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Screening for Colorectal Cancer: A Systematic Review for the U.S. Preventive Services Task Force

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Prepared by:
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research
Portland, OR

Investigators:
Jennifer S. Lin, MD, MCR
Margaret A. Piper, PhD, MPH
Leslie A. Perdue, MPH
Carolyn Rutter, PhD
Elizabeth M. Webber, MS
Elizabeth O'Connor, PhD
Ning Smith, PhD
Evelyn P. Whitlock, MD, MPH

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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 three questions: 1) What is the effectiveness of screening programs in reducing incidence of and mortality from CRC? 2) What are the test performance characteristics of the different screening tests for detecting CRC, advanced adenomas, and/or adenomatous polyps based on size? and 3) What are the adverse effects of the different screening tests, and do adverse effects vary by important subpopulations?

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 31, 2014.

Study Selection: We reviewed 8,492 abstracts and 696 articles against the specified inclusion criteria. We carried an additional 33 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.

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 synthesized results by key question and type of screening test. We primarily used qualitative synthesis. We used random-effects meta-analyses when appropriate. We also summarized the overall strength of evidence for each key question.

Results: *Key question 1.* We included 25 unique fair- to good-quality studies that assessed the effectiveness or comparative effectiveness of screening tests as a single application or in a screening program on CRC incidence and mortality. Based on four randomized, controlled trials (RCTs) (n=458,002), flexible sigmoidoscopy (FS) consistently decreased CRC-specific mortality compared to no screening at 11 to 12 years of followup (incidence rate ratio, 0.73 [95% CI, 0.66 to 0.82]). Based on five RCTs (n=404,396), biennial screening with the guaiac-based fecal occult blood test (Hemoccult II) compared to no screening resulted in reduction of CRC-specific mortality at 11 to 30 years of followup, ranging from 9 to 22 percentage points after two to nine rounds of screening. One prospective cohort (n=88,902) found that the CRC-specific mortality rate was lower at 24 years in persons who self-reported screening with colonoscopy (adjusted hazard ratio, 0.32 [95% CI, 0.24 to 0.45]) compared to those who had never had screening endoscopy.

Key question 2. We included 33 unique studies evaluating the one-time diagnostic accuracy of various screening tests compared to an adequate reference standard. Only four fair- to good-quality studies (n=4,821) reported the diagnostic accuracy of colonoscopy generalizable to community practice. Based on three studies comparing colonoscopy to CTC or CTC-enhanced colonoscopy (n=2,290), the per-person sensitivity for adenomas 10 mm or larger ranged from 89.1 percent (95% CI, 77.8 to 95.7) to 94.7 percent (95% CI, 74.0 to 99.9), and the per-person sensitivity for adenomas 6 mm or larger ranged from 74.6 percent (95% CI, 62.9 to 84.2) to 92.8 percent (95% CI, 88.1 to 96.0).

Based on studies of computed tomographic colonography (CTC) with bowel preparation (k=7), the per-person sensitivity and specificity to detect adenomas 10 mm or larger ranged from 66.7 percent (95% CI, 45.4 to 83.7) to 93.5 percent (95% CI, 83.6 to 98.1) and 86.0 percent (95% CI, 84.6 to 87.3) to 97.9 percent (95% CI, 95.7 to 99.1), respectively. The per-person sensitivity and specificity to detect adenomas 6 mm or larger ranged from 72.7 percent (95% CI, 58.4 to 84.1) to 98.0 percent (95% CI, 90.9 to 99.8) and 79.6 percent (95% CI, 77.1 to 82.0) to 93.1 percent (95% CI, 89.5 to 95.7), respectively.

The sensitivity varied considerably across different qualitative and quantitative fecal immunochemical test (FIT) assays in the included diagnostic accuracy studies. Based on studies using colonoscopy as the reference standard (k=14), we focused on selected qualitative and quantitative tests cleared by the U.S. Food and Drug Administration (i.e., OC-Light and OC FIT-CHEK, respectively) and evaluated in more than one study. Lowest sensitivity with accompanying specificity for CRC in studies using one stool specimen was 73.3 percent (95% CI, 48.3 to 90.2) and 95.5 percent (95% CI, 94.6 to 96.3), respectively. Similarly, the highest sensitivity and paired specificity was 87.5 percent (95% CI, 54.6 to 98.6) and 90.0 percent (95% CI, 89.2 to 92.4), respectively. In the largest studies, sensitivity ranged from 73.8 percent (95% CI, 62.3 to 83.3) for quantitative (n=9,989) to 78.6 percent (95% CI, 61.0 to 90.5) for qualitative (n=18,296) test categories. In one small study (n=770) that tested three stool specimens, sensitivity was 92.3 percent (95% CI, 69.3 to 99.2) and specificity was reduced to 87 percent (95% CI, 85 to 89). Results from studies using differential followup generally fell within these ranges. One fair-quality study (n=9,989) evaluated a multitarget stool DNA (mtsDNA) assay (FIT plus stool DNA) in comparison to an OC FIT-CHEK test and found that the sensitivity to detect CRC was higher than for FIT (92.3% [95% CI, 84.0 to 97.0]) but with a tradeoff of a lower specificity to detect CRC (84.4% [95% CI, 83.6 to 85.1]).

