				Proximal	5/1426	(0.35)	NR	NR
				Stage I	7/1426	(0.49)	NR	NR
				Stage II	1/1426	(0.07)	NR	NR
				Stage III	1/1426	(0.07)	NR	NR
				Stage IV	0/1426	(0)	NR	NR
		FS	9.0	Total	13/2435	(0.53)	NR	NR
				Distal	11/2435	(0.45)	NR	NR
				Proximal	2/2435	(0.08)	NR	NR
				Stage I	10/2435	(0.41)	NR	NR
				Stage II	0/2435	(0)	NR	NR
				Stage III	3/2435	(0.12)	NR	NR
				Stage IV	0/2435	(0)	NR	NR
Regge, 2017[7] (Proteus 2)	1	CTC	10.2	Total	9/2673	(0.003)	NR	NR
				Male	7/1375	(0.005)	NR	NR
				Female	2/1298	(0.001)	NR	NR
		FS	10.1	Total	10/2595	(0.004)	NR	NR
				Male	5/1329	(0.004)	NR	NR
				Female	5/1266	(0.004)	NR	NR
Sali, 2016[8] (SAVE)	1	Colonoscopy	NR	Total	0/153	(0.0)	NR	NR
				Proximal	0/153	(0.0)	NR	NR
		CTC (Reduced cathartic preparation CTC + Full cathartic preparation CTC)	9.8	Total	7/1286	(0.005)	NR	NR
				Rectosigmoid	4/1286	(0.003)	NR	NR
				Proximal	3/1286	(0.002)	NR	NR

Appendix D Table 2. Key Question 1: Direct Visualization Comparative Effectiveness Studies

Author, year (Trial name)	Round	Test	Test pos, %	Group analyzed	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Stoop, 2012[9] (COCOS)	1	Colonoscopy	8.7	Total	7/1276	(0.005)	NR	NR
				Rectosigmoid	5/1276	(0.004)	NR	NR
				Proximal	2/1276	(0.002)	NR	NR
		CTC	8.6	Total	5/982	(0.005)	NR	NR
				Rectosigmoid	4/982	(0.004)	NR	NR
				Proximal	1/982	(0.001)	NR	NR
Segnan, 2007[10] (SCORE III)	1	Colonoscopy	5.1	Total	13/1596	(0.8)	NR	NR
		FS	7.2	Total	12/1922	(0.6)	NR	NR

Abbreviations: COCOS = COlonoscopy or COlonography for Screening; CRC = colorectal cancer; CTC = computed tomographic colonography; FS = flexible sigmoidoscopy; n = number; NR = not reported; SCORE = Screening for COlon Rectum.

Appendix D Table 3. Key Question 1: Direct Visualization vs. Stool Tests Comparative Effectiveness

Author, year	Round	Test	Test pos	Group analyzed	n CRC/ n Analyzed	(%)	N Interval CRC/n Analyzed	(%)
Grobbee, 2019 (COCOS and others)[6]	1	Colonoscopy	NR	Total	9/1426	(0.63)	1/NR	(0.01)
				Distal	4/1426	(0.28)	NR	NR
				Proximal	5/1426	(0.35)	NR	NR
				Stage I	7/1426	(0.49)	NR	NR
				Stage II	1/1426	(0.07)	NR	NR
				Stage III	1/1426	(0.07)	NR	NR
				Stage IV	0/1426	(0)	NR	NR
	1	FS	9.0	Total	13/2435	(0.53)	6/NR	(0.09)
				Distal	11/2435	(0.45)	NR	NR
				Proximal	2/2435	(0.08)	NR	NR
				Stage I	10/2435	(0.41)	NR	NR
				Stage II	0/2435	(0)	NR	NR
				Stage III	3/2435	(0.12)	NR	NR
				Stage IV	0/2435	(0)	NR	NR
	4	FIT	19.1	Total	83/10743	(0.77)	19/NR	(0.13)
				Distal	56/10743	(0.52)	NR	NR
				Proximal	27/10743	(0.25)	NR	NR
				Stage I	45/10743	(0.42)	NR	NR
				Stage II	11/10743	(0.10)	NR	NR
				Stage III	26/10743	(0.24)	NR	NR
				Stage IV	1/10743	(0.009)	NR	NR
Sali, 2016[8] SAVE	1	Colonoscopy	NR	Total	0/153	(0.0)	NR	NR
				Rectosigmoid	0/153	(0.0)	NR	NR
				Proximal	0/153	(0.0)	NR	NR
		CTC (Reduced cathartic preparation CTC + Full cathartic preparation CTC)	r-CTC: 9.8%, f-CTC: 9.8%	Total	7/1286	(0.005)	NR	NR
				Rectosigmoid	4/1286	(0.003)	NR	NR
				Proximal	3/1286	(0.002)	NR	NR
		FIT (OC-Sensor)	NR	Total	6/4677	(0.001)	NR	NR
				Rectosigmoid	3/4677	(0.0006)	NR	NR
				Proximal	3/4677	(0.0006)	NR	NR
Quintero, 2012[11] COLONPREV	1	Colonoscopy	32.3% (any finding);	Total - Intention to screen	30/26703	(0.001)	NR	NR
				Total - As screened	27/5059	(0.005)	NR	NR

Appendix D Table 3. Key Question 1: Direct Visualization vs. Stool Tests Comparative Effectiveness

Author, year	Round	Test	Test pos	Group analyzed	n CRC/ n Analyzed	(%)	N Interval CRC/n Analyzed	(%)
			10.3% (AN)	Stage I - As Screened	19/5059	(0.004)	NR	NR
				Stage II - As Screened	6/5059	(0.001)	NR	NR
				Stage III - As Screened	2/5059	(0.0004)	NR	NR
				Proximal - Intention to screen	6/26703	(0.0002)	NR	NR
				Distal - Intention to screen	23/26703	(0.0009)	NR	NR
		FIT (OC-Sensor)	7.2	Total - Intention to screen	33/26599	(0.001)	NR	NR
				Total - As screened	36/10611	(0.003)	NR	NR
				Stage I - As Screened	24/10611	(0.002)	NR	NR
				Stage II - As Screened	6/10611	(0.0006)	NR	NR
				Stage IV - As Screened	0/10611	(0.0)	NR	NR
				Stage III - As Screened	6/10611	(0.0006)	NR	NR
				Stage IV - As Screened	0/5059	(0.0)	NR	NR
				Proximal - Intention to screen	11/26599	(0.0004)	NR	NR
				Distal - Intention to screen	23/26599	(0.0009)	NR	NR
Segnan, 2007[10] SCORE III	1	Colonoscopy	5.1	Total	13/1596	(0.008)	NR	NR
				Male	8/811	(0.01)	NR	NR
				Female	5/785	(0.006)	NR	NR
				Age 55-59	4/899	(0.004)	NR	NR
				Age 60-64	9/697	(0.01)	NR	NR
		FIT (Immudia-HemSp)	4.7	Total	2/1965	(0.001)	NR	NR
				Male	0/904	(0.0)	NR	NR
				Female	2/1061	(0.002)	NR	NR
				Age 55-59	0/1090	(0.0)	NR	NR

Appendix D Table 3. Key Question 1: Direct Visualization vs. Stool Tests Comparative Effectiveness

Author, year	Round	Test	Test pos	Group analyzed	n CRC/ n Analyzed	(%)	N Interval CRC/n Analyzed	(%)
				Age 60-64	2/875	(0.002)	NR	NR
Hol, 2010*[12]	1	gFOBT (Hemoccult II)	2.8	Total	6/2351	(0.3)	NR	NR
				Stage I	1/2351	NR	NR	NR
				Stage II	2/2351	NR	NR	NR
				Stage III	2/2351	NR	NR	NR
				Stage IV	1/2351	NR	NR	NR
		FIT (OC-Sensor Micro)	4.8	Total	14/2975	(0.5)	NR	NR
				Stage I	5/2975	NR	NR	NR
				Stage II	7/2975	NR	NR	NR
				Stage III	2/2975	NR	NR	NR
				Stage IV	0/2975	(0.0)	NR	NR
		FS	10.2	Total	8/1386	(0.6)	NR	NR
				Stage I	6/1386	NR	NR	NR
				Stage II	0/1386	(0.0)	NR	NR
				Stage III	2/1386	NR	NR	NR
				Stage IV	0/1386	(0.0)	NR	NR
Segnan, 2007[10] SCORE III	1	FIT (Immudia-HemSp)	4.7	Total	2/1965	(0.1)	NR	NR
				Male	0/904	(0.0)	NR	NR
				Female	2/1061	(0.002)	NR	NR
				Age 55-59	0/1090	(0.0)	NR	NR
				Age 60-64	2/875	(0.002)	NR	NR
		FS	7.2	Total	12/1922	(0.6)‡	NR	NR
				Male	9/985	(0.009)	NR	NR
				Female	3/937	(0.003)	NR	NR
				Age 55-59	7/1100	(0.006)	NR	NR
				Age 60-64	5/822	(0.006)	NR	NR
				Proximal	0/1922	(0.0)	NR	NR
				Distal	12/1922	(0.006)	NR	NR
Segnan, 2005[13] SCORE II	1	FIT (Immudia-HemSp)	4.6	Total	8/2336	(0.3)	NR	NR
				Male	6/1032	(0.006)	NR	NR
				Female	2/1304	(0.002)	NR	NR
				Age 55-59	3/917	(0.003)	NR	NR
				Age 60-64	5/1419	(0.004)	NR	NR
		FS +/- FIT (Immudia-HemSp)	7.6**	Total	14/4075	(0.3)	NR	NR
				Male	9/2013	(0.004)	NR	NR
				Female	5/2012	(0.002)	NR	NR

Appendix D Table 3. Key Question 1: Direct Visualization vs. Stool Tests Comparative Effectiveness

Author, year	Round	Test	Test pos	Group analyzed	n CRC/ n Analyzed	(%)	N Interval CRC/n Analyzed	(%)
				Age 55-59	4/1661	(0.002)	NR	NR
				Age 60-64	10/2364	(0.004)	NR	NR
Rasmussen, 1999[14]	1	gFOBT (Hemoccult II)	2.4	Total	4/3055	(0.1)	18/2210†	(0.8)
		gFOBT (Hemoccult II) + FS	19.4	Total	12/2222	(0.5)‡	8/3051†‡	(0.3)
Verne, 1998[15]	1	gFOBT (Hemoccult II)	8.2	Total	1/854	(0.1)	NR	NR
		FS	9.9	Total	4/1116	(0.4)	NR	NR
		gFOBT (Hemoccult II) + FS	NR	Total	1/401	(0.2)	NR	NR
Berry, 1997[16]	1	gFOBT (Hemoccult II)	NR	Total	2/3128	(0.0006)	NR	NR
		gFOBT (Hemoccult II) + FS	NR	Total	3/3243	(0.0009)	NR	NR
Brevinge, 1997[17]	1	gFOBT (Hemoccult II)	4.4	Total	2/1893	(0.1)	NR	NR
				Dukes' Stage B	1/1893	(0.0005)	NR	NR
				Dukes' Stage C	1/1893	(0.0005)	NR	NR
		FS	NR	Total	5/1371	(0.4)	NR	NR
				Dukes' Stage A	4/1371	(0.003)	NR	NR
				Dukes' Stage B	1/1371	(0.0007)	NR	NR

* p<0.05
** Test positivity includes flexible sigmoidoscopy by patient choice.
† Followup for 24-62 months
‡ p<0.01

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; n = number; NR = not reported; pos = positivity; SCORE = Screening for COlon Rectum.

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Schreuders, 2019[18]	1	FIT (OC-Sensor Micro), 1 sample	19	Total	29/5986	(0.5)	NR	NR
		FIT (OC-Sensor Micro), 2 samples	28	Total	13/1875	(0.7)	NR	NR
	2	FIT (OC-Sensor Micro), 1 sample	19	Total	11/5200	(0.2)	NR	NR
		FIT (OC-Sensor Micro), 2 samples	28	Total	4/1582	(0.3)	NR	NR
	3	FIT (OC-Sensor Micro), 1 sample	19	Total	8/4998	(0.2)	NR	NR
		FIT (OC-Sensor Micro), 2 samples	28	Total	6/1474	(0.4)	NR	NR
	4	FIT (FOB Gold), 1 sample	19	Total	5/4385	(0.1)	NR	NR
		FIT (OC-Sensor Micro), 2 samples	28	Total	3/1171	(0.3)	NR	NR
	1-4	FIT (OC-Sensor Micro, FOB Gold), 1 sample	19	Total	53/7310	(0.7)	NR	NR
				Male	33/3530	(0.9)	NR	NR
				Female	20/3780	(0.5)	NR	NR
		FIT (OC-Sensor Micro), 2 samples	28	Total	26/2269	(1.1)	NR	NR
				Male	15/1101	(1.4)	NR	NR
				Female	11/1168	(0.9)	NR	NR
Passamonti, 2018[19]	1	FIT (OC-Sensor)	6.5	Total	5/2138	(0.2)	NR	NR
				Male	2/960	(0.2)	NR	NR
				Male 50-54	0/560	(0.0)	NR	NR
				Male 55-59	0/97	(0.0)	NR	NR
				Male 60-64	0/101	(0.0)	NR	NR
				Male 65-69	1/133	(0.8)	NR	NR
				Male 70-74	1/69	(1.4)	NR	NR
				Female	3/1178	(0.3)	NR	NR
				Female 50-54	0/808	(0.0)	NR	NR
				Female 55-59	0/99	(0.0)	NR	NR
				Female 60-64	1/76	(1.3)	NR	NR
				Female 65-69	1/124	(0.8)	NR	NR

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
				Female 70-74	1/71	(1.4)	NR	NR
				50-54 years	0/1368	(0.0)	NR	NR
				55-59 years	0/196	(0.0)	NR	NR
				60-64 years	1/177	(0.6)	NR	NR
				65-69 years	2/257	(0.8)	NR	NR
				70-74 years	2/140	(1.4)	NR	NR
		HM-JACKarc, cutoff 20 ug Hb/g feces	6.2	Total	5/2109	(0.2)	NR	NR
				Male	3/975	(0.3	NR	NR
				Male 50-54	2/659	(0.3)	NR	NR
				Male 55-59	0/91	(0.0)	NR	NR
				Male 60-64	0/75	(0.0)	NR	NR
				Male 65-69	0/101	(0.0)	NR	NR
				Male 70-74	1/49	(2.0)	NR	NR
				Female	2/1134	(0.2)	NR	NR
				Female 50-54	2/771	(0.3)	NR	NR
				Female 55-59	0/88	(0.0)	NR	NR
				Female 60-64	0/114	(0.0)	NR	NR
				Female 65-69	0/109	(0.0)	NR	NR
				Female 70-74	0/52	(0.0)	NR	NR
				50-54 years	4/1430	(0.3)	NR	NR
				55-59 years	0/179	(0.0)	NR	NR
				60-64 years	0/189	(0.0)	NR	NR
				65-69 years	0/210	(0.0)	NR	NR
				70-74 years	1/101	(1.0)	NR	NR
	2	FIT (OC-Sensor)	5.6	Total	14/12444	(0.1)	NR	NR
				Male	7/5687	(0.1)	NR	NR
				Male 50-54	0/440	(0.0)	NR	NR
				Male 55-59	0/860	(0.0)	NR	NR
				Male 60-64	2/1844	(0.1)	NR	NR

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
				Male 65-69	3/1452	(0.2)	NR	NR
				Male-70-74	2/1091	(0.2)	NR	NR
				Female	7/6757	(0.1)	NR	NR
				Female 50-54	1/575	(0.2)	NR	NR
				Female 55-59	0/1050	(0.0)	NR	NR
				Female 60-64	3/2198	(0.1)	NR	NR
				Female 65-69	2/1703	(0.1)	NR	NR
				Female 70-74	1/1231	(0.05)	NR	NR
				50-54 years	1/1015	(0.1)	NR	NR
				55-59 years	0/1910	(0.0)	NR	NR
				60-64 years	5/4042	(0.1)	NR	NR
				65-69 years	5/3155	(0.2)	NR	NR
				70-74 years	3/2322	(0.1)	NR	NR
		FIT (HM-JACKarc)	4.4	Total	16/12307	(0.1)	NR	NR
				Male	3/5601	(0.05)	NR	NR
				Male 50-54	0/457	(0.0)	NR	NR
				Male 55-59	0/876	(0.0)	NR	NR
				Male 60-64	1/1692	(0.06)	NR	NR
				Male 65-69	2/1467	(0.1)	NR	NR
				Male 70-74	0/1109	(0.0)	NR	NR
				Female	13/6706	(0.2)	NR	NR
				Female 50-54	0/565	(0.0)	NR	NR
				Female 55-59	1/1102	(0.09)	NR	NR
				Female 60-64	3/2162	(0.1)	NR	NR
				Female 65-69	4/1687	(0.2)	NR	NR
				Female 70-74	5/1190	(0.4)	NR	NR
				50-54 years	0/1022	(0.0)	NR	NR
				55-59 years	1/1978	(0.05)	NR	NR
				60-64 years	4/3854	(0.1)	NR	NR

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
				65-69 years	6/3154	(0.2)	NR	NR
				70-74 years	5/2299	(0.2)	NR	NR
Santare, 2016[20]	1	FIT (FOB Gold)	NR	10 ug/g cutoff	5/2094	(0.2)	NR	NR
				15 ug/g cutoff	5/2094	(0.2)	NR	NR
				20 ug/g cutoff	5/2094	(0.2)	NR	NR
		FIT (OC-Sensor)	NR	10 ug/g cutoff	1/2303	(0.04)	NR	NR
				15 ug/g cutoff	1/2303	(0.04)	NR	NR
				20 ug/g cutoff	1/2303	(0.04)	NR	NR
Zubero, 2014[21]	1	FIT (OC-Sensor), 1 sample	6.6	Total	35/11153	(0.3)	NR	NR
				Male	NR	NR	NR	NR
				Male 50-54	NR	NR	NR	NR
				Male 55-59	NR	NR	NR	NR
				Male 60-64	NR	NR	NR	NR
				Male 65-69	NR	NR	NR	NR
				Female	NR	NR	NR	NR
				Female 50-54	NR	NR	NR	NR
				Female 55-60	NR	NR	NR	NR
				Female 60-64	NR	NR	NR	NR
				Female 65-69	NR	NR	NR	NR
				Stage I	18/11153	(0.2)	NR	NR
				Stage II	10/11153	(0.09)	NR	NR
				Stage III	6/11153	(0.05)	NR	NR
				Stage IV	1/11153	(0.009)	NR	NR
		FIT (FOB Gold), 1 sample	8.5	Total	44/11725	(0.4)	NR	NR
				Male	5529	NR	NR	NR
				Male 50-54	NR	NR	NR	NR
				Male 55-59	NR	NR	NR	NR
				Male 60-64	NR	NR	NR	NR
				Male 65-69	NR	NR	NR	NR

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
				Female	NR	NR	NR	NR
				Female 50-54	NR	NR	NR	NR
				Female 55-60	NR	NR	NR	NR
				Female 60-64	NR	NR	NR	NR
				Female 65-69	NR	NR	NR	NR
				Stage I	17/11725	(0.1)	NR	NR
				Stage II	8/11725	(0.07)	NR	NR
				Stage III	13/11725	(0.1)	NR	NR
				Stage IV	5/11725	(0.04)	NR	NR
van Roon, 2013*[22] (intervals)	1	FIT (OC-Sensor Micro), 1-year interval	8.4	Total – As screened	4/1543	(0.3)	NR	NR
		FIT (OC-Sensor Micro), 2-year interval		Total – As screened	10/1481	(0.7)	NR	NR
		FIT (OC-Sensor Micro), 3-year interval		Total – As screened	8/1499	(0.5)	NR	NR
		FIT (OC-Sensor Micro), all intervals combined		Total – As screened	22/4523	(0.5)	NR	NR
				Stage I – As screened	14/4523	(0.3)	NR	NR
				Stage II – As screened	3/4523	(0.07)	NR	NR
				Stage III – As screened	5/4523	(0.1)	NR	NR
	2	FIT (OC-Sensor Micro), 1-year interval	6.0	Total – As screened	1/1286	(0.08)	NR	(0.0)
		FIT (OC-Sensor Micro), 2-year interval		Total – As screened	4/1280	(0.3)	NR	(0.08)
		FIT (OC-Sensor Micro), 3-year interval		Total – As screened	2/1298	(0.2)	NR	(0.2)
		FIT (OC-Sensor Micro), all intervals combined		Total – As screened	7/3864	(0.2)	NR	NR
				Stage I – As screened	5/3864	(0.1)	NR	NR

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Author, year	Round	Test	Test pos	Screened group	n CRC/ n Analyzed	(%)	Interval CRC	(%)
				Stage II – As screened	1/3864	(0.03)	NR	NR
				Stage III – As screened	1/3864	(0.03)	NR	NR
Hol, 2010*[12]	1	gFOBT (Hemoccult II)	2.8	Total	6/2351	(0.3)	NR	NR
				Stage I	1/2351	(0.04)	NR	NR
				Stage II	2/2351	(0.08)	NR	NR
				Stage III	2/2351	(0.08)	NR	NR
				Stage IV	1/2351	(0.04)	NR	NR
		FIT (OC-Sensor Micro)	4.8	Total	14/2975	(0.5)	NR	NR
				Stage I	5/2975	(0.17)	NR	NR
				Stage II	7/2975	(0.24)	NR	NR
				Stage III	2/2975	(0.07)	NR	NR
				Stage IV	0/2975	(0.0)	NR	NR
van Rossum, 2008[23]	1	gFOBT (Hemoccult II)	2.4%, 2.8% (Amsterdam region only)	Total	11/10301	(0.001)	NR	NR
				Male	5/4924	(0.001)	NR	NR
				Female	6/5377	(0.001)	NR	NR
				Age <60 years	8/5109	(0.002)	NR	NR
				Age ≥60 years	3/5192	(0.0006)	NR	NR
		FIT (OC-Sensor Micro), single sample	5.5%, 8.1% (Amersterdam region only)	Total	24/10322	(0.002)	NR	NR
				Male	16/5037	(0.003)	NR	NR
				Female	8/5285	(0.002)	NR	NR
				Age <60 years	18/4986	(0.004)	NR	NR
				Age ≥60 years	6/5336	(0.001)	NR	NR
Faivre, 2012[24]	1	gFOBT (Hemoccult II)	5.2	Total	117/85149	(0.1)	NR	NR
		FIT (FOB Gold), 2 samples	5.2	Total	91/32215	(0.3)†	NR	NR
		FIT (Magstream), 2 samples	4.6	Total	65/19244	(0.3)†	NR	NR
		FIT (OC-Sensor), 2 samples	3.7	Total	92/33690	(0.3)†	NR	NR

* Overlapping study populations
† p<0.01 versus gFOBT

Appendix D Table 4. Key Question 1: Stool Testing vs. Stool Testing Comparative Effectiveness

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; n = number; NR = not reported; Pos = positivity.

Appendix D Table 5. Key Question 2: Results for FIT Test Accuracy (Registry Followup)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)
Allison, 1996[25]	HemeSelect	300	All	7,493	0.688 (0.511, 0.864)	0.944 (0.938, 0.949)
Allison, 2007[26]	FlexSure OBT	300	Distal	5,356	0.818 (0.478, 0.968)	0.969 (0.964, 0.974)
Arana-Arri, 2017[27]	OC-Sensor	20	All	296,378	0.88 (0.86, 0.90)*	0.94 (0.94, 0.94)*
			50-54 years	NR	0.86 (0.80, 0.90)*	NR
			55-59 years	NR	0.88 (0.84, 0.91)*	NR
			60-64 years	NR	0.87 (0.83, 0.90)*	NR
			65-69 years	NR	0.91 (0.88, 0.94)*	NR
			Female	NR	0.88 (0.84, 0.91)*	NR
			Male	NR	0.89 (0.86, 0.91)*	NR
Castiglione, 2007[28]	OC-Hemodia	20*	All	27,503	0.81 (0.71, 0.88)*	0.95 (0.95, 0.95)*
Chen, 2011[29]	OC-Sensor	20	All	46,355	0.51 (0.44, 0.59)*	0.96 (0.96, 0.96)*
Chen, 2016[30]	OC-Sensor	20	All	512,066	0.933 (0.916, 0.949)	0.960 (0.959, 0.960)
			<50 years	371,021	0.930 (0.891, 0.970)	0.966 (0.965, 0.967)
			≥50 years	141,045	0.933 (0.915, 0.951)	0.944 (0.943, 0.945)
			Female	268,156	0.947 (0.925, 0.970)	0.965 (0.964, 0.966)
			Female <50 years	191,345	0.933 (0.877, 0.990)	0.970 (0.969, 0.970)
			Female ≥50 years	76,811	0.950 (0.926, 0.975)	0.954 (0.952, 0.955)
			Male	243,910	0.923 (0.900, 0.945)	0.954 (0.953, 0.955)
			Male <50 years	179,676	0.928 (0.872, 0.983)	0.962 (0.961, 0.963)
			Male ≥50 years	64,234	0.922 (0.897, 0.946)	0.932 (0.930, 0.934)
Chen, 2018[31]	HM-Jack	20	All	208,929	0.74 (0.70, 0.77)*	0.96 (0.96, 0.96)*
	OC-Sensor	10	Female 60-69 years	NR	0.80 (NR)	0.923 (NR)
			Female 60-69 years	NR	0.804 (NR)	0.923 (NR)
		12	All	NR	0.815 (NR)	0.937 (NR)
			Female 50-59 years	NR	0.822 (NR)	0.95 (NR)
			Male 50-59 years	NR	0.838 (NR)	0.935 (NR)
		15	Male 50-59 years	NR	0.819 (NR)	0.95 (NR)
		16	All	NR	0.80 (NR)	0.946 (NR)
			Female 50-59 years	NR	0.811 (NR)	0.964 (NR)

Appendix D Table 5. Key Question 2: Results for FIT Test Accuracy (Registry Followup)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)
			Female 60-69 years	NR	0.76 (NR)	0.95 (NR)
			Male 50-59 years	NR	0.819 (NR)	0.950 (NR)
			Male 60-69 years	NR	0.80 (NR)	0.938 (NR)
		18	Female 50-59 years	NR	0.809 (NR)	0.968 (NR)
			Female 60-69 years	NR	0.747 (NR)	0.958 (NR)
			Male 60-69 years	NR	0.799 (NR)	0.938 (NR)
		20	All	723,113	0.787 (0.769, 0.804)	0.962 (0.961, 0.963)
			Female 50-59 years	278,722	0.76 (0.72, 0.80)*	NR
			Female 60-69 years	167,349	0.69 (0.65, 0.73)*	NR
			Male 50-59 years	157,262	0.77 (0.73, 0.81)*	NR
			Male 60-69 years	119,780	0.76 (0.72, 0.79)*	NR
		24	Male 60-69 years	NR	0.768 (NR)	0.95 (NR)
Garcia, 2015[32]	OC-Auto (cutoff 100-1 sample)	20	All	4,568	0.88 (0.69, 0.96)*	0.94 (0.93, 0.95)*
Haug, 2017[33]	OC-Sensor Micro	10	All	4,523	0.78 (0.62, 0.88)*	0.88 (0.87, 0.89)*
		2.2	All	4,523	0.75 (0.59, 0.86)*	0.82 (0.81, 0.83)*
		2.8	All	4,523	0.75 (0.59, 0.86)*	0.84 (0.83, 0.85)*
		4.4	All	4,523	0.72 (0.56, 0.84)*	0.88 (0.87, 0.89)*
		7.2	All	4,523	0.64 (0.48, 0.78)*	0.90 (0.89, 0.91)*
		9	All	4,523	0.61 (0.45, 0.75)*	0.91 (0.90, 0.92)*
Itoh, 1996[34]	OC-Hemodia	10	All	27,860	0.865 (0.78, 0.92)*	0.95 (0.95, 0.95)*
Juul, 2018[35]	OC-Sensor	20	All	245,299	0.94 (0.92, 0.95)*	0.94 (0.94, 0.94)*
Launoy, 2005[36]	Magstream 1000	100-200*	All	7,421	0.85 (0.69, 0.94)*	0.94 (0.94, 0.95)*
Levi, 2011[37]	OC-Sensor	(~14*)	All	1,204	1.0 (0.61, 1.0)*	0.88 (0.86, 0.89)*
Mlakar, 2018[38]	OC-Sensor	20	All	251,948	0.86 (0.83, 0.89)*	0.94 (0.94, 0.94)*
			≤9 years of school	NR	0.91 (0.88, 0.93)*	NR
			≥10 years of school	NR	0.84 (0.80, 0.87)*	NR

Appendix D Table 5. Key Question 2: Results for FIT Test Accuracy (Registry Followup)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)
			50-54 years	NR	0.88 (0.80, 0.93)*	NR
			55-59 years	NR	0.90 (0.83, 0.95)*	NR
			60-64 years	NR	0.88 (0.82, 0.91)*	NR
			≥65 years	NR	0.81 (0.74, 0.86)*	NR
			Distal	NR	0.91 (0.88, 0.93)*	NR
			Proximal	NR	0.74 (0.66, 0.80)*	NR
			Female	NR	0.86 (0.81, 0.90)*	NR
			Male	NR	0.86 (0.82, 0.89)*	NR
			Stage I	NR	0.94 (0.90, 0.96)*	NR
			Stage II	NR	0.85 (0.78, 0.91)*	NR
			Stage III	NR	0.81 (0.73, 0.87)*	NR
			Stage IV	NR	0.67 (0.54, 0.78)*	NR
Nakama, 1996[39]	Monohaem	20	All - 1 year followup	3,365	0.909 (0.62, 0.98)*	0.96 (0.95, 0.96)*
			All - 2 year followup	3,365	0.833 (0.55, 0.95)*	0.96 (0.95, 0.96)*
			All - 3 year followup	3,365	0.714 (0.45, 0.88)*	0.96 (0.95, 0.96)*
Selby, 2018[40]	OC FIT-CHEK	10	50-59 years	323,855	0.827 (0.788, 0.862)	0.887 (0.886, 0.888)
			60-69 years	234,665	0.788 (0.751, 0.822)	0.857 (0.856, 0.859)
			70-75 years	82,056	0.749 (0.694, 0.799)	0.837 (0.835, 0.840)
			BL FIT and any FIT within 2 years	640,859	0.793 (0.769, 0.815)	0.87 (0.869, 0.871)
			Female	337,588	0.777 (0.739, 0.811)	0.882 (0.881, 0.883)
			Male	303,271	0.805 (0.774, 0.833)	0.856 (0.855, 0.857)
		15	50-59 years	323,855	0.799 (0.726, 0.810)	0.920 (0.919, 0.921)
			60-69 years	234,665	0.755 (0.716, 0.791)	0.900 (0.898, 0.901)
			70-75 years	82,056	0.724 (0.668, 0.776)	0.884 (0.882, 0.886)
			BL FIT and any FIT within 2 years	640,859	0.763 (0.738, 0.786)	0.908 (0.907, 0.909)
			Female	337,588	0.735 (0.695, 0.772)	0.918 (0.917, 0.919)
			Male	303,271	0.784 (0.752, 0.813)	0.897 (0.896, 0.898)
		20	50-59 years	323,855	0.790 (0.748, 0.827)	0.935 (0.934, 0.936)
			60-69 years	234,665	0.734 (0.694, 0.771)	0.919 (0.918, 0.920)
			70-75 years	82,056	0.689 (0.632, 0.743)	0.906 (0.904, 0.908)
			BL FIT and 1 additional FIT	250,519	0.713 (0.66, 0.76)*	0.935 (0.93, 0.94)*
			BL FIT and 2 additional FITs	231,298	0.98 (0.90, 1.0)*	0.96 (0.96, 0.96*)
			BL FIT and any FIT within 2 years	640,859	0.743 (0.718, 0.767)	0.926 (0.925, 0.926)
			BL FIT only	159,042	0.741 (0.71, 0.77)*	0.856 (0.85, 0.86)*
			Female	337,588	0.706 (0.666, 0.745)	0.934 (0.933, 0.935)