Thus far, only one blood test, which detects circulating methylated *SEPT9* DNA, has been prospectively evaluated in a screening population. This test had a sensitivity of only 48.2 percent (95% CI, 32.4 to 63.6) to detect CRC.

Key question 3. We included 98 fair- to good-quality studies for the harms of CRC screening. Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons are relatively uncommon, with a pooled estimate of 4 perforations (k=26) (95% CI, 2 to 5) and 8 major bleeds (k=22) (95% CI, 5 to 14) per 10,000 procedures. Serious adverse events from screening FS are even less common, with a pooled estimate of 1 perforation (k=16) (95% CI, 0.4 to 1.4) and 2 major bleeds (k=10) (95% CI, 1 to 4) per 10,000 procedures. Complication rates are higher in diagnostic/therapeutic colonoscopy conducted as followup to positive stool tests or FS. Eighteen studies provided analyses of differential harms of colonoscopy by age (groups). These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding. The risk of perforation for screening CTC (k=14) was less than 2 events per 10,000 examinations. CTC may also have harms resultant from exposure to low-dose ionizing radiation (range, 1 to 7 mSv per examination). Approximately 5 to 37 percent of examinations have extracolonic findings that necessitate actual diagnostic followup.

Limitations: Comparative effectiveness studies to date do not provide evidence of the relative benefit of different screening programs on CRC incidence or mortality. Variation of CTC test

performance may be due to differences in bowel preparation, CTC imaging, or differences in reader experience or reading protocols. FITs do not represent a class of testing; therefore, evidence should be considered per family of FIT. Evidence for mtsDNA testing is limited to one study. Serious harms from endoscopy other than perforations and bleeding are subject to reporting bias, and few studies of endoscopy harms report rates of adverse events in nonendoscopy comparator arms. It is unclear if detecting extracolonic findings represents a net benefit or harm.

Conclusions: Since the 2008 USPSTF recommendation, we have more evidence on the effectiveness of FS on reducing CRC mortality, the test performance of screening CTC, and the decreasing radiation exposure from CTC, as well as the test performance of a number of promising FITs, including one FIT plus stool DNA test, that are available in the United States and approved by the U.S. Food and Drug Administration for screening. Currently used screening modalities, including colonoscopy, FS, CTC, and various high-sensitivity stool-based tests, each have different levels of evidence to support their use and different test performance to detect cancer and precursor lesions, as well as different risks of harms. Recommendations on which screening tests to use or 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

The U.S. Preventive Services Task Force (USPSTF) will use this report to update its 2008 recommendation on screening for colorectal cancer.

Condition Background

Condition Definition

Colorectal cancer (CRC) or colorectal adenocarcinoma is a malignant tumor arising 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 tumors or polyps that can progress to adenocarcinomas (**Table 1**). Adenomas or adenomatous polyps can be pedunculated (polypoid) or sessile (flat). Adenomas can have different degrees of dysplasia or different histologic characteristics (i.e., tubular, tubulovillous, and villous). Advanced adenomas are benign tumors with an increased likelihood to progress to CRC. The term advanced neoplasia, on the other hand, refers to a composite outcome of advanced adenomas and all stages of CRC (**Table 1**). Although there is some variation in the exact definition of advanced adenomas, they generally refer to adenomas 1 cm or larger, with villous components (tubulovillous or villous), or with high-grade or severe dysplasia.

Prevalence and Burden of Disease

CRC causes significant morbidity and mortality in the United States. Although CRC incidence rates have been declining for the past 20 years, among all cancers, CRC is third in incidence and cause of cancer death for both men and women.[1] In 1999, the National Program of Cancer registries estimated the age-adjusted incidence rate of invasive CRC to be 56.5 cases per 100,000 persons. By 2011, the estimate had fallen to 39.9 cases per 100,000 persons.[2] The National Cancer Institute (NCI) estimates that more than 50,000 persons will die in the United States from CRC in 2014.[3] Data from the NCI's Surveillance, Epidemiology, and End Results (SEER) Program from 2007–2011 indicate that the annual incidence of CRC in the United States is 43.7 cases per 100,000 persons, with approximately 95 percent of diagnoses occurring in adults older than age 45 years.[3] The lifetime risk of acquiring CRC in the United States is about 5 percent, with an age-adjusted death rate of 15.9 deaths per 100,000 persons. 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 70 percent, however, for those diagnosed with regionalized disease (cancer spread to regional lymph nodes). These rates drop to 12 percent for those with distantly metastasized disease.[3]