Appendix D Table 5. Key Question 2: Results for FIT Test Accuracy (Registry Followup)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)
			Male	303,271	0.770 (0.737, 0.800)	0.916 (0.915, 0.917)
		25	50-59 years	323,855	0.736 (0.692, 0.777)	0.946 (0.945, 0.946)
			60-69 years	234,665	0.693 (0.652, 0.732)	0.933 (0.932, 0.934)
			70-75 years	82,056	0.643 (0.584, 0.699)	0.922 (0.920, 0.924)
			BL FIT and any FIT within 2 years	640,859	0.696 (0.67, 0.722)	0.938 (0.938, 0.939)
			Female	337,588	0.663 (0.621, 0.703)	0.945 (0.945, 0.946)
			Male	303,271	0.721 (0.687, 0.754)	0.930 (0.929, 0.931)
		30	50-59 years	323,855	0.696 (0.650, 0.740)	0.953 (0.952, 0.953)
			60-69 years	234,665	0.661 (0.619, 0.701)	0.943 (0.942, 0.944)
			70-75 years	82,056	0.604 (0.545, 0.662)	0.933 (0.931, 0.935)
			BL FIT and any FIT within 2 years	640,859	0.66 (0.633, 0.687)	0.947 (0.946, 0.947)
			Female	337,588	0.631 (0.588, 0.672)	0.953 (0.952, 0.954)
			Male	303,271	0.682 (0.647, 0.716)	0.939 (0.938, 0.940)
Stegeman, 2015[41]	OC-Sensor	10	All	2,871	0.60 (0.68, 0.84)*	0.92 (0.87, 0.93)
			Distal	NR	0.55 (0.28, 0.79)*	(,)
			Proximal	NR	0.67 (0.35, 0.88)*	(,)
			Stage I	NR	0.67 (0.35, 0.88)*	(,)
			Stage II	NR	0.67 (0.21, 0.94)*	(,)
			Stage III	NR	0.67 (0.30, 0.90)*	(,)
			Stage IV	NR	0 (0, 0.66)*	(,)
Toes-Zoutendijk, 2019[42]	FOB Gold	15	All	127,411	0.90 (0.88, 0.91)	0.89 (0.88, 0.89)
			Female	66,475	0.89 (0.86,0.92)	0.91 (0.90, 0.91)
			Male	60,936	0.90 (0.88, 0.92)	0.86 (0.86, 0.87)
		47	All	398,505	0.83 (0.82, 0.85)	0.94 (0.94, 0.94)
			Female	203,968	0.79 (0.77, 0.82)	0.96 (0.95, 0.96)
			Male	194,537	0.86 (0.84, 0.88)	0.93 (0.93, 0.93)
van der Vlugt, 2017[43]	OC-Sensor/FOB Gold	10	All	18,716	0.82 (0.75, 0.87)*	0.84 (0.84, 0.85)*
			>70 years	NR	0.80 (0.67, 0.89)*	NR
			50-59 years	NR	0.83 (0.67, 0.92)*	NR
			60-69 years	NR	0.84 (0.73, 0.91)*	NR
			Average SES	NR	0.81 (0.72, 0.87)*	NR
			Distal	NR	0.83 (0.75, 0.89)*	NR
			Female	NR	0.81 (0.70, 0.89)*	NR
			High SES	NR	0.85 (0.66, 0.94)*	NR
			Low SES	NR	0.88 (0.66, 0.97)*	NR
			Male	NR	0.83 (0.74, 0.89)*	NR
			Proximal	NR	0.80 (0.68, 0.89)*	NR
			Stage I	NR	0.89 (0.79, 0.94)*	NR

Appendix D Table 5. Key Question 2: Results for FIT Test Accuracy (Registry Followup)

Author, year	Test name	Cutoff, µg Hb/g	Screened group	N analyzed	CRC Sensitivity (95% CI)	CRC Specificity (95% CI)
			Stage II	NR	0.73 (0.52, 0.87)*	NR
			Stage III	NR	0.81 (0.67, 0.90)*	NR
			Stage IV	NR	0.69 (0.42, 0.87)*	NR

* Calculated sensitivity, specificity, or CI

Abbreviations: BL = baseline; CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; n = number; NR = not reported; µg Hb/g = micrograms hemoglobin per gram feces

Appendix D Table 6. Key Question 3: Harms of Screening Colonoscopy for Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI	n	OR or RR (95% CI)
Grossberg, 2019[44]	US	60 (median)	7 days	50-75 years	27799‡	NR	NR	NR	NR	Hospitalization: 35‡ ED visit: 157‡	NR
				76-85 years	2422‡	NR	NR	NR	NR	Hospitalization: 16‡ ED visit: 28‡	NR
				>85 years	188‡	NR	NR	NR	NR	Hospitalization: 3‡ ED visit: 3‡	NR
Wang, 2018[45] (Newly identified)	US	NR	7 days	Female	265227	NR	NR	NR	NR	Hospitalization - due to infection: 292	OR: 0.94 (0.79, 1.11)
				Male	196841	NR	NR	NR	NR	Hospitalization - due to infection: 217	Ref
				40-49 yrs	35117	NR	NR	NR	NR	Hospitalization - due to infection: 49	OR: 1.28 (0.93, 1.76)
				50-59 yrs	183903	NR	NR	NR	NR	Hospitalization - due to infection: 166	Ref
				60-69 yrs	148324	NR	NR	NR	NR	Hospitalization - due to infection: 148	OR: 1.09 (0.88, 1.37)
				70-79 yrs	77627	NR	NR	NR	NR	Hospitalization - due to infection: 109	OR: 1.40 (1.09, 1.78)
				80-100 yrs	17559	NR	NR	NR	NR	Hospitalization - due to infection: 44	OR: 1.96 (1.39, 2.76)
				White	306351	NR	NR	NR	NR	Hospitalization - due to infection: 337	Ref
				Black	46669	NR	NR	NR	NR	Hospitalization - due to infection: 84	OR: 1.57 (1.22, 2.01)
				Hispanic	69310	NR	NR	NR	NR	Hospitalization - due to infection: 90	OR: 1.11 (0.87, 1.42)
				Asian or Pacific Islander	18483	NR	NR	NR	NR	Hospitalization - due to infection: 9	OR: 0.50 (0.27, 0.96)
				Native American	1386	NR	NR	NR	NR	Hospitalization - due to infection: 6	OR: 3.68 (1.51, 8.89)
				Other race	19869	NR	NR	NR	NR	Hospitalization - due to infection: 12	OR: 0.70 (0.39, 1.25)
Zwink, 2017[46] 5065 (Newly identified)	DEU	61*	4 wks	Female	2731	NR	NR	NR	NR	Physician-confirmed complication: 8†	NR
			4 wks	Male	2521	NR	NR	NR	NR	Physician-confirmed complication: 12†	NR

Appendix D Table 6. Key Question 3: Harms of Screening Colonoscopy for Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI	n	OR or RR (95% CI)
Zafar, 2014[47]	US	74	30 days	66-74 years	NR	NR§	Ref	NR‡	Ref	NR‡§	Ref
				75-84 years	NR	NR§	OR: 1.14 (0.87, 1.48)	NR‡	OR: 1.02 (0.49, 2.14)	NR‡§	OR: 0.92 (0.70, 1.22)
				≥85 years	NR	NR§	OR: 1.49 (0.81, 2.75)	NR‡	OR: 1.99 (0.45, 8.69)	NR‡§	OR: 1.22 (0.68, 2.2)
Pox, 2012[48]	DEU	65	NR	Female 55-59	NR	NR	NR	NR	NR	SAE: NR (Total major and minor complications)	OR reported as reference
				Female 60-64	NR	NR	NR	NR	NR	SAE: NR	OR: 1.5 (1.3, 1.7)
				Female 65-69	NR	NR	NR	NR	NR	SAE: NR	OR: 1.8 (1.6, 2.0)
				Female 70-74	NR	NR	NR	NR	NR	SAE: NR	OR: 2.1 (1.8, 2.4)
				Female 75-79	NR	NR	NR	NR	NR	SAE: NR	OR: 2.8 (2.4, 3.2)
				Female ≥79	NR	NR	NR	NR	NR	SAE: NR	OR: 3.4 (2.8, 4.1)
				Male 55-59	NR	NR	NR	NR	NR	SAE: NR	Ref
				Male 60-64	NR	NR	NR	NR	NR	SAE: NR	OR: 1.2 (1.0, 1.3)
				Male 65-69	NR	NR	NR	NR	NR	SAE: NR	OR: 1.3 (1.2, 1.5)
				Male 70-74	NR	NR	NR	NR	NR	SAE: NR	OR: 1.5 (1.3, 1.7)
				Male 75-79	NR	NR	NR	NR	NR	SAE: NR	OR: 1.7 (1.5, 2.0)
				Male ≥79	NR	NR	NR	NR	NR	SAE: NR	OR: 1.6 (1.3, 2.0)
Rutter, 2012[49]	US	NR	30 days	40-49 years	2450	6‖¶	NR	0¶	NR	Hospitalization: 28	NR
										ED visit: 77	NR
				50-64 years	28565	66‖¶	NR	10¶	NR	Hospitalization: 277	NR
										ED visit: 684	NR
				65-74 years	5804	31‖¶	NR	7¶	NR	Hospitalization: 141	NR
										ED visit: 177	NR
					1653		NR		NR	Hospitalization: 62	NR

Appendix D Table 6. Key Question 3: Harms of Screening Colonoscopy for Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI	n	OR or RR (95% CI)
				75-85 years		19‖¶		4¶		ED visit: 81¶	NR
Ferlitsch, 2011[50]	AUT	61	NR	Male	21752	39‖	NR	2	NR	Cardiopulmonary event: 16	NR
										Other SAE: 6	NR
				Female	22598	15‖	NR	1	NR	Cardiopulmonary event: 30	NR
										Other SAE: 2	NR
				50-60 yrs	19326	NR#	NR	NR	NR	Cardiopulmonary event: 10**	NR
				70-80 yrs	6279	NR#	NR	NR	NR	Cardiopulmonary event: 16**	NR
Crispin, 2009[51]	DEU	64*	NR	Female	31216	NR	OR: 1.0001 (1.0001, 1.0002)	NR	NR	Cardiopulmonary event: NR	NR
				Age squared, per year	NR	NR	OR: 0.822 (0.686, 0.984)	NR	OR: 1.0003 (1.0002, 1.0005)	Cardiopulmonary event: NR	OR: 1.0003 (1.0002, 1.0004)
Warren, 2009[52]	US	NR	30 days	66-69 yrs	12942 (IG); 12986 (CG)	NR	NR	NR	NR	Cardiovascular event: NR (12.6/1000 persons [IG]; 10.7/1000 persons [CG])† Serious GI events: NR (5.0/1000 persons [IG]; 1.3/1000 persons [CG])†	NR
				70-74 yrs	16606 (IG); 16548 (CG)	NR	NR	NR	NR	Cardiovascular event: NR (16.0/1000 persons [IG]; 13.6/1000 persons [CG])† Serious GI events: NR (5.8/1000 persons [IG]; 1.5/1000 persons [CG])†	NR

Appendix D Table 6. Key Question 3: Harms of Screening Colonoscopy for Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI	n	OR or RR (95% CI)
				75-79 yrs	13289 (IG); 13295 (CG)	NR	NR	NR	NR	Cardiovascular event: NR (20.6/1000 persons [IG]; 17.5/1000 persons [CG])† Serious GI events: NR (7.2/1000 persons [IG]; 1.9/1000 persons [CG])†	NR
				80-84 yrs	7453 (IG); 7441 (CG)	NR	NR	NR	NR	Cardiovascular event: NR (25.7/1000 persons [IG]; 21.9/1000 persons [CG])† Serious GI events: NR (8.8/1000 persons [IG]; 2.3/1000 persons [CG])†	NR
				≥85 yrs	2930 (IG); 2950 (CG)	NR	NR	NR	NR	Cardiovascular event: NR (31.8/1000 persons [IG]; 27.1/1000 persons [CG])† Serious GI events: NR (12.1/1000 persons [IG]; 3.2/1000 persons [CG])†	NR

* Median age
† Physician confirmed hospitalizations due to bleeding and/or perforation
‡ Increasing risk of bleeding, perforation, and other GI events with older ages (only odds ratios presented; not statistically significant; also includes 1384 people total who received CT colonography)
§ Increasing risk of cardiovascular events with older ages (only odds ratios presented; statistically significant; also includes 1384 people total who received CT colonography)
‖ Unspecified bleeding
¶ Number of events (rather than number of people)
# Bleeding events were unchanged by age (p=0.23)
** Cardiopulmonary adverse events increased with age, from 0.05% in patients age 50-60 yrs to 0.25% in patients age 70-80 yrs (p<0.001)

Appendix D Table 6. Key Question 3: Harms of Screening Colonoscopy for Subgroups

Abbreviations: AUT = Austria; CI = confidence interval; DEU = Germany; F/U = followup;IG = intervention (screening) group; CG = control (no screening) group; n = number; NR = not reported; MI = myocardial infarction; perf = perforation; SAE = serious adverse events; GI = gastrointestinal; OR = odds ratio; RR = rate ratio; SAE = serious adverse events; US = United States; wks = weeks; yrs = yrs

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
Chukmaitov, 2019[53]	US	NR	30 days	19-49 yrs	NR	NR	NR	NR	NR	Hospitalization due to perforations and GI bleeding: NR	OR reported as reference
				50-64 yrs	NR	NR	NR	NR	NR	Hospitalization due to perforations and GI bleeding: NR	OR: 1.60 (1.10, 2.34)
				65-74 yrs	NR	NR	NR	NR	NR	Hospitalization due to perforations and GI bleeding: NR	OR: 2.26 (1.51, 3.38)
				75-84 yrs	NR	NR	NR	NR	NR	Hospitalization due to perforations and GI bleeding: NR	OR: 3.06 (2.02, 4.62)
				85 yrs and older	NR	NR	NR	NR	NR	Hospitalization due to perforations and GI bleeding: NR	OR: 4.22 (2.56, 6.97)
Laanani, 2019[54]	FRA	NR	5 days	30-39 yrs	319498	NR	aOR: 1.00	NR	aOR: 1.00	NR	NR
				40-49 yrs	737285	NR	aOR: 0.83 (0.62, 1.12)	NR	aOR: 1.24 (0.75, 2.07)	NR	NR
				50-59 yrs	1134487	NR	aOR: 0.99 (0.75, 1.31)	NR	aOR: 1.85 (1.15, 2.95)	NR	NR
				60-69 yrs	1123714	NR	aOR: 1.13 (0.86, 1.49)	NR	aOR: 2.90 (1.83, 4.59)	NR	NR
				70-79 yrs	605787	NR	aOR: 1.18 (0.89, 1.56)	NR	aOR: 4.91 (3.09, 7.80)	NR	NR
				80 yrs and older	168028	NR	aOR: 1.95 (1.44, 2.63)	NR	aOR: 8.20 (5.04, 13.3)	NR	NR
Thulin, 2019[55]	SWE	63	30 days	Female	320386	NR†	RR reported as reference	NR	RR reported as reference	NR	NR
				Male	272922	NR†	RR: 0.62 (0.54, 0.72)	NR	RR: 1.16 (0.98, 1.37)	NR	NR
				18-30 yrs	NR	NR†	RR reported as reference	NR	RR reported as reference	NR	NR
				30-40 yrs	NR	NR†	RR: 1.11 (0.62, 1.98)	NR	RR: 1.06 (0.54, 2.06)	NR	NR
				40-50 yrs	NR	NR†	RR: 1.84 (1.10, 3.08)	NR	RR: 1.34 (0.75, 2.43)	NR	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				50-60 yrs	NR	NR†	RR: 2.01 (1.24, 3.25)	NR	RR: 1.62 (0.94, 2.78)	NR	NR
				60-70 yrs	NR	NR†	RR: 2.39 (1.51, 3.80)	NR	RR: 2.65 (1.60, 4.40)	NR	NR
				70-80 yrs	NR	NR†	RR: 3.12 (1.96, 4.96)	NR	RR: 3.46 (2.08, 5.75)	NR	NR
				80 yrs and older	NR	NR†	RR: 3.88 (2.42, 6.22)	NR	RR: 5.24 (3.12, 8.80)	NR	NR
Forsberg, 2017[56] (Newly identified)	SWE	63	30 days	Female	238874	NR*	RR: 0.62 (0.54, 0.72)	NR*	RR: 1.15 (0.98, 1.36)	NR	NR
				Male	187686	NR*	NR	NR*	NR	NR	NR
				18-30 yrs	43755	23†	NR	19	NR	NR	NR
				30-40 yrs	48373	29†	NR	23	NR	NR	NR
				40-50 yrs	68462	68†	NR	41	NR	NR	NR
				50-60 yrs	97891	123†	NR	71	NR	NR	NR
				60-70 yrs	153703	250†	NR	169	NR	NR	NR
				70-80 yrs	124450	296†	NR	194	NR	NR	NR
Garcia-Albeniz, 2017[57] (Newly identified)	US	NR	30 days	70-74 yrs	46872 (IG); 1762816 (CG)	20 (IG); 130 (CG)	NR	20 (IG); 51 (CG)	NR	Other GI events: 257 (IG); 4331 (CG)	NR
										Cardiovascular event: 473 (IG); 14026 (CG)	NR
				75-79 yrs	31193 (IG); 1628020 (CG)	14 (IG); 180 (CG)	NR	11 (IG); 71 (CG)	NR	Other GI events: 206 (IG); 5003 (CG)	NR
										Cardiovascular event: 538 (IG); 17638 (CG)	NR
Johnson, 2017[58] (Newly identified)	US	NR	30 days	Female	262689	NR	NR	NR	NR	Non GI SAE‡: 3030	NR
				Male	225817	NR	NR	NR	NR	Non GI SAE‡: 3532	NR
				<50 yrs old	87437	NR	NR	NR	NR	Non GI SAE‡: 595	NR
				≥50 yrs	401069	NR	NR	NR	NR	Non GI SAE‡: 5967	NR
	US	61	NR	Female	63337	NR	NR	22	NR	NR	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
Adeyemo, 2014[59]				Male	54667	NR	NR	26	NR	NR	NR
Bielawska, 2014[60]	US	NR	NR	Female	548587	NR	NR	103	OR: 1.26 (0.95, 1.67)	NR	NR
				Male	596309	NR	NR	89	OR reported as reference	NR	NR
				<60 yrs	566952	NR	NR	39	OR reported as reference	NR	NR
				60-74 yrs	426305	NR	NR	83	OR: 2.83 (1.94, 4.14)	NR	NR
				≥75 yrs	151210	NR		70	OR: 6.73 (4.55, 9.96)	NR	NR
Blotiere, 2014[61]	FRA	NR	3 days	Male	420852	NR§	NR	NR§	OR: 0.99 (0.81, 1.20)	NR	NR
				0-39 yrs	92188	NR§	OR: 1.00	NR§	OR reported as reference	NR	NR
				40-49 yrs	143604	NR§	OR: 1.06 (0.70, 1.62)	NR§	OR: 0.78 (0.38, 1.58)	NR	NR
				50-59 yrs	249746	NR§	OR: 1.75 (1.22, 2.52)	NR§	OR: 1.56 (0.87, 2.79)	NR	NR
				60-69 yrs	252689	NR§	OR: 2.51 (1.76, 3.58)	NR§	OR: 2.89 (1.66, 5.05)	NR	NR
				70-79 yrs	155861	NR§	OR: 4.54 (3.19, 6.45)	NR§	OR: 5.75 (3.32, 9.97)	NR	NR
				≥80 yrs	52973	NR§	NR	NR§	OR: 10.83 (6.16, 19.05)	NR	NR
Chukmaitov, 2013[62]	US	NR	30 days	Female	NR	NR‖	OR: 0.65 (0.61, 0.70)	NR‖	OR: 1.33 (1.15, 1.55)	NR	NR
				55-64 yrs	NR	NR‖	OR: 1.08 (0.94, 1.25)	NR‖	OR: 1.38 (1.01, 1.87)	NR	NR
				65-74 yrs	NR	NR‖	OR: 1.22 (1.03, 1.45)	NR‖	OR: 1.80 (1.24, 2.62)	NR	NR
				75-84 yrs	NR	NR‖	OR: 1.71 (1.43, 2.05)	NR‖	OR: 2.36 (1.61, 3.48)	NR	NR
				≥85 yrs	NR	NR‖	OR: 2.88 (1.75, 4.72)	NR‖	OR: 2.88 (1.75, 4.72)	NR	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				Black	NR	NR‖	OR: 1.32 (1.13, 1.53)	NR‖	OR: 0.86 (0.60, 1.25)	NR	NR
				Hispanic	NR	NR‖	OR: 1.23 (1.08, 1.39)	NR‖	OR: 0.99 (0.75, 1.31)	NR	NR
				Other race	NR	NR‖	OR: 1.00 (0.87, 1.14)	NR‖	OR: 0.90 (0.68, 1.20)	NR	NR
Cooper, 2013[63]	US	76	30 days	66-69 yrs	38391	NR	NR	NR	OR reported as reference	Perforation, splenic injury, or aspiration pneumonia: NR¶	OR reported as reference
				70-74 yrs	44690	NR	NR	NR	OR: 3.36 (2.03, 5.56)	Perforation, splenic injury, or aspiration pneumonia: NR¶	OR: 3.36 (2.03, 5.56)
				75-79 yrs	35061	NR	NR	NR	OR: 3.63 (2.18, 6.05)	Perforation, splenic injury, or aspiration pneumonia: NR¶	OR: 3.63 (2.18, 6.05)
				80-84 yrs	19839	NR	NR	NR	OR: 5.97 (3.58, 9.97)	Perforation, splenic injury, or aspiration pneumonia: NR¶	OR: 5.97 (3.58, 9.97)
				≥85 yrs	8723	NR	NR	NR	OR: 10.41 (6.18, 17.54)	Perforation, splenic injury, or aspiration pneumonia: NR¶	OR: 10.41 (6.18, 17.54)
Hamdani, 2013[64]	US	NR	7 days	Female	41121	NR	NR	34	NR	NR	NR
				Male	38988	NR	NR	16	NR	NR	NR
				18-49 yrs	13703	NR	NR	5	NR	NR	NR
				50-64 yrs	38705	NR	NR	10	NR	NR	NR
				65-79 yrs	22974	NR	NR	20	NR	NR	NR
				≥80 yrs	4736	NR	NR	15	NR	NR	NR
Ko, 2010[65]	US	NR	30 days	Female	9612	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 25	NR
										Hospitalization - directly related to colonoscopy**: 16	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				Male	11763	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 43	NR
										Hospitalization - directly related to colonoscopy**: 27	NR
				40-59 yrs	9234	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 18	NR
										Hospitalization - directly related to colonoscopy**: 11	NR
				60-69 yrs	6676	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 21	NR
										Hospitalization - directly related to colonoscopy**: 12	NR
				70-79 yrs	4318	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 23	NR
										Hospitalization - directly related to colonoscopy**: 15	NR
				≥80 yrs	1147	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 6	NR
										Hospitalization - directly related to colonoscopy**: 5	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				White	19301	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 60	NR
										Hospitalization - directly related to colonoscopy**: 38	NR
				Black	1617	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 7	NR
										Hospitalization - directly related to colonoscopy**: 5	NR
				Hispanic	269	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 2	NR
										Hospitalization - directly related to colonoscopy**: 1	NR
				Not Hispanic	21080	NR	NR	NR	NR	Hospitalization - directly or potentially related to colonoscopy#: 66	NR
										Hospitalization - directly related to colonoscopy**: 42	NR
Arora, 2009[66]	US	NR	7 days	Female	175816	NR	NR	138	OR: 21.09 (13.77, 32.29)	NR	NR
				Male	101618	NR	NR	90	OR: 50.85 (23.57, 109.73)	NR	NR
				18-50 yrs	49678	NR	NR	33	OR: 26.42 (10.31, 67.67)	NR	NR

Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				50-65 yrs	74235	NR	NR	53	OR: 20.99 (10.68, 41.26)	NR	NR
				65-80 yrs	118294	NR	NR	100	OR: 24.80 (14.41, 42.68)	NR	NR
				≥80 yrs	35227	NR	NR	42	OR: 83.86 (20.30, 346.43)	NR	NR
				White	108946	NR	NR	105	OR: 34.44 (18.51, 64.10)	NR	NR
				Hispanic	48365	NR	NR	34	OR: 28.54 (6.53, 124.79)	NR	NR
				Black	26824	NR	NR	15	OR: 33.07 (12.93, 84.57)	NR	NR
				Other race	93299	NR	NR	74	OR: 19.44 (10.98, 34.42)	NR	NR
Rabeneck, 2008[67]	CAN	61	30 days	Female	52641	NR††	OR: 0.52 (0.36, 0.74)	NR††	OR: 1.21 (0.97, 1.50)	NR	NR
				Male	44450	NR††	OR: 1.00	NR††	OR: 1.00	NR	NR
				50-59 yrs	46967	NR††	OR: 1.00	NR††	OR: 1.00	NR	NR
				60-75 yrs	50124	NR††	OR: 1.60 (1.20, 2.16)	NR††	OR: 2.06 (1.79, 2.37)	NR	NR
Levin, 2006[68]	US	62	30 days	Female	6575	NR	NR	NR	RR: 2.3 (0.9, 6.0)	Perforation, bleeding with transfusion, and diverticulitis requiring surgery: NR‡‡	RR reported as reference
				Male	9743	NR	NR	NR	RR: 1.0	Perforation, bleeding with transfusion, and diverticulitis requiring surgery: NR‡‡	RR: 1.1 (0.6, 2.3)

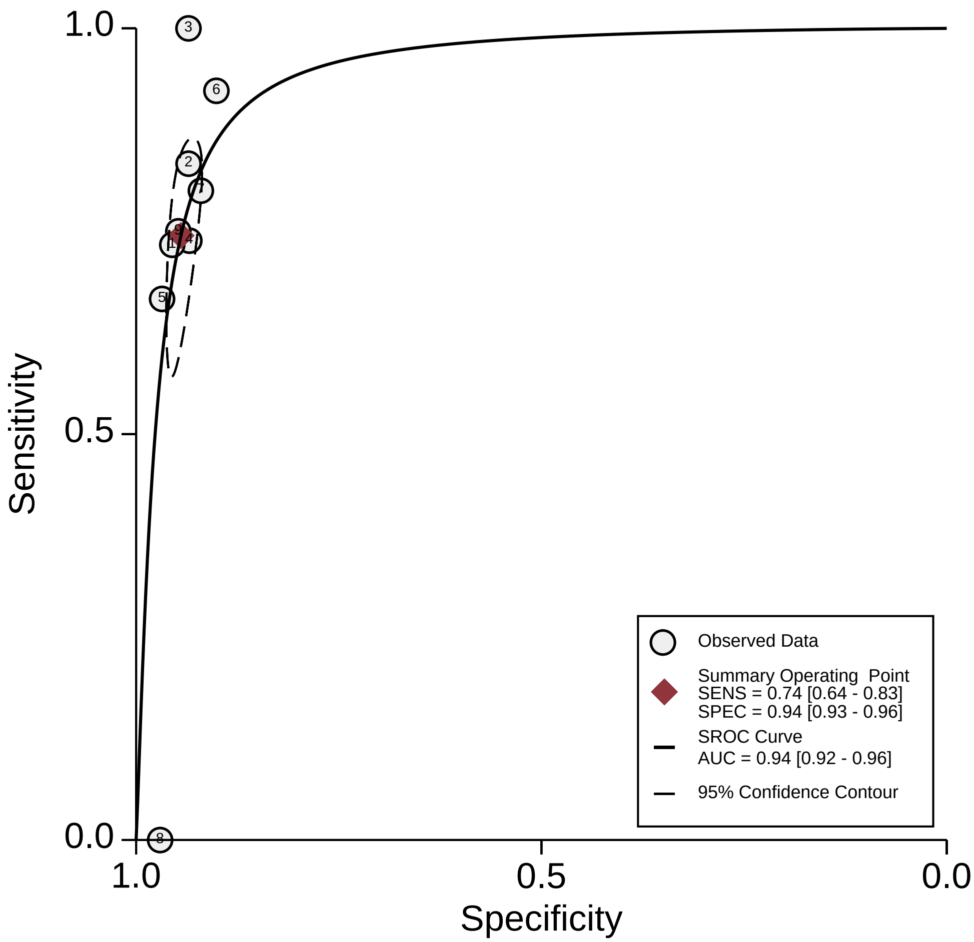
Appendix D Table 7. Key Question 3: Harms of Mixed Colonoscopies - Subgroups

Author, year	Country	Age, mean	F/U	Group	n	Serious bleeding events		Perforation events		Other SAEs	
						n	OR or RR (95% CI)	n	OR or RR (95% CI)	n	OR or RR (95% CI)
				40-59 yrs	6962	NR	NR	NR	RR: 1.0	Perforation, bleeding with transfusion, and diverticulitis requiring surgery: NR‡‡	RR reported as reference
				≥60 yrs	9356	NR	NR	NR	RR: 5.2 (1.4, 19.2)	Perforation, bleeding with transfusion, and diverticulitis requiring surgery: NR‡‡	RR: 2.7 (1.4, 1.5)
Rathgaber, 2006[69]	US	60	30 days	Female	6482	6§§	NR	1	NR	NR	NR
				Male	5925	17§§	NR	1	NR	NR	NR

*Study presents risk ratios for risk of bleeding and perforation by sex. Male sex was associated with a higher risk of bleeding compared with female sex; no significant differences by sex were found for perforations
† Unspecified bleeding
‡ Includes cardiac events, pulmonary events, and neurovascular events
§Study reports odds ratios for risk of bleeding and perforation by age subgroups with 0-39 as reference group. Older age groups (e.g., age >=70) were associated with higher risks of bleeding and perforation
‖ Study reports odds ratios for risk of bleeding and perforation by age, sex, and race/ethnicity subgroups. Older age groups (e.g., age >=65) were associated with higher risks of bleeding and perforation compared with age 19-49, and Hispanic ethnicity and black or African American race were associated with higher risks of bleeding compared with white race. No significant differences were found for perforation by race/ethnicity, and no significant differences were found for bleeding or perforation by sex
¶ Study reports odds ratios for risk of complications (defined as perforation, splenic injury, or aspiration pneumonia) by age subgroups. Older age groups (e.g., age >=70 yrs) were associated with higher risks of complications compared with age 66-69 yrs
#Includes serious bleeding, diverticulitis, perforation, post-polypectomy syndrome, cardiovascular events, neurologic events, abdominal pain, biliary colic, perirectal abscess, pneumonia, splenic hematoma, prolonged recovery from sedation, nausea and vomiting from bowel prep, and ileus
** Includes serious bleeding, diverticulitis, perforation, post-polypectomy syndrome
†† Study reports odds ratios for risk of bleeding and perforation by age and sex groups. Older age groups (e.g., age 60-75) were associated with higher risk of bleeding and perforation compared with age 50-59 yrs. Male sex was associated with a higher risk of bleeding compared with female sex; the study found no significant differences in perforations by sex.
‡‡ Study reports rate ratios for risk of perforation, bleeding with transfusion, and diverticulitis requiring surgery by age and sex groups. Older age groups (e.g., age >= 60 yrs) were associated with higher risk of these complications compared with age 50-59 yrs. No significant differences were found by sex
§§ Serious bleeding occurring post-polypectomy