Increasing age, male sex, and black race are all associated with an increased incidence of CRC

(**Table 2**). The median age at diagnosis is 68 years, and nearly half of all new cases are diagnosed in persons ages 65 to 84 years.[3] Black men and women have the highest incidence of CRC compared to other racial/ethnic subgroups. This is troubling given that black men and women also have a disproportionately high mortality from CRC.[4,5] This disparity has increased in the past 20 years, illustrated by the fact that CRC mortality rates have decreased more among whites than blacks.[6] While the overall annual CRC-related death rate is 19.1 deaths per 100,000 men and 13.5 deaths per 100,000 women, it is 27.7 deaths per 100,000 black men and 18.5 deaths per 100,000 black women, which is nearly double the mortality for Hispanics and Asians or Pacific Islanders.[3]

Natural History

CRC usually develops over a period of several years, with the cancer beginning as a precancerous lesion.[7,8] Experts estimate that at least 95 percent of cases of CRC arise from preexisting adenomas.[9,10] 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[11-13] and from observational studies showing a reduction in CRC incidence after polypectomy during colonoscopy or flexible sigmoidoscopy (FS).[14-21]

Colorectal adenomas are very common. Based on a review of 14 studies (n=13,618), for example, the prevalence of adenomas in average-risk screening populations ranged from 22 to 58 percent.[22] 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.[23,24] In general, larger adenomas and those with greater dysplasia are more likely to progress to cancer.[25] Sessile serrated adenomas, as opposed to other adenomas, may not have dysplasia but do have malignant potential.[26] These lesions are the major precursor lesion of serrated pathway cancers and are thought to represent 20 to 35 percent of CRC cases.[26] Overall, the rate of progression of adenoma to cancer is variable and unknown, such that some lesions grow quickly and others very slowly. Better understanding of both the natural history of smaller adenomas and differences in the natural history of proximal versus distal lesions has implications for screening, as certain modalities may be better suited toward identifying smaller or proximal lesions.

Small Polyps or Adenomas (6–9 mm)

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 small polyps (<10 mm) is not clear.[27,28] This stems from the fact that the natural history of smaller adenomas, particularly those 6 to 9 mm, remains uncertain. 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. Although promising, in vivo polyp discrimination methods are not yet (widely) used in clinical practice to distinguish neoplastic from nonneoplastic lesions.[29,30]

Studies using colonoscopy registries report the prevalence of advanced histology or CRC in polyps of various sizes. A limited number of studies have been conducted in screening cohorts. A systematic review by Hassan and colleagues, for example, assessed the distribution of advanced adenomas in average-risk screening populations according to polyp size and reported that the overall prevalence of advanced adenomas was 5.6 percent (95% CI, 5.3 to 5.9) in four studies (n=20,562). Polyps <10 mm were very common in this sample. 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) as the largest lesions accounted for 4.6 percent (95% confidence interval [CI], 3.4 to 5.8) of patients with advanced adenomas. Small polyps (6–9 mm) accounted for 7.9 percent (95% CI, 6.3 to 9.4) of patients with advanced adenomas. In contrast, large lesions (≥10 mm) accounted for 87.5 percent (95% CI, 86.0 to 89.4) of advanced adenomas.[31] The largest screening study included in this review[31] was a prospective cohort derived from the Clinical Outcomes Research Initiative (CORI) database by Lieberman and colleagues.[32] In this study, polyps 6–9 mm were detected in 9.1 percent (1,275/13,992) of patients. The proportion of advanced histology was 6.6 percent in those with polyps 6–9 mm. Only two of these patients had CRC (0.2%).

Until very recently, only small, pilot-sized studies conducted in nonscreening populations have followed the natural history of smaller (<10 mm) lesions. These were observed in situ by serial endoscopy, suggesting that many remain dormant or regress during a 2- to 3-year period.[23,33] More recently, however, a large cohort (n=22,006) of asymptomatic adults undergoing routine CRC screening with CTC at two U.S. medical centers has been published. In this study, the volumes and linear sizes of polyps in vivo were measured with CTC at baseline and surveillance (mean surveillance interval, 2.3 years).[34] Nine 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, 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 advanced adenomas compared to 37 percent (31/84) of proven nonadvanced adenomas progressed.

Proximal Versus Distal Lesions

The distal large intestine can be defined as distal to the splenic flexure (including the descending colon, sigmoid colon, and rectum). Some definitions are more limited and include only the sigmoid colon and rectum, or exclude rectal cancers (for a distinction between the distal large intestine vs. the distal colon). The proximal large intestine or colon is generally defined as proximal to the splenic flexure (including the cecum, ascending and transverse colon) (**Figure 1**).