Abbreviations: CAN = Canada; CI = confidence interval; FRA = France; F/U = followup; IG = intervention (screening) group; CG = control (no screening) group; n = number; NR = not reported; MI = myocardial infarction; SAE = serious adverse events; GI = gastrointestinal; ED = emergency department; OR = odds ratio; RR = rate ratio; SAE = serious adverse events; SWE = Sweden; US = United States; wks = weeks; yrs = years

Appendix E Figure 1. Key Question 2: Summary ROC Curve of OC-Sensor to Detect CRC (All Colonoscopy Follow-Up), 20 µg Hb/g Feces Cutoff



Abbreviations: AUC = area under the curve; SENS = sensitivity; SPEC = specificity; ROC = receiver operating characteristic; µg Hb per g feces = microgram hemoglobin per gram feces

Appendix E Figure 2. Key Question 2: Forest Plot of OC-Sensor Sensitivity and Specificity to Detect CRC (Registry Follow-Up), by Cutoff (µg Hb/g Feces)

Author, year	TP	FN	FP	TN	Total	Sensitivity (95% CI)	Specificity (95% CI)
10							
Haug, 2017	28	8	552	3935	4523	0.78 (0.62, 0.88)	0.88 (0.87, 0.89)
Selby, 2018	987	258	83306	556308	640859	0.79 (0.77, 0.81)	0.87 (0.87, 0.87)
Stegeman, 2015	12	8	221	2630	2871	0.60 (0.39, 0.78)	0.92 (0.91, 0.93)
Subtotal (I-squared = 45.4%, p = 0.160)						0.76 (0.68, 0.84)	0.89 (0.86, 0.92)
.							
15							
Selby, 2018	950	295	58919	580695	640859	0.76 (0.74, 0.79)	0.91 (0.91, 0.91)
Subtotal (I-squared = .%, p = .)						0.76 (0.74, 0.79)	0.91 (0.91, 0.91)
.							
20							
Arana-Arri, 2017	1032	136	17241	277969	296378	0.88 (0.86, 0.90)	0.94 (0.94, 0.94)
Chen, 2011	87	82	1944	44242	46355	0.51 (0.44, 0.59)	0.96 (0.96, 0.96)
Chen, 2016	859	62	20494	490651	512066	0.93 (0.92, 0.95)	0.96 (0.96, 0.96)
Chen, 2018	1496	509	26894	694214	723113	0.79 (0.77, 0.80)	0.96 (0.96, 0.96)
Garcia, 2015	21	3	266	4278	4568	0.88 (0.69, 0.96)	0.94 (0.93, 0.95)
Juul, 2018	916	60	15290	229033	245299	0.94 (0.92, 0.95)	0.94 (0.94, 0.94)
Selby, 2018	925	320	47636	591978	640859	0.74 (0.72, 0.77)	0.93 (0.93, 0.93)
Subtotal (I-squared = 98.5%, p = 0.000)						0.81 (0.74, 0.88)	0.95 (0.93, 0.96)
.							

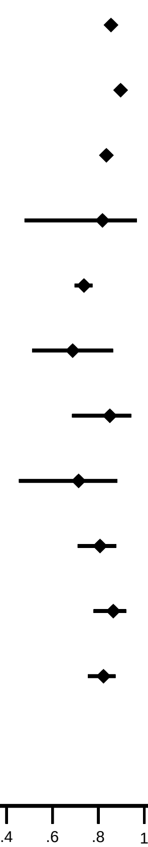
0 .2 .4 .6 .8 1   0 .2 .4 .6 .8 1

Note: For 20 µg Hb/g feces cutoff, bivariate sensitivity was 0.84 (95% CI, 0.72 to 0.91) and specificity was 0.95 (95% CI, 0.94 to 0.96) .

Abbreviations: CI = Confidence interval; CRC = Colorectal cancer; FN = False negative; FP = False positive; Hb/g = hemoglobin per gram feces; TN = True negative; TP = True positive; ug = Microgram

Appendix E Figure 3. Key Question 2: Forest Plot of Other FITs Sensitivity and Specificity to Detect CRC (Registry Follow-Up)

FIT	Author, year	TP	FN	FP	TN	Total	Sensitivity (95% CI)	Specificity (95% CI)
FOB Gold	Toes-Zoutendijk, 2019	3200	544	37742	484430	525916	0.86 (0.84, 0.87)	0.93 (0.93, 0.93)
FOB Gold (cutoff 15)	Toes-Zoutendijk, 2019	1102	126	14509	111674	127411	0.90 (0.88, 0.91)	0.89 (0.88, 0.89)
FOB Gold (cutoff 47)	Toes-Zoutendijk, 2019	2108	418	23223	372756	398505	0.83 (0.82, 0.85)	0.94 (0.94, 0.94)
FlexSure OBT	Allison, 1996 (Distal)	9	2	164	5181	5356	0.82 (0.48, 0.97)	0.97 (0.96, 0.97)
HM-Jack	Chen, 2018	359	128	7762	200680	208929	0.74 (0.70, 0.77)	0.96 (0.96, 0.96)
HemeSelect	Allison, 1996	22	10	418	7043	7493	0.69 (0.51, 0.86)	0.94 (0.94, 0.95)
Magstream 1000	Launoy, 2005	24	4	410	6983	7421	0.85 (0.69, 0.94)	0.94 (0.94, 0.95)
Monohaem	Nakama, 1996	10	4	147	3204	3365	0.71 (0.45, 0.88)	0.96 (0.95, 0.96)
OC-Hemodia	Castiglione, 2007	67	16	1030	26390	27503	0.81 (0.71, 0.88)	0.96 (0.96, 0.96)
OC-Hemodia	Itoh, 1996	77	12	1413	26358	27860	0.87 (0.78, 0.92)	0.95 (0.95, 0.95)
OC-Sensor/FOB Gold	van der Vlugt, 2017	125	27	2880	15684	18716	0.82 (0.75, 0.87)	0.84 (0.84, 0.85)



Abbreviations: CI = Confidence interval; CRC = Colorectal cancer; FP = False positive; FIT = Fecal immunochemical test; FN = False negative; TP = True positive; TN = true negative.

Appendix F Table 1. Study Characteristics and Reported Lesions for OC-Sensor

Author	Countries	Age, mean or range*	Female, %	Total n	CRC, n (%)	AA, n (%)	Non-advanced adenoma, n (%)	No adenoma, n (%)
Brenner, 2013[70]	DEU	63	51	2235	15 (0.67)	207 (9.3)	398 (17.8)	1615 (72.3)
Chang, 2017[71]	TWN	59	49	6198	0 (0)	428** (6.9)	1254 (20.2)	4516 (72.9)
Chiu, 2016[72]	AUS, JPN, SGP, HKG, KOR, TWN, CHN, BRN, MYS, PAK, PHL, THA	58	49	4434	28 (0.15)	632 (3.5)	--	--
Cooper, 2018[73]	US	57	60	760	2 (0.26)	49 (6.4)	--	--
de Wijkerslooth, 2012[74]	NLD	60†	49	1256	8 (0.64)	111 (8.8)	--	--
Hernandez, 2014[75]	ESP	58	50	779‡	5 (0.64)	92 (11.8)	204 (26.2)	482 (61.9)
Imperiale, 2014[76]	US, CAN	64	54	9989	65 (0.65)	757** (7.6)	2893 (29.0)	6274 (62.8)
Kim, 2017[77]	KOR	≥40	30	14912	15 (0.06)	363 (2.4)	2972 (19.9)	11562 (77.5)
Liles, 2018[78]	US	NR	51	2771	2 (0.07)	209 (7.5)	--	--
Park, 2010[79]	KOR	59	49	770	13 (1.7)	59 (7.7)	219 (28.4)	479 (62.2)
Redwood, 2016[80]	US	40-85	60	661	10 (1.5)	82 (12.4)	235 (35.6)	334 (50.5)
Shapiro, 2017[81]	US	50-75	54	1006	2 (0.2)	53** (5.3)	--	--

* Range if mean not reported

† Median

‡ Row does not add to 779 participants; query to author could not resolve the extra participants in the non-advanced adenoma and no adenoma columns.

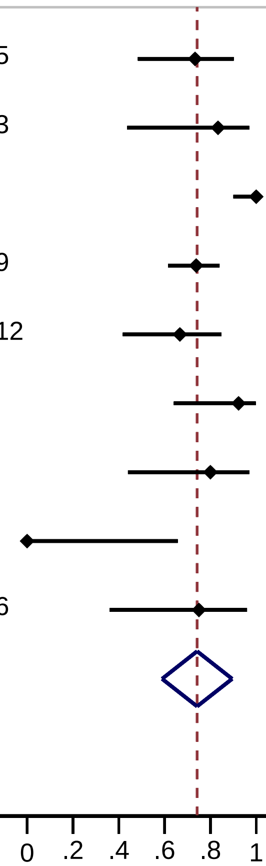
** Includes SSL

Note: Some data obtained through personal communication with authors.

Abbreviations: AA = advanced adenoma; AUS = Australia; BRN = Brunei Darussalam; CAN = Canada; CHN = China; CRC = colorectal cancer; DEU = Germany; ESP = Spain; HKG = Hong Kong; KOR = the Republic of Korea; JPN = Japan; MYS = Malaysia; n = number; NLD = the Netherlands; PAK = Pakistan; PHL = the Philippines; SGP = Singapore; THA = Thailand; TWN = Taiwan; US = United States of America.

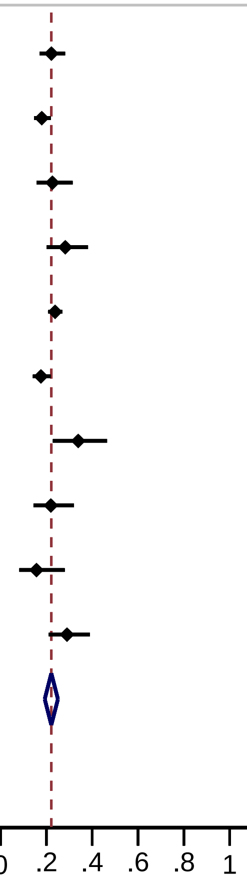
Appendix F Figure 1. Pooled Sensitivity of OC-Sensor at Cutoff 20 ug Hb/g Feces to Detect CRC

Author, year	TP	FN	FP	TN	Total n	Sensitivity (95% CI)
Brenner, 2013	11	4	99	2121	2235	0.73 (0.48, 0.90)
Chiu, 2016	5	1	181	2616	2803	0.83 (0.44, 0.97)
Hernandez, 2014	5	0	50	724	779	1.00 (0.90, 1.00)
Imperiale, 2014	48	17	652	9272	9989	0.74 (0.62, 0.84)
Kim, 2017	10	5	477	14420	14912	0.67 (0.42, 0.85)
Park, 2010	12	1	75	682	770	0.92 (0.64, 1.00)
Redwood, 2016	8	2	52	599	661	0.80 (0.44, 0.97)
Shapiro, 2017	0	2	28	917	947	0.00 (0.00, 0.66)
de Wijkerslooth, 2012	6	2	65	1183	1256	0.75 (0.36, 0.96)
Overall (I-squared = 86.8%, p = 0.000)						0.74 (0.59, 0.89)



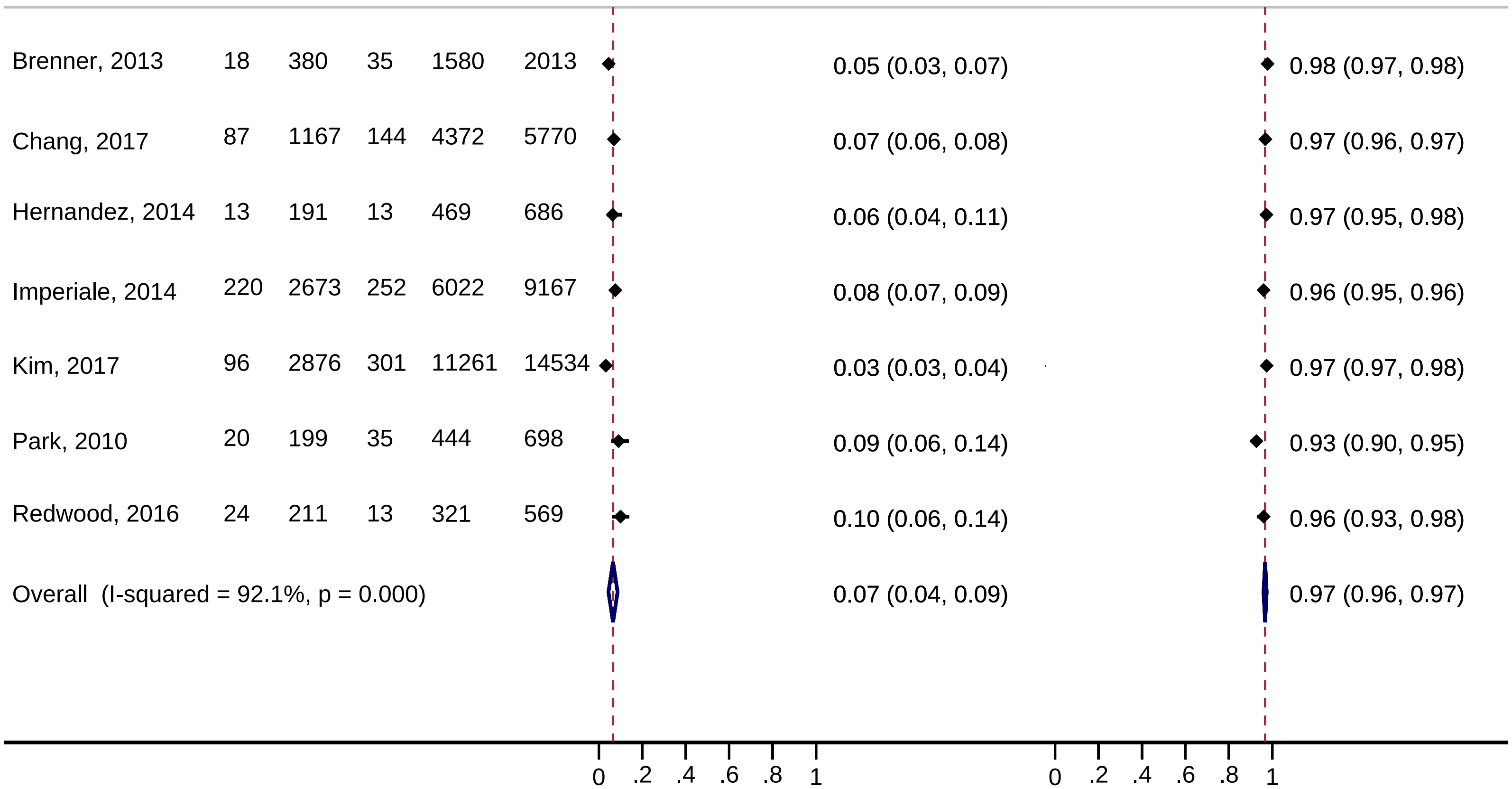
Appendix F Figure 2. Pooled Sensitivity of OC-Sensor at Cutoff 20 ug Hb/g Feces to Detect AA