While overall CRC incidence and mortality is decreasing over time, this trend is more apparent in distal than proximal cancers.[35,36] Data from the NCI's SEER Program, for example, demonstrate a proximal migration of CRC in the past two decades, which is attributed to a decrease in incidence of distal CRC (i.e., screening for primary prevention of cancer) and an aging population in which proximal lesions are more common.[37] A growing body of evidence also suggests that colonoscopy is less effective in reducing proximal compared to distal CRC incidence and mortality.[38-42] The reason for this finding remains unclear, however, 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.[43] Cancers in the proximal and distal colon appear to arise from different molecular pathways (e.g., microsatellite instability and *BRAF* mutations in proximal cancers).[43,44] Molecular differences may explain differences in morphology (e.g., higher proportion of flat polyps in the proximal colon) and natural history (e.g., hypothesized more rapid progression of adenoma to cancer).[45]

Based on data from the NCI's SEER Program and the North American Association of Central Cancer Registries from 2006–2010, the age-adjusted incidence of cancer is 22.6 cases per 100,000 persons in the distal colon/rectum and 18.9 cases per 100,000 persons in the proximal colon. The proportion of proximal to total cancers is 42 percent.[46] CRC prognosis and mortality also differ by tumor location in the colon. Analyses of SEER data have shown a higher late- to early-stage incidence for proximal compared to distal colon/rectum cancer.[47] Proximal cancers have lower 5-year survival and greater mortality and SEER data show differences in stage at presentation.

Adenomas also appear to be more common in the distal colon/rectum than in the proximal colon. In the National Polyp Study, for example, the proportion of proximal to total adenomas was 36 percent.[21] In more recent screening colonoscopy or CTC cohorts, the proportion of proximal to total adenomas ranges from 27 to 52 percent.[48-52] Data suggest that there is a higher rate of invasive cancer in adenomas in the rectum versus the colon; however, it is still unclear if there is a significant difference in cancer rates in adenomas in the proximal versus distal colon.[53] One large retrospective cross-sectional analysis suggests that proximal polyps with advanced neoplasia are smaller than distal polyps (7.6 vs. 11.1 mm, respectively).[54]

The distribution of CRC (and adenomas) differs by age, sex, and race/ethnicity. The incidence of proximal cancers as well as the proportion of proximal cancers (to total cancers) is higher with advancing age.[46] Again, based on data from the NCI's SEER Program and the North American Association of Central Cancer Registries from 2006–2010, proximal cancers are also more common in women than in men; the proportion of proximal to total cancers is 46 versus 38 percent, respectively.[46] Despite this difference, however, men have higher rates of CRC (distal and proximal) incidence and mortality.[46]

Based on SEER data, black men and women appear to have a higher proportion of proximal cancers than other racial/ethnic groups. In addition, 5-year survival rates for proximal cancers are worse for blacks (best for Asians and Pacific Islanders), and these survival disparities persist after adjusting for age, sex, stage of presentation, and therapy received.[55] 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 whites, blacks, and Asians and Pacific Islanders.[47]

There is some evidence from separate analyses conducted from screening colonoscopy cohorts derived from the CORI database on the difference of prevalence and distribution of polyps

among different racial/ethnic subgroups. However, the clinical importance of some of these differences is still unclear. These studies found that blacks (both men and women) had higher prevalence of large adenomas and proximal lesions (adenomas and advanced neoplasia).[56-59] Based on analogous data from CORI, there does not appear to be a difference in the distribution of large adenomas in Hispanics compared to whites, although Hispanics appear to have a lower age-adjusted prevalence of large adenomas than whites.[59,60]

Risk Factors

Most cases of CRC are sporadic, with 75 percent developing in average-risk persons, versus about 20 percent developing in persons with some type of family history. The remainder of cases develop in persons 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).[61-64] Family history of CRC that is not attributable to any known inherited syndromes is a well-established risk factor, with an average 2- to 4-fold increase in risk of CRC compared to those with no family history. Despite this finding, however, there is great heterogeneity in the published literature in how family history is defined (e.g., the age, number, and relationship to relative[s] with CRC).[65-67] As a result, the risk of developing CRC varies approximately 20-fold between persons in the lowest quartile (average lifetime risk, 1.25%) and the highest quartile (average lifetime risk, 25% in persons with an inherited familial syndrome).[68]

Some lifestyle factors have also been linked to risk of developing CRC, including lack of exercise, long-term smoking, heavy alcohol use, being overweight or obese, and having type 2 diabetes.[1] Despite the large range in risk and known risk factors for CRC, risk prediction and use of risk prediction models for CRC is suboptimal.[69]

CRC Screening

Rationale and Current Clinical Practice

Because CRC has precursor lesions and survival largely depends on the stage at the time of diagnosis, screening can affect both primary prevention (finding precancerous lesions that could later become malignant) and secondary prevention (detecting early cancers that can be more effectively treated).

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 from less than 25 percent in the 1980s to about 52 percent in 2002 and about 65 percent in 2012.[70] Despite increases in CRC screening over time, screening rates remain well below optimal, as evidenced by the fact that approximately 28 percent of U.S. adults eligible for screening have never been screened for CRC.[70] There is also 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.[71] Multiple patient, clinician, and

health care 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 health care.[72]

Screening Tests

Multiple tests are available to screen for CRC, including stool-based tests (e.g., guaiac-based fecal occult blood test [gFOBT], fecal immunochemical test [FIT], fecal DNA tests), endoscopy (e.g., FS or colonoscopy), and imaging tests (e.g., double-contrast barium enema [DCBE], CTC, magnetic resonance colonography [MRC], capsule endoscopy). Screening tests currently used in the United States that have evidence to support their use include high- sensitivity gFOBT (Hemoccult SENSA®; Beckman Coulter, Brea, CA), FIT, FS, and colonoscopy.[73]

Despite being designated under a single test type, FITs are not a homogeneous class of stool testing. In fact, various types of FITs are available from multiple manufacturers (and therefore different proprietary names), with differing test methods and performance characteristics. Of the FITs available in the United States, some have been reviewed by the U.S. Food and Drug Administration (FDA) and cleared as test kits via 510(k) review, while many more have been granted waived status by the FDA.[74] Waived status may be granted under the Clinical Laboratory Improvements Amendments of 1988 if the device is simple to use, is demonstrated at intended use sites to be accurate, and poses an insignificant risk of erroneous results. In contrast to FITs, high-sensitivity gFOBT is produced in the United States by one primary manufacturer (Hemoccult SENSA, Beckman Coulter). Stool testing is generally 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.[75,76]

Since 2001, when the Centers for Medicare & Medicaid Services (CMS) started covering screening colonoscopy, colonoscopy utilization for screening has increased and the use of FS has decreased.[77,78] Despite lack of RCT evidence demonstrating a reduction in CRC mortality from a program of screening with colonoscopy, and some studies suggesting screening colonoscopy is not as effective in reducing incidence of or mortality from proximal compared to distal CRC,[40,41,79-81] colonoscopy remains the most commonly used screening modality in the United States.[78,82] In 2012, for example, 62 percent of persons who were screened had colonoscopy compared to 10.4 percent who were screened with stool testing and only 0.7 percent who were screened with FS in combination with stool testing.[70] Public and clinician perceptions of accuracy of colonoscopy versus FS, given the reach of endoscopy, also play an important role in this issue.[83] Newer technologies, specifically CTC and stool DNA testing, have a growing evidence base, and may play an important role in CRC screening. In 2013, the FDA Medical Advisory Panel agreed that the benefits of using CTC to screen for CRC outweigh the risks (e.g., radiation exposure and identification of extracolonic findings).[84] Only one stool DNA test, a multitarget stool DNA (mtsDNA) test incorporating FIT testing, is currently available and approved by the FDA for use for CRC screening. One new blood test to detect circulating methylated septin 9 gene DNA (m*SEPT9*) is currently available.

While other screening tests are available for CRC, they are no longer widely used. The original gFOBT (i.e., Hemoccult I or II), for example, has largely been replaced by stool testing with

higher sensitivity (i.e., Hemoccult SENSA or selected FITs). DCBE is also largely no longer used because of its suboptimal performance compared to other screening tests.[73] Two newer technologies, MRC and capsule endoscopy (PillCam®; Given Imaging, Yokne'am Illit, Israel), are primarily used as diagnostic tools and are not currently used as screening tests. MRC, similar to CTC, can image the lumen of the colon but without the radiation exposure. Capsule endoscopy has the advantage of being noninvasive and requiring no sedation. Thus far, however, the efficacy of MRC and capsule endoscopy in screening populations have only had limited evaluation in small studies.[85,86]

Current Screening Recommendations

Most organizations agree that any CRC screening is better than no screening. Existing guidelines recommend that the age to begin screening in adults at average risk for CRC is 50 years. However, the optimal age to start screening may vary by sex or race/ethnicity based on differences in onset and incidence of CRC. The optimal time to stop screening in average-risk adults is uncertain, such that screening from ages 76 to 85 years should be individualized based on the patient's 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 gFOBT or FIT, and FS every 5 years with stool blood testing (FOBT or FIT).[87,88] There remains a number of important areas of disagreement about these options, however, as reflected by the variation in screening recommendations across professional societies in the United States and internationally (**Appendix A Table 1**).