Author, year	TP	FN	FP	TN	Total n	Sensitivity (95% CI)
Brenner, 2013	46	161	51	1960	2220	0.22 (0.17, 0.28)
Chang, 2017	77	351	231	5539	6198	0.18 (0.15, 0.22)
Chiu, 2016	24	82	157	2534	2797	0.23 (0.16, 0.31)
Hernandez, 2014	26	66	24	658	774	0.28 (0.20, 0.38)
Imperiale, 2014	180	577	472	8695	9924	0.24 (0.21, 0.27)
Kim, 2017	64	299	397	14137	14897	0.18 (0.14, 0.22)
Park, 2010	20	39	55	643	757	0.34 (0.23, 0.47)
Redwood, 2016	18	64	34	535	651	0.22 (0.14, 0.32)
Shapiro, 2017	8	43	20	874	945	0.16 (0.08, 0.28)
de Wijkerslooth, 2012	34	80	34	1103	1248	0.29 (0.21, 0.39)
Overall (I-squared = 54.8%, p = 0.018)						0.22 (0.19, 0.25)

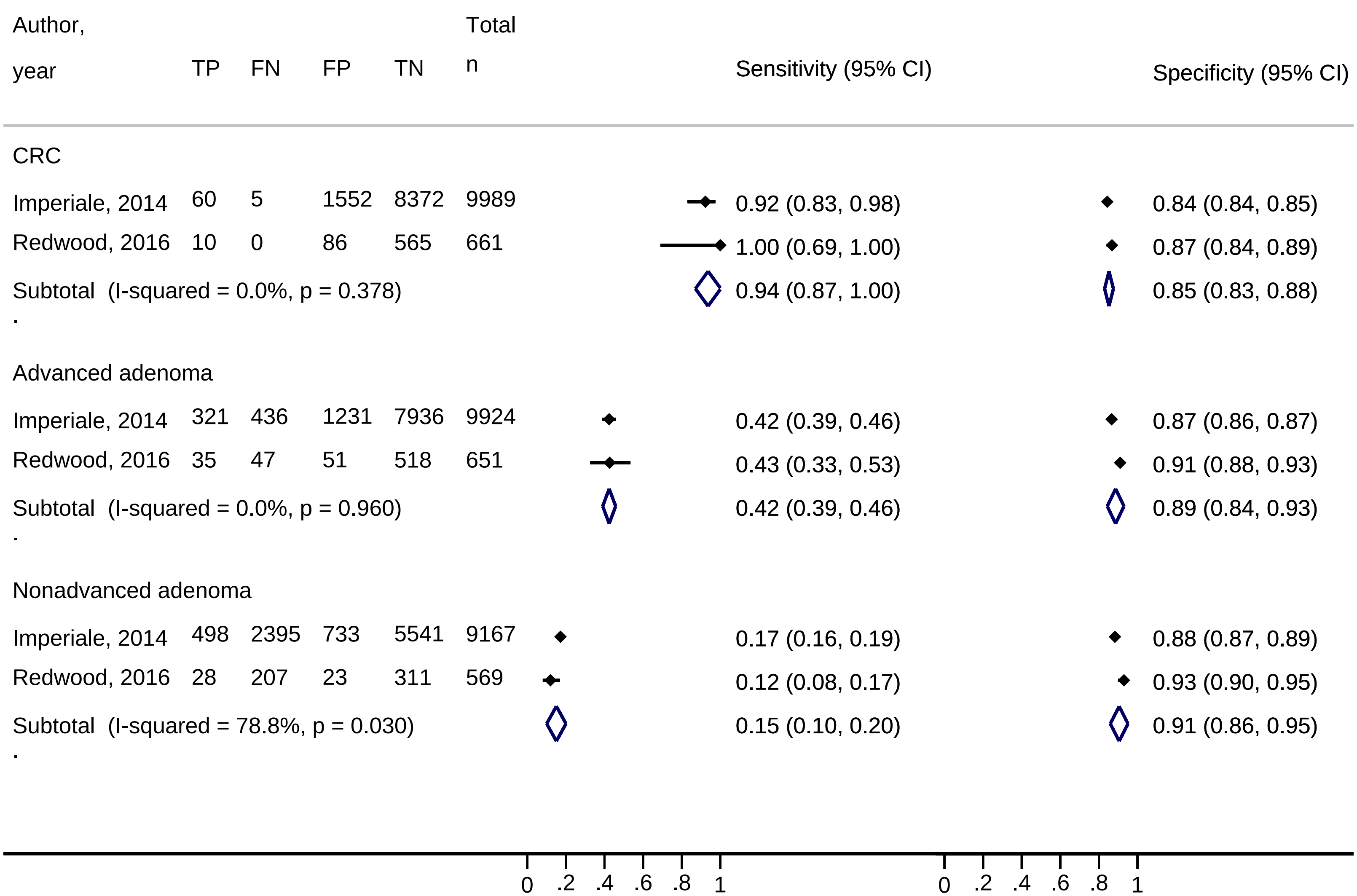


Appendix F Figure 3. Pooled Sensitivity and Specificity of OC-Sensor at Cutoff 20 µg Hb/g Feces to Detect Non-Advanced Adenoma

Author, year	TP	FN	FP	TN	Total n	Sensitivity (95% CI)	Specificity (95% CI)
Brenner, 2013	18	380	35	1580	2013	0.05 (0.03, 0.07)	0.98 (0.97, 0.98)
Chang, 2017	87	1167	144	4372	5770	0.07 (0.06, 0.08)	0.97 (0.96, 0.97)
Hernandez, 2014	13	191	13	469	686	0.06 (0.04, 0.11)	0.97 (0.95, 0.98)
Imperiale, 2014	220	2673	252	6022	9167	0.08 (0.07, 0.09)	0.96 (0.95, 0.96)
Kim, 2017	96	2876	301	11261	14534	0.03 (0.03, 0.04)	0.97 (0.97, 0.98)
Park, 2010	20	199	35	444	698	0.09 (0.06, 0.14)	0.93 (0.90, 0.95)
Redwood, 2016	24	211	13	321	569	0.10 (0.06, 0.14)	0.96 (0.93, 0.98)
Overall (I-squared = 92.1%, p = 0.000)						0.07 (0.04, 0.09)	0.97 (0.96, 0.97)

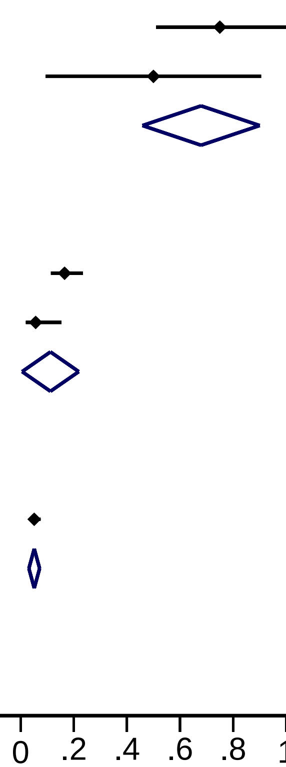


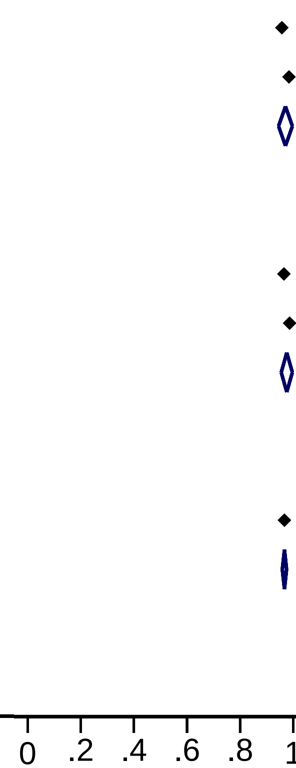
Appendix F Figure 4. Pooled Sensitivity and Specificity of Cologuard to Detect CRC, Advanced Adenomas, and Non-Advanced Adenomas



Appendix F Figure 5. Pooled Sensitivity and Specificity of Hemoccult Sensa to Detect CRC, Advanced Adenomas, and Non-Advanced Adenomas

Author, year	TP	FN	FP	TN	Total n	Sensitivity (95% CI	Specificity (95% CI)
CRC							
Ahlquist, 2008	9	3	106	2379	2497	0.75 (0.51, 1.00)	0.96 (0.95, 0.96)
Shapiro, 2017	1	1	16	988	1006	0.50 (0.09, 0.91)	0.98 (0.97, 0.99)
Subtotal (I-squared = 6.5%, p = 0.301)						0.68 (0.46, 0.90)	0.97 (0.94, 1.00)
Advanced adenoma							
Ahlquist, 2008	24	121	82	2258	2485	0.17 (0.11, 0.23)	0.96 (0.96, 0.97)
Shapiro, 2017	3	50	13	938	1004	0.06 (0.02, 0.15)	0.99 (0.98, 0.99)
Subtotal (I-squared = 82.1%, p = 0.018)						0.11 (0.01, 0.22)	0.98 (0.95, 1.00)
Nonadvanced adenoma							
Ahlquist, 2008	24	445	62	1809	2340	0.05 (0.03, 0.08)	0.97 (0.96, 0.97)
Subtotal (I-squared = .%, p = .)						0.05 (0.03, 0.07)	0.97 (0.96, 0.98)





There are several decision models for colorectal cancer screening in addition to the three microsimulation models in the CISNET-CRC consortium. These Markov and microsimulation models have been used to evaluate the comparative effectiveness and cost effectiveness of various CRC screening strategies. All of these models account for many parameters on the natural history of disease and the screening process; however, they vary in the sources of information and assumptions for the inputs for these parameters. There are numerous challenges to adequate representation of the disease's natural history and screening process, as well as to evaluation of the models' structural uncertainty. Here we briefly summarize the models' findings as they relate to age to start/stop and the comparative effectiveness of the various screening strategies.

Age to start/stop

Two recent decision analyses evaluated the cost-effectiveness of initiating screening before age 50.[82, 83] Both analyses found that beginning screening at age 45 years could be cost effective; however earlier initiation would increase colonoscopy demand and could have less favorable incremental benefits than screening at ages 50 to 74 or 75 years. One Markov model by Ladabaum and colleagues found that initiating screening at age 45 years instead of 50 years would prevent four CRC cases and two CRC-related deaths and require 758 additional colonoscopies.[82] Ladabaum and colleagues modeled the impact of the additional colonoscopies (recognizing that colonoscopies are a fixed resource) on unscreened people (recognizing that many people over age 50 are not screened). They estimated that the 758 colonoscopies could instead be performed on 231 unscreened 55-year-old people or 342 unscreened 65-year-old people and avert 13 to 24 CRC cases and six to seven CRC-related deaths. Likewise, improving colonoscopy completion rates after abnormal FIT (from 60% to 90%) could avert 22 CRC cases and 10 CRC-related deaths. To estimate the population impact and resource impact of recommended earlier age to start screening in the US, the decision analyses found that shifting age specific screening to 5 years earlier could avert 29,400 CRC cases and 11,100 CRC deaths but would require an additional 10.7 million colonoscopies and cost an incremental $10.4 billion, while improving screening rates to 80% in persons age 50-75 years old would avert nearly 3-fold more CRC deaths at one third the incremental cost.

Another decision analysis by Lew and colleagues that used a microsimulation model found that initiating screening with biennial FIT at age 45 years instead of age 50 (based on the Australian National Bowel Cancer Screening Program) would result in an additional reduction of 2–3 percent in CRC cases and 2–4 percent reduction in CRC-related deaths, with an increase in colonoscopies by 3–14 percent (55 to 170 additional colonoscopies per additional CRC death prevented).[83] Lew and colleagues' analyses also estimated the incremental benefit of extending the age to stop screening beyond 74 years. They estimated that biennial FIT until age 79 years would result in an additional reduction of 1–2 percent in CRC cases and 3–5 percent in CRC-related deaths, with an increase in colonoscopies of 9 to 24 percent, and extending screening until age 84 years would result in a reduction of 2–3 percent in CRC cases and 5–7 percent in CRC-related deaths, with an increase in colonoscopies of 27 to 53 percent.[83]

Comparative screening tests

One decision analysis by D'Andrea and colleagues using a microsimulation model evaluated the impact of adherence on screening effectiveness (using CRC incidence, CRC-related deaths, and incremental LYG).[84] The analysis compares 100 percent adherence to reported adherence, using estimates to initial screening and followup colonoscopy (and assuming 100% adherence to surveillance colonoscopies) derived from the literature. Assuming 100 percent adherence, the analyses demonstrated near-equivalent benefit for annual hs-gFOBT or FIT, sDNA+FIT every 3 years, CTC every 5 years, annual mSEPT9 serum testing, and colonoscopy every 10 years. However, when using adherence reported in the literature, colonoscopy was superior to other strategies in reducing cancer incidence and mortality, and the authors concluded that adherence rates higher than 65 to 70 percent would be required for any stool- or blood-based screening to match the benefits of colonoscopy. Their model makes assumptions regarding reported adherence inputs beyond the adherence estimates to initial screening in an attempt to take into account the complexity of modeling real world adherence.

Two systematic reviews summarize the cost-effectiveness of different screening strategies, one by Landsdorp-Vogelaar and colleagues and the second an update of that review by Ran and colleagues.[85, 86] Both reviews include CISNET models. Collectively, the reviews found that a variety of strategies—annual or biennial gFOBT, annual or biennial FIT, FS every 5 years, colonoscopy every 10 years, CTC every 5 or 10 years, sDNA every 3 or 5 years, capsule endoscopy every 5 or 10 years—are all cost effective when compared to no screening, although details and estimates of cost-effectiveness vary. However, compared with common strategies (annual or biennial gFOBT or FIT, FS every 5 years, or colonoscopy every 10 years), CTC was often, but not always, less cost effective, and sDNA and capsule endoscopy were both more expensive and less effective than the majority of common strategies.[85, 86] Three additional published non-CISNET decision analyses were not included in these reviews. One additional microsimulation decision analysis by Coldman and colleagues found that screening with FIT is an effective alternative to colonoscopy, using considerably less colonoscopy resources. One additional Markov decision analysis by Senore and colleagues found that FS plus FIT was more cost effective than FS alone.[87] Lastly, one decision analysis based on the Archimedes model, conducted by Exact Sciences, found that annual sDNA+FIT testing had similar reductions in CRC cases and CRC-related deaths compared with colonoscopy every 10 years; however, concluded that sDNA+FIT every 3 years, although less effective than annual testing, was likely more achievable in clinical practice because of greater cost-effectiveness (and patient preference).[88]

We can estimate adherence to initial screening and subsequent testing in the United States from several types of study designs, including screening trials and observational studies of existing screening programs. Studies of European screening programs also provide estimates, though these are of limited use in estimating adherence in the United States.

Colonoscopy is the most common screening test used by commercially insured people in the United States.[89] Among those who underwent screening in 2015, the test was used by 58.3 percent of the population, followed by FOBT (includes FIT) (7.17%) and rarely, sigmoidoscopy with FOBT (0.7%).[90] Worldwide, FIT is the most commonly used CRC screening test, and most European CRC screening programs use it.[91-93]

Estimates of adherence to initial colorectal cancer screening

Behavioral Risk Factor Surveillance System (BRFSS) survey data show that the overall proportion of U.S. adults ages 50–75 with “up-to-date” CRC screening increased from 65.5 percent in 2012 to 67.3 percent in 2016.[94] However, in 2016, about 26 percent of U.S. adults ages 50–75 had never been screened.[95] According to National Health Interview Survey data, rates of up-to-date CRC screening steadily increased between 2000 and 2015 to 62.4 percent. Adherence to CRC screening has consistently lagged behind that for breast (71.5% age adjusted in 2015) or cervical cancer screening (83.0% age adjusted in 2015).[96]

Adherence to initial screening in included studies

One included trial, The Minnesota Colon Cancer Control Study of screening with Hemoccult II, had 90 percent adherence to at least one round of screening (not reported for individual rounds),[97] which was higher than adherence in Hemoccult II trials conducted outside the United States (range, 60% to 70%).