The largest difference in recommendations exists between the USPSTF's 2008 recommendation and the American Cancer Society (ACS), U.S. Multi-Society Task Force (MSTF), and American College of Radiology (ACR) 2008 joint recommendations (**Appendix A Table 1**).[73,87,88] While the USPSTF recommendations stated that any number of options (listed above) are suitable for CRC screening, the ACS-MSTF-ACR joint recommendations supported newer technologies (i.e., stool DNA testing and CTC) and gave preference to "structural exams," including colonoscopy and CTC as a means of preventing CRC.

Previous USPSTF Recommendation

In 2008, the USPSTF issued the following recommendations about screening for CRC:

- The USPSTF recommends screening for CRC using FOBT, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years (A recommendation).
- The USPSTF recommends against routine screening for CRC in adults ages 76 to 85 years (C recommendation). There may be considerations that support CRC screening in an individual patient.
- The USPSTF recommends against screening for CRC in adults older than age 85 years (D recommendation).

- The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of CTC and stool DNA testing as screening modalities for CRC (I statement).

The USPSTF determined that for all screening modalities, starting screening at age 50 years resulted in a balance between life-years gained and colonoscopy risks that was more favorable than commencing screening earlier. Despite the increasing incidence of colorectal adenomas with age, for individuals previously screened, the gain in life-years associated with extending screening from age 75 to 85 years was small in comparison to the risks of screening persons in this age group. For adults who have not previously been screened, decisions about first-time screening in this age group should be made in the context of the individual's health status and competing risks, given that the benefit of screening is not seen in trials until at least 7 years later. For persons older than age 85 years, competing causes of mortality preclude a mortality benefit that outweighs the harms.

The USPSTF concluded that there was insufficient evidence to assess the sensitivity and specificity of stool DNA testing for colorectal neoplasia; therefore, the balance of benefits and harms could not be determined for this test. The USPSTF concluded that the evidence for CTC to assess the harms related to extracolonic findings was insufficient, and, as a result, could not determine the balance of benefits and harms. It did state, however, that the option of CTC could help reduce CRC mortality in the population if patients who would otherwise refuse screening found it to be an acceptable alternative.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review to update its 2008 recommendation statement on screening for CRC in conjunction with microsimulation decision models from the Cancer Intervention and Surveillance Modeling Network (CISNET).[89] This review addresses the benefit and harms associated with CRC screening and the diagnostic accuracy of the individual screening tests currently available, and most commonly used, in U.S. clinical practice. While this review primarily updates our previous work to support the prior USPSTF recommendation,[90] it also addresses evidence on new considerations, including:

1. Observational evidence on the benefits of screening tests or screening programs on cancer incidence and/or mortality for screening technologies without trial evidence (i.e., colonoscopy, CTC, high-sensitivity stool testing)
2. Comparative effectiveness of screening tests on cancer incidence and/or mortality
3. Diagnostic accuracy of newly available screening technologies (i.e., FDA-approved mtsDNA test, blood test)

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 based on any of the following screening tests (alone or in combination) in reducing a) incidence of and b) mortality from CRC?
    i. Colonoscopy
    ii. FS
    iii. CTC
    iv. Stool screening tests:
        a. Any gFOBT
        b. FIT
        c. Stool DNA or multitarget stool test
    v. Blood screening test: m*SEPT9*
2. What are the test performance characteristics (e.g., sensitivity and specificity) of the following screening tests (alone or in combination) for detecting a) CRC, b) advanced adenomas, and/or c) adenomatous polyps based on size?
    i. Colonoscopy
    ii. FS
    iii. CTC
    iv. Stool screening tests:

a. high-sensitivity gFOBT
b. FIT
c. Stool DNA or multitarget stool test

v. Blood screening test: m*SEPT9*

3a. What are the adverse effects (i.e., serious harms) of the different screening tests (either as single application or in a screening program)?

3b. Do adverse effects vary by important subpopulations (e.g., age)?

Data Sources and Searches

We searched MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials to locate relevant studies for all key questions. We searched for articles published from the end of our prior review (January 1, 2008) to December 31, 2014. We supplemented our database searches with expert suggestions and through reviewing reference lists from all other recent relevant existing systematic reviews. We also searched selected grey literature sources, including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform, for ongoing trials.

Study Selection

Two investigators independently reviewed 8,492 titles and abstracts using an online platform (abstrackr[91]) and 696 articles (**Appendix B Figure 1**) with specified inclusion criteria (**Appendix B Table 1**). We resolved discrepancies through consensus and consultation with a third investigator. We carried forward 33 studies (40 articles) from our prior review. Twenty-eight articles from the previous review were not included in this review due to differences in inclusion criteria. We excluded articles that did not meet inclusion criteria or those we rated as poor quality. **Appendix C** 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 or who were not selected for inclusion based on CRC risk factors. We excluded symptomatic populations or populations selected for personal or family history of CRC, known genetic susceptibility syndromes (e.g., Lynch syndrome, familial adenomatous polyposis), personal history of inflammatory bowel disease, previous screening test positive (e.g., gFOBT or FIT), iron deficiency anemia, or surveillance for previous colorectal lesion. In studies with mixed populations, we limited our inclusion to those with less than 50 percent surveillance populations and/or less than 10 percent with symptoms, positive 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 may detect rare or uncommon harms. We arrived at the number 10,000 based on estimates derived from our previous systematic review.[90] Because many studies reporting extracolonic findings on CTC limited population descriptions to asymptomatic or symptomatic, we included any studies in asymptomatic persons that could include persons at high risk for CRC (e.g., anemia, FOBT positive, 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. We included only studies that published their results in English because of resource constraints.

We included studies that evaluated the following screening tests: colonoscopy, FS, CTC, gFOBT, FIT, mtsDNA tests, and the blood test for m*SEPT9*. Although we did review 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 and FIT testing in U.S. practice. We excluded stool testing based on in-office digital rectal examination, DCBE, capsule endoscopy (i.e., PillCam), and MRC. 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 (i.e., colonoscopy, FIT), we examined well-conducted prospective cohort or population-based nested case-control studies. We included trials and observational studies that shared outcomes of cancer incidence and/or CRC-specific or all-cause mortality. We 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 diagnostic accuracy studies that used colonoscopy as a reference standard. We generally excluded studies whose design was subject to a high risk of bias, including studies that did not apply colonoscopy to at least a random subset of screen-negative persons (verification bias),[92] although we made an exception for otherwise well-conducted diagnostic accuracy studies of FITs in which the screen-negative persons 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) (e.g., case-control studies).[92-96] Diagnostic accuracy studies had to include outcomes of test performance (i.e., sensitivity, specificity, positive and negative predictive value) for the detection of CRC, advanced adenoma, and/or adenomatous polyp by size ($\leq$5, 6–9, or $\geq$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., persons 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., persons 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 B Table 2**).[97] We supplemented this criteria with the National Institute for Health and Care Excellence methodology checklists,[98] AMSTAR for systematic reviews,[99] Newcastle Ottawa Scales for cohort and case-control studies,[100] and QUADAS I and II for studies of diagnostic accuracy[101,102] (**Appendix B Table 2**). 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 if 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. The most common fatal flaw for diagnostic studies included application of the reference standard to only those who screened positive (because when missing data are not random or selective, analysis will generate biased estimates of diagnostic accuracy,[92,93,96,103] and verification of only screen-positive patients will generally lead to an overestimation of both sensitivity and specificity). We also excluded diagnostic studies that did not provide a description of followup of screen-negative persons for poor quality because of limitations in reporting. We excluded poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, consultation with a third independent reviewer.

One reviewer extracted key elements of included studies into standardized evidence tables in Excel or Microsoft Access (FIT diagnostic accuracy studies). 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 it was 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. We used a standardized summary of evidence table to summarize the overall strength of evidence for each key question. This table included: number and design of included studies, summary of results, consistency/precision of results, reporting bias, summary of study quality, limitations of the body of evidence, and applicability of findings.

Key Question 1

We organized the syntheses primarily by study design and separated them into three main categories: 1) trials designed to test the effectiveness of screening tests (either as a one-time application or in a screening program) compared to no screening on CRC-specific and/or all-cause mortality; 2) well-conducted observational studies designed to test the effectiveness of a one-time application of a screening test or a screening program of screening tests without trial evidence (i.e., colonoscopy) compared to 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). These latter trials, however, were primarily designed to determine the differential uptake of different tests and/or to determine the comparative yield between different tests (i.e., not powered to detect differences in CRC outcomes or mortality). Primary outcomes of interest were: CRC incidence, 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 to allow for comparisons across different studies. We did conduct quantitative analyses for four large FS trials for the above stated outcomes. We conducted random-effects meta-analyses using the profile likelihood method to estimate the incidence rate ratio (IRR) (events per person-year) in R version 3.0.2 (The R Project for Statistical Computing; Vienna, Austria).[104,105] We assessed the presence and magnitude of statistical heterogeneity among the studies using the I^2 statistic.