Based on trials conducted in western European countries, adherence to a single round of gFOBT ranged from 32 to 59 percent, while for FIT it was 32 to 65 percent; for FS, from 28 to 47 percent; for FS plus stool testing, from 20 to 39 percent; for colonoscopy, from 17 to 27 percent; and for CTC, approximately 34 percent.[98] One Dutch trial found greater adherence to CTC than to colonoscopy.[9] However, estimates of adherence to colonoscopy and CTC are based on a limited number of studies, none of which was conducted in the United States. We found no studies comparing the relative adherence of FIT versus sDNA-FIT testing.

Adherence to initial screening in other studies

A comprehensive review of adherence (Khalid-de Bakker and colleagues) included 100 prospective studies of CRC screening, only 10 of which were conducted in the United States.[99] The review included a meta-analysis to determine a pooled estimate of adherence to a first-time invitation to screening that spanned a wide range of studies over nearly three decades. They found that overall adherence was 47 percent for gFOBT, 42 percent for FIT, 35 percent for FS, 28 percent for colonoscopy, and 22 percent for CTC. A comprehensive systematic review conducted by Holden and colleagues found a wide variation in adherence in studies whose purpose was to improve adherence to CRC screening.[100] Adherence in usual care groups (no intervention to improve adherence to screening) ranged from 17 to 51 percent for stool tests, from 5 to 59 percent for colonoscopy, and from 23 to 55 percent for any CRC screening test. A study in the Veterans Health Administration (VA) population found significantly higher adherence rates to FIT compared with FOBT in a direct comparison over time (42.6% vs. 33.4%).[101] This may be due in part to the relative ease of completing a FIT (fewer restrictions, fewer samples) than gFOBT.[101] In Spain, overall adherence to guaiac or immunochemical stool-based testing increased over time and rescreening rates were high, but overall adherence rates did not go above 35.9 percent during the study period,[102] while FIT testing adherence was higher (58.1% increasing to 70.3% over 5 years) in a population-based screening program.[103] In a French population-based screening program, adherence to stool-based testing declined from 51.0% to 33.9% over six rounds of biennial gFOBT screening, and then increased to 53.4% with the implementation of FIT screening.[93]

A large study of adherence to sDNA-FIT in a Medicare population found that 71 percent of persons age 65 to 85 years old completed the stool test within 1 year.[104] A small study of completion of sDNA-FIT testing in Medicare patients found that 88.3 percent of those with no colonoscopy in the previous 10 years or fecal test within the previous 1 year completed the test.[105]

A randomized trial (n=413) of blood test-based screening (Epi proColon) versus FIT testing at two integrated health systems found higher adherence to the blood test (99.5%, 95% CI 97.3%, 100% versus 88.1%, CI 83.0%, 91.8%), and considerably higher adherence to both tests than seen in observational studies.[106] Another trial conducted in Australia (n=1800) compared adherence among those who received mailed a FIT (control group), those who received a blood test as a “rescue” strategy after 12 weeks of FIT nonparticipation (rescue group), and those offered a choice of FIT or blood testing (choice group). After 24 weeks, the trial found no significant difference in adherence among groups (control, 37.8%; rescue, 36.9%; choice, 33.8%).[107]

Adherence to repeated screening

The effectiveness of screening over time depends on continued adherence to screening recommendations,[108, 109] particularly for stool-based tests. Adherence to repeated stool-based screening is inconsistent and remains suboptimal; however adherence to repeated stool testing may be higher than initial adherence to stool testing. Limited U.S. data suggest that adherence to one-time colonoscopy is the main driver of up-to-date screening.[90, 110, 111] Limited emerging evidence suggests that repeated screening colonoscopies in people with initial negative findings may be overused, while surveillance colonoscopy remains suboptimal.

Repeated colonoscopy screening

Limited data are available on adherence to repeated colonoscopy in people with an initial negative finding. A study in the VA population found that 16 percent of people with no adenomas received a second colonoscopy earlier than recommended guidelines, while 54 percent of people with high-risk adenomas did not receive surveillance colonoscopy at the guideline-recommended interval.[112] A Canadian study found that 33.7 percent of people with initial negative results received early repeated colonoscopy.[113]

Repeated stool-based test screening

Adherence to repeated stool-based testing after an initial negative test declines over time. A 2019 systematic review assessed adherence to repeated FOBT testing across 27 studies (8 U.S. based (n=753,495). Adherence to repeated FOBT testing ranged widely, from 0.8% to 3 rounds of opportunistic screening to 60.3% to 2 consecutive rounds of screening using varied outreach methods.[114] One study in a U.S. health system using 2007–2008 data (Kaiser Permanente), showed that initial adherence to FIT was 47 percent, but only 24 percent of patients adhered to the recommended annual testing over four years.[115] A nested observational analysis of data from the STOP CRC Trial, based in U.S. federally qualified health centers, found that rates of completed FIT kits were lower (41%) in the second round of screening invitations compared with the first round (46%), and that physician orders for eligible patients also decreased between the first and second rounds of screening.[116] Similarly, a retrospective analysis of VA medical centers found that only 14 percent of veterans received at least four stool tests over 5 years.[111] A cluster randomized trial of FOBT, colonoscopy, or patient choice of screening found adherence to all 3 years of FOBT was 14 percent, compared with one-time colonoscopy (38%) or choice (42%).[110]

A Kaiser Permanente study using data from 2007–2011 (sites from PROSPR consortium) found that following an initial adherence rate of 48 percent to FIT, adherence over the subsequent 3 years was 75.3 to 86.1 percent, but the analysis included only people who had been adherent in the previous round.[117] A similar pattern was seen in a U.S. study using 2000–2003 Group Health Cooperative data,[118] in the review by Murphy and colleagues,[114] and in international studies. In a U.K.-based study, gFOBT increased over three biennial rounds (57.4% in the first, 60.9% in the second, and 66.2% in third), but consistent screening over all rounds was more limited (44%) and participation in the first round was strongly predictive of continued screening.[119] In a Norwegian study, initial adherence to FIT screening was 44.7 percent; among these completers, 83.1 percent completed a second round of screening.[120] An analysis of French data found that 14.3 percent of the invited population participated in four consecutive rounds of gFOBT screening, with participation decreasing over time.[121, 122] An Australian study of population-based screening found similar rates (43.1%) of "consistent" screening of FIT test completion over four rounds,[123] as did a Canadian screening program that found initial adherence of 81.7 percent to FIT testing, with a 86.0% of those initial completers also completing a second round of testing.[124] In an Italian national screening program of FIT screening, initial adherence was 69 percent and above 94 percent in each subsequent round of previous completers.[125]

A study of a 2010–2011 analysis of repeated gFOBT screening in people in four large U.S. health systems in the PROSPR consortium found wide variation in consistent repeat screening over 3 years following one negative test (mean rate 46%).[126] In a study with older data among insured people (2000–2001) who had completed one FOBT screening, 44.4 percent completed a second screening over 2 years. Receipt of a preventive health examination was strongly associated with FOBT adherence relative to no CRC screening.[118] Another U.S. study found that 41 percent adhered to three rounds of screening with gFOBT, much lower than the 85 percent that received a one-time colonoscopy.[127]

We found no data on adherence to multiple rounds of other screening modalities, including FS, FS plus stool testing, CTC, and sDNA-FIT.

Predictors of adherence to CRC screening

Health insurance coverage and access to care is a major explanatory factor for screening adherence in the United States[128] and often explains observed racial/ethnic differences in screening uptake.[90, 129] Geospatial considerations also affect access to screening and subsequent adherence, including rural/urban and neighborhood-level disparities.[130-134]

Patient selection of a screening test is multifactorial, based on the test's ability to detect and/or prevent cancer, its side effects or adverse effects (including those from bowel preparation and the test itself), the risk of false-positives, convenience of the test, and the screening frequency (interval of testing).[135] Several patient factors may affect uptake and adherence to screening, including age, sex, socioeconomic status/education, race/ethnicity, acculturation, health status, cancer risk, risky health behaviors, marital status, cancer experiences of friends and family, receiving a physician recommendation, and psychosocial factors (including but not limited to patient knowledge, attitudes, beliefs, and concerns about test comfort or invasiveness).[100, 136-140] People who have previously been adherent to CRC screening or other preventive care recommendations are likely to continue to adhere to CRC screening.[141]

Differential adherence by race/ethnicity, sex, and age

In the United States, adherence to CRC screening recommendations varies by population. According to 2015 NHIS data, white adults have the highest rates of up-to-date CRC screening (63.7%), followed closely by black adults (59.3%). CRC screening rates are lower among Asian adults (52.1%) and American Indian/Alaska Native adults (48.4%), and individuals with Hispanic ethnicity have lower screening rates (47.4%) compared with non-Hispanic individuals (64.2%).[96] CRC screening rates also vary within ethnic groups. For example, an analysis of the 2009–2014 Medical Expenditure Panel Survey identified variation in CRC screening rates across Asian-American subgroups, ranging from 48.6 percent among Asian Indians to 50.9 percent among Chinese and 55.0 percent among Filipinos.[142]

Some evidence suggests racial/ethnic disparities in CRC screening vary by health care setting. According to research from the PROSPR consortium, non-Hispanic white and black adults have similar adherence to CRC screening in health care systems with low overall screening rates, but black adults have lower adherence than white adults in systems with high overall screening rates.[143] In a California-based integrated health system, CRC screening rates were similar among non-Hispanic white and black adults, higher among Asian adults, and marginally lower among Hispanic adults.[144] One VA study found black adults had slightly lower adherence (72%) compared with white adults (77%), but the disparity was attenuated (compared with national averages) and was accounted for by confounders of single marital status and lower levels of education.[145] The STOP CRC trial, which was conducted in FQHCs in Oregon and California, found that Asian race, Hispanic ethnicity, and non-English preference were associated with higher odds of screening completion.[116]

Data are mixed for differences in adherence by sex. Data from the 2016 BRFSS found rates of up-to-date CRC screening were slightly lower for males (65.9%) compared with females (69.4%),[146] while data from the 2015 NHIS found similar screening rates for males (63.2%) and females (62.2%).[96, 147] Rates of fecal test completion (FOBT or FIT) in the previous year were slightly higher among males (7.6%) compared with females (6.8%) in the 2015 NHIS data. However, an international meta-analysis of FIT screening studies found lower uptake in men compared with women.[148]

CRC screening rates also vary by age. According to the 2015 NHIS, adherence is lower among people ages 50–64 years (57.9%) compared with people ages 65–75 years (71.8%).[96] There are less data on screening in populations younger than age 50. A study using 2010 NHIS data found CRC screening adherence was 41.4 percent among adults ages 40–49 years who had a first-degree relative with CRC.[149]An observational study of screening adherence in African Americans ages 45–49 years found 17.4 percent had received at least one screening procedure, most commonly colonoscopy.[150]

Adherence to CRC screening also varies by other demographic characteristics. Use of CRC screening is lower among foreign-born people (52.3% [U.S. residence ≥10 years], 36.3% [U.S. residence <10 years]) than among U.S.-born people (64.6%).[96] In addition, CRC screening is higher in groups with the highest education (70.7%) and income levels (70.0%), and lower among people without a usual source of health care (26.3%) or health insurance (25.1%).[96] Screening rates also vary by U.S. state of residence, ranging from 58.5 percent in New Mexico to 75.9 percent in Maine.[94]

Differential adherence by family history

A family history of CRC is associated with an increased likelihood of screening.[151, 152] According to a 2015 systematic review, adults with a family history of colorectal cancer (typically defined as at least one first-degree relative with CRC) are about 1.4–3.3 times more likely to adhere to CRC screening recommendations than individuals with no family history.[151] A study using 2010 NHIS data found CRC screening adherence was 57.0 percent (ages 50–64) and 65.9% (age ≥65) among those with no family history of CRC, compared with 70.8 percent (age 50-64) and 72.5 percent (age ≥65) among those with a first-degree relative with CRC.[149] Adherence was lower (41.4%) among adults ages 40–49 years with a first-degree relative with CRC,[149] despite recommendations from several groups to initiate screening at age 40 among those who had a first-degree relative diagnosed with CRC at age <60.[153]

Interventions to Increase CRC screening

A 2018 systematic review and meta-analysis of U.S.-based randomized clinical trials of interventions to increase colorectal cancer screening (73 included trials) found that fecal blood test outreach, patient navigation, patient education, patient reminders, and clinician-focused interventions (academic detailing or clinician reminders) were associated with increased completion of colonoscopy or initial stool-based screening.[154] Multicomponent interventions were more effective than single-component interventions, and mailed fecal blood tests with patient navigation improved adherence to repeated stool-based testing.[154] The Holden systematic review found strong evidence for the effectiveness of interventions including patient reminders or one-on-one interactions, eliminated structural barriers (e.g. improving access), and system-level changes (e.g., systematic screening) in improving CRC screening.[100] A 2019 systematic review of interventions to improve FIT screening (15 of 25 studies were U.S.-based) found that mailed kit outreach improved adherence by 21.5 percentage points, while reminders only were much less effective (4.1%).[155] Increased awareness of CRC and decision aids that help patients choose among various CRC screening options are associated with higher rates of screening uptake.[156]

The Community Preventive Services Task Force recommends multicomponent interventions to increase screening for colorectal cancers on the basis of strong evidence of effectiveness in increasing screening with colonoscopy or FOBT.[157]

Adherence to followup colonoscopy for abnormal screening test results

Completion of followup colonoscopy is a critical step in the screening process for people with positive stool-based test results. Lack of colonoscopy within 12 months is associated with higher risk of CRC and later stage at diagnosis,[158] based on a review of modeling following a positive stool-based test due to increasing risk of cancer and late-stage disease with increasing delays between positive stool-based test and followup colonoscopy.[159]

Observational U.S.-based evidence of completion of colonoscopy after positive stool-based testing

Since the previous USPSTF review, several large U.S.-based observational studies on this topic have been published, as well as one meta-analysis and one systematic review of interventions. These studies together suggest that adherence to followup colonoscopy is incomplete overall, with adherence estimates between 50 percent and 87 percent. There is limited evidence of increasing adherence with time. Completion of followup colonoscopy ranges widely across institutions and may be lower in safety net settings.

Adherence appeared highest in studies of large health systems. In two observational studies from the PROSPR consortium using data from four large health systems (including Kaiser Permanente Northern California and Kaiser Permanente Southern California), estimates of adherence using 2010–2012 data were overall 79.6 percent at 3 months in people ages 50–74[141] and 58.1 to 83.8 percent across sites at 6 months in people ages 50–89.[160] In two studies using Kaiser Permanente data alone (southern California and northern California), adherence was 78.4 percent at 12 months according to 2006–2008 data,[117] and 83.2 percent at 12 months in peoples ages 50-74.[158] National screening programs in the Netherlands and Spain reported particularly high completion rates of followup colonoscopy, both above 90 percent.[103, 161]

Two studies of VA populations found lower adherence. In a study of completion of followup colonoscopy in people with positive stool-based tests, completion was approximately 50 percent at 6 months at 120 clinics using 2009–2011 data. In this study, black individuals were more likely to receive colonoscopy than white individuals.[162] In a more recent study of VA clinics in southern California using 2014–2016 data, completion was 62.1 percent at 6 months, and median time to colonoscopy was 83 days.[163]

Four studies suggest that completion rates may be even lower in these settings. In four studies of large safety net settings using data from 2010–2015, adherence ranged from 51.5 to 57.7 percent at 6 to 12 months' followup.[164-167] In one study, Spanish language speakers were more likely to complete colonoscopy than English speakers, and people with one to two visits were more likely to complete than those with no visits.[164] In another, completion was less likely among those ages 61–64 compared with those ages 50–55.[165]

A recent systematic review (2019) and meta-analysis including studies published though 2017 (13 of 42 studies were U.S.-based) found that the pooled estimate of colonoscopy completion was 80.4 percent. Rates increased incrementally with each 10-year increment studied.[168] An older systematic review found that adherence to followup colonoscopy for positive stool testing (within 1 year) in integrated health systems ranged from 44 to 86 percent.[100] In a review of interventions to improve followup colonoscopy completion, rates in the control group ranged from 2 percent over 60 days' followup to 80 percent within 6 months.[91]

One retrospective population based study found that the rates of follow-up colonoscopy were higher following a positive sDNA-FIT versus FIT screening test, 84.9 versus 42.6 percent respectively.[169] Another large retrospective study of 15,469 patients at Mayo Clinic sites reported that 87 percent of persons with a positive sDNA-FIT underwent follow-up colonoscopy.[170]

Variation by race, ethnicity, or age in completion of followup colonoscopy

Very little data exist to explain disparities in adherence to followup colonoscopy by subgroups. Based on the PLCO trial, however, it appears that blacks had lower adherence (63%) to followup colonoscopy after screening FS than whites (72%).[171] Evidence of variation in completion by race/ethnicity or age was less consistently reported, and the available evidence was less clear, than in studies of adherence to initial screening (see CQ1).