Key Question 2

This question focused explicitly on the one-time test performance of currently available CRC screening tests. We organized our synthesis by type of screening test (i.e., CTC, high-sensitivity stool-based testing, and m*SEPT9*). Our analyses primarily focus on per-person test sensitivity to detect adenomas (by size, where reported, of <6, ≥6, or ≥10 mm), advanced adenomas (as defined by the study), CRC, and advanced neoplasia (a composite outcome of advanced adenoma plus CRC). In one instance, the per-person sensitivity was not reported and could not be calculated, so 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 advanced adenomas excluding CRC lesions (persons who had CRC were removed from the 2x2 table). We calculated sensitivity and specificity in Stata using Jeffrey's CIs. We used 2x2 tables constructed from data

reported in the primary studies. If the observed sensitivity or specificity was 100%, only the lower 95% CI was calculated. In many cases the data presented in our report differ slightly from the published paper because of these calculations.

For test performance of CTC, we synthesized results for examinations with bowel preparation separately from those without bowel preparation. For each study that reported both sensitivity and specificity, we plotted results in receiver operating characteristic (ROC) space (sensitivity vs. 1-specificity) to determine whether summary ROC curve analysis was necessary. Summary ROC curves are used when sensitivity and specificity are related through the test positivity threshold.[106] We observed relatively constant specificity with variability in sensitivity across studies, however, and therefore these joint modeling approaches were not needed. We conducted random-effects meta-analyses using the empirical Bayes method to (separately) estimate sensitivity and specificity in R.[107] We assessed the presence and magnitude of statistical heterogeneity among the studies using the I^2 statistic. We did not quantitatively pool results if data were limited to three or fewer studies.

For studies of FITs, we focused on study designs in which all patients received colonoscopy (the reference standard) regardless of the screening FIT result. In this way we avoided potential test referral bias, which increases apparent test sensitivity and decreases apparent test specificity in the study population. We separately evaluated studies that employed differential followup. Studies in our evidence base utilized several different FITs, which we grouped into qualitative and quantitative tests; similarities and differences are shown in **Table 3**. We further characterized FITs by name and alias if applicable (with name variations resulting from changes in company ownership, distribution in different countries, or other reasons). We grouped similar FITs into "families" for results display and discussion. 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.

FIT sensitivity is likely to depend on the chosen cutoff value (i.e., the value that is used to determine a positive or negative result), which in turn depends on the detection limit of the test. Many manufacturers express the test cutoff value in ng hemoglobin (Hb)/mL buffer, units that are unique to the device or test system and cannot be compared across different tests.[108] Cutoff values expressed in μg Hb/g feces are more comparable across tests, although there is variability due to differences in sampling probes and stool mass. In lieu of a better method, however, we attempted to compare tests according to cutoff values expressed in μg Hb/g feces. In some cases there was insufficient information to convert values expressed in ng Hb/mL to μg Hb/g feces.

Despite efforts to consolidate study information, the heterogeneity of tests, test cutoffs, and study design remained high and we did not quantitatively pool sensitivity and specificity for FITs. In these instances, we used summary tables and forest plots, prepared using Stata, to provide a graphical summary of results.

Key Question 3

We organized our synthesis by type of screening test, study design, and type of harm. Our synthesis is organized into three main categories: 1) harms of programs of screening, which

include downstream harms of subsequent diagnostic/therapeutic endoscopy; 2) harms of individual screening tests focusing on CTC and endoscopy, as we did not hypothesize any serious harms for stool- or blood/serum-based screening tests; and 3) extracolonic findings on CTC. Although we included our discussion of results for extracolonic findings with harms, we recognize that detection of extracolonic findings can represent either a benefit or harm.

For harms of programs of screening as well as radiation exposure from and extracolonic findings on CTC, we primarily synthesized results qualitatively using summary tables to allow for comparisons across different studies. When possible, we conducted quantitative analyses for serious harms, including perforation and major bleeding, 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 author. Quantitative analyses were not performed for other serious adverse events, as they were not routinely or consistently reported or defined. We used random-effects models to estimate rates of serious adverse events for colonoscopy and FS separately. We applied the restricted maximum likelihood estimation method when the number of studies to be synthesized was 10 or greater and the profile likelihood estimation method otherwise. Exploratory meta-regression analysis was conducted by fitting random-effects logistic models to examine the association of the risk of serious adverse events with the following study-level characteristics: study design, year of study, sample size, study setting by country, and indication for endoscopy. The analyses were performed using R version 3.0.2.

Expert Review and Public Comment

A draft research plan that included the analytic framework, key questions, and inclusion criteria was available for public comment in January 2014. We made no substantive changes to our review methods based on comments received. A draft version of this report was reviewed by seven invited content experts as well as federal partners from the Centers for Disease Control and Prevention, National Institutes of Health, Department of Veterans Affairs (VA), and Indian Health Service. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and subsequently addressed, as appropriate, in the final version of the report. Additionally, a draft of the full report was posted on the USPSTF Web