Interventions to increase adherence to followup colonoscopy

A systematic review of interventions to improve adherence to followup colonoscopy after stool testing found that interventions could increase the proportion of test-positive patients receiving a followup colonoscopy by up to 23 percentage points.[91]

A review of the 29 CDC-funded centers in the Colorectal Cancer Control Program (CRCCP) was published in 2019 using 2009–2015 data. Across centers, 82.9 percent of people ages 50–64 completed a colonoscopy after a positive stool test, 79.8 percent within 90 days, and 95.2 percent within 180 days.[172] The CRCCP supports implementation of evidence-based interventions in accordance with the Guide to Community Preventive Services[157]to increase CRC screening for under- or uninsured people.

Completion of colonoscopy after positive stool-based testing in included studies

In the Minnesota trial, 10 percent of participants on average had positive Hemoccult II tests and 83 percent of those participants underwent a followup evaluation (most often colonoscopy).[97] In the PLCO trial, 33 percent of people with screening FS were recommended to follow up with colonoscopy; 77 percent of which actually received the followup colonoscopy.[173]

Family history of CRC represents an approximation of genetic risk and is typically characterized in terms of the number of affected relatives, the degree of relatedness to them, and their age at CRC diagnosis. Individuals at the highest risk are those from families with known genetic syndromes, multiple affected relatives, and/or relatives with early-age cancer diagnosis, particularly before age 50. At more moderate risk levels are people with one or more first-degree relatives (FDRs) or second-degree relatives (SDRs) with later onset cancer.

A systematic review of eight large population-based cohorts found that the prevalence of family history of one FDR with early-onset cancer (age 60 or younger) was approximately 0.3 percent, while the prevalence of a single FDR with history of late-onset CRC (after age 60) was more than 3 percent.[151] Based on California Health Interview Survey data, "moderate risk" of family history (defined as either one FDR with late onset cancer, two SDRs from the same lineage with late-onset cancer, or one SDR with early onset cancer and the other SDR with an associated cancer) has a prevalence of 4.2 percent.[174] The risk of CRC also increases with the number of affected FDRs. A systematic review of 42 case-control and 20 cohort studies found the pooled relative risk of CRC in patients with 1 affected FDR was 1.92 (95% CI, 1.53 to 2.41) in case-control and 1.37 (95% CI, 0.76 to 2.46) in cohort studies, compared to the relative risk of CRC with 2 or more affected FDRs was 2.81 in case-control studies (95% CI, 1.73 to 4.55) and 2.40 in cohort studies (95% CI, 1.76 to 3.28).[175]

A systematic review and meta-analysis of 63 studies (n=9.83 million) found further evidence that patient age is an important variable in assessing CRC risk due to family history. In this study, meta-analysis of 10 studies suggested that family history-associated CRC risk was higher in people younger than age 50 compared with people over age 50 (RR 2.81; 95% CI, 1.94 to 4.07).[176]

Measurement issues

Family history is a complex risk factor because it can represent genetic risk as well as aggregate behavioral risk (e.g., smoking, diet) and because it can change over time (e.g., can be altered with CRC screening and polyp removal). Furthermore, self-report of family history, while specific, may not be very sensitive. A Scottish case-control study comparing the accuracy of self-reported family history and relatives' medical records found that cases underreported colorectal cancer in FDRs (sensitivity 0.57 [95% CI, 0.43, 0.69]; specificity 0.99 [95% CI, 0.98, 0.99]) and SDRs (sensitivity 0.27 [95% CI 0.17, 0.41]; specificity 0.99 [95% CI 0.99, 1.0]); similar patterns were reported in controls.[177] A systematic review for the AHRQ Effective Healthcare Program found similar results, also concluding that accuracy is higher in reporting of cancer history in FDRs than in more distant relatives.[178]

Screening recommendations based on family history

CRC screening guidelines generally recommend early and more frequent colonoscopy for people at the highest levels of risk due to family history, typically those with a single FDR with early onset cancer (before age 60) or multiple relatives with CRC diagnoses that suggest genetic risk. In these high-risk groups, colonoscopy is typically recommended at age 40 years or 10 years before the relative's age at diagnosis, repeated at 5–10 years.[153, 179] (**Appendix H Table 1**) In addition, family members of people with known genetic syndromes may be invited to receive cascade genetic testing and/or enhanced surveillance.[180]

There is less consensus on screening guidelines for people with a more moderate family history risk—those with a single FDR and/or SDR diagnosed after age 60 (**Appendix H Table 1**). Recommendations for this group range from a single screening with any modality at age 40 years and subsequent screening assuming average risk (U.S. Multi-Society Task Force on Colorectal Cancer) to screening in people with one or more FDR between age 40 and 50 years or 10 years before the affected relative's age of diagnosis, and typical screening beginning at age 50 for people with affected SDRs (Canadian Association of Gastroenterology guidelines).

Risk of CRC in people under age 50 at moderately increased risk for CRC based on family history

A large body of observational evidence from multiple countries and populations suggests that CRC risk increases as the intensity of family history of CRC increases (more relatives, closer in relation, younger age at diagnosis), providing a plausible hypothesis for a screening benefit in these groups. Pooled risk estimates for the highest risk groups compared with people with no known family history range from 3.55 (95% CI, 1.84-6.83) for people with a single FDR diagnosed before age 50 to 3.97 (95% CI, 2.6 to 6.06) for people with two or more affected FDRs.[153] Pooled risk estimates for a single FDR with CRC over age 60 years remain elevated compared with people who have no family history (1.83, 95% CI, 1.47-2.25).[153] A systematic review and meta-analysis of relative risks for CRC associated with family history found a pooled risk of RR 2.24 (95% CI, 2.06-2.44), and 3.97 (95% CI, 2.60 to 6.06) for people with at least two affected FDRs.[184] It also found that lifetime risks for CRC for a 50-year-old increased from 1.8 percent if there was no family history to 3.4 percent (95% CI, 2.8-4.0) if there was at least one affected relative and to 6.9 percent if there were two or more affected relatives.[184] The review of reviews conducted for the CAG guidelines found similar increased levels of risk for nearly all types of studies and populations.[179] Two studies additional studies using data from the Swedish Cancer Registry similarly add to this large body of observational evidence. One study found similar lifetime cumulative CRC risk associated with having either a half- or full-sibling with CRC (standardized incidence ratio 1.65, 95% CI, 1.58 to 1.73 for full sibling; SIR 1.55, 95% CI,1.30 to 1.83 for half sibling).[185] The second study modeled starting ages for CRC screening based on family history, finding that people with family history reached the population level 10-year cumulative risk (0.44) 3 to 29 years (earlier according to higher intensity of family history) earlier than people without family history.[186]

In the PLCO trial, family history of CRC was a predictor of CRC incidence and mortality.[187] Mortality risk estimates were highest for people who had two or more affected FDRs (RR 1.53; 95% CI, 0.7 to 3.3), and people who had a FDR with CRC before age 60 years (RR 1.66, 95% CI, 1.1 to 2.5).[187] However, the PLCO trial did not include people under age 50.

Evidence on the effectiveness of screening for CRC in people under age 50 at moderate risk for CRC based on family history

We found no direct evidence of the effectiveness of screening people under age 50 at moderately increased CRC risk due to family history. Included studies for KQ1 generally did not include people under age 50 nor report results stratified by family history.

None of the included flex sig screening trials included participants under age 50. Two FS trials reported including about 10 percent of participants with a family history of CRC.[188, 189] Neither of these trials reported stratified results by family history. Three of the included gFOBT screening trials include participants under age 50 (starting screening age 45) but did not report results by age strata nor family risk.[24, 190, 191]

One included observational colonoscopy study included people under age 50, but did not report age-stratified results.[192] This study (in health professionals) found that in people with a FDR family history of CRC, the association was no longer statistically significant after 5 years (multivariate HR 0.91; 95% CI, 0.55 to 1.52) compared with a sustained association beyond 5 years in people without a family history (multivariate HR 0.43; 95% CI, 0.32 to 0.58) (p=0.04 for interaction). Another population-based German case-control study found that previous colonoscopy was associated with decreased CRC risk in people with all levels of family history. Regardless of family history status, colonoscopy was associated with a lower CRC risk (OR: 0.25; 95% CI, 0.22 to 0.28 for people without family history and OR 0.45; 95% CI, 0.36 to 0.56 for people with family history). However, only about a fraction of the study population was under age 50 (5.4% of cases and 4.4% of controls).[193]

Evidence on the test accuracy of screening for CRC in people under age 50 at moderate risk for CRC based on family history

While several studies of test accuracy included people under age 50 and those with a family history of CRC, no studies reported variation of test accuracy by family history.

Four CTC and colonoscopy accuracy studies included people age 40 years and older[58, 194-196], three of which [194-196] required a family history for people ages 40 to 50 years. None of these studies reported age-stratified results for people under age 50 years nor by family risk. Likewise, several stool test-accuracy studies (high-sensitivity gFOBT, FIT, or sDNA) included participants under age 50 years and/or people with a family history of CRC (range 3–13% when reported), but no studies reported stratified results by family history. Five studies reported the test accuracy of OC-Sensor for a variety of age groups (i.e., 40–49 years, 50–75 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–75 years). Across all studies, there were no patterns or differences in the sensitivity and specificity to detect CRC among different age groups.

Evidence on the harms of screening for CRC in people under age 50 at moderate risk for CRC based on family history

We found no studies that reported variation of test accuracy by family history. Harms of colonoscopy generally increase with age, and few studies included people younger than age 50 years, none of these studies reported harms by family history.

Appendix H Table 1. Recommendations From Professional Societies for Those With a Family History

Group	Family History	Recommendation	Strength of recommendation
Canadian Association of Gastroenterology[179]	1+ FDR with CRC	Screening over no screening	Strong recommendation, Moderate evidence quality
	2+ FDR with CRC	Colonoscopy (1st)	Strong recommendation, Very low evidence quality
		Begin at 40 years or 10 years younger than age of diagnosis of FDR	Conditional recommendation, Very low evidence quality
	1 FDR with CRC	Colonoscopy (1st)	Conditional recommendation, Very low evidence quality
		FIT (2nd)	Conditional recommendation, Very low evidence quality
		Begin at 40 years or 10 years younger than age of diagnosis of FDR	Conditional recommendation, Very low evidence quality
	1+ SDR with CRC	Screening over no screening	Strong recommendation, Very low evidence quality
		Begin at 50 years	Conditional recommendation, Low evidence quality
		Screening tests in accordance with average-risk guidelines	Conditional recommendation, Very low evidence quality
	1+ FDR with AA	Screening over no screening	Strong recommendation, Very low evidence quality
		Colonoscopy or FIT	Conditional recommendation, Very low evidence quality
		Begin at 40 years or 10 years younger than age of diagnosis of FDR	Conditional recommendation, Very low evidence quality
	1+ FDR with non-AA	Screening in accordance with average-risk guidelines	Conditional recommendation, Low evidence quality
U.S. Multi-Society Task Force on Colorectal Cancer[181] (American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy)	2+ FDR with CRC or AA or advanced serrated lesion (any age) *or* 1+ FDR with CRC or AA or advanced serrated lesion (age <60 years)	Colonoscopy (1st)	Weak recommendation, Low evidence quality
		FIT (2nd)	Strong recommendation, Moderate evidence quality
		Begin at 40 years or 10 years younger than age of diagnosis of FDR	Weak recommendation, Low evidence quality
	1 FDR with CRC or AA or advanced serrated lesion (age ≥60 years)	Begin at 40 years; screening tests in accordance with average-risk guidelines	Weak recommendation, Very low evidence quality
	1+ FDR with non-AA	Screening in accordance with average-risk guidelines	NR
National Comprehensive Cancer Network[182]	1+ FDR with CRC (any age)	Colonoscopy at 40 years or 10 years before earliest CRC (whichever is earlier)	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
	1+ FDR with AA or advanced SSP	Colonoscopy at 40 years or at age of onset of adenoma in relative (whichever is earlier)	
American Cancer Society[183]	NA	No high-risk recommendation. Refers to the USMSTF guideline	NA

Abbreviations: AA = advanced adenoma; CRC = colorectal cancer; FDR = first-degree relative; FIT = fecal immunochemical test; SDR = second-degree relative; SSL = sessile serrated polyp

Appendix I. Ongoing Trials

Study Reference Trial Identifier	Study Name Location	Recruitment age, years	Estimated N	Description	Relevant Outcomes	2019 Status
Colonoscopy and FIT as colorectal cancer screening test in the average risk population. https://clinicaltrials.gov/ct2/show/NCT02078804. Accessed February 9, 2015. NCT02078804	SCREESCO Sweden	59-62	200,000	Randomized trial comparing FIT and colonoscopy to usual care	CRC mortality and incidence	Recruiting
Pilot study of a national screening programme for bowel cancer in Norway. https://clinicaltrials.gov/ct2/show/NCT01538550. Accessed February 9, 2015. NCT01538550	NR Norway	50-74	140,000	Randomized trial comparing FOBT to FS	CRC mortality and incidence; adverse events	Active, not recruiting Psychological harms reported[197]
Kaminski MF, Bretthauer M, Zauber AG, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Eur J Radiol 2012 Jul;44(7):695-702. NCT00883792	NordICC Nordic countries; The Netherlands; Poland	55-64	66,000	Randomized trial comparing colonoscopy to usual care	CRC mortality and incidence; all-cause mortality	Active, not recruiting Baseline detection rates reported[198]
Colorectal Cancer Screening in Average-risk Population: Immunochemical Fecal Occult Blood Testing Versus Colonoscopy. https://clinicaltrials.gov/ct2/show/NCT00906997. Accessed September 25, 2018. NCT00906997	COLONPREV Spain	50-69	55,498	Randomized trial comparing FIT to colonoscopy	CRC mortality and incidence; adverse events	Active, not recruiting Baseline detection rates reported[199]
Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM). https://clinicaltrials.gov/ct2/show/NCT01239082. Accessed December 15, 2014. NCT01239082	CONFIRM US	50-75	50,000	Randomized trial comparing FIT to colonoscopy	CRC mortality	Active, not recruiting
Regge D, Iussich G, Senore C, et al. Population screening for colorectal cancer by flexible sigmoidoscopy or CT colonography: study protocol for a multicenter randomized trial. Trials 2014;15:97. PMID: 24678896 NCT01739608	NR Italy	58-60	20,000	Randomized trial comparing CTC to FS	AN incidence; adverse events	Active, not recruiting Baseline detection rates reported[7]

Appendix I. Ongoing Trials

Study Reference Trial Identifier	Study Name Location	Recruitment age, years	Estimated N	Description	Relevant Outcomes	2019 Status
Randomized Controlled trial to evaluate the effectiveness of total colonoscopy in colorectal cancer screening. http://apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000001980. Accessed February 9, 2015.	NR Japan	40-74	10,000	Randomized trial comparing FOBT to FOBT and colonoscopy	CRC mortality and incidence	Active, not recruiting

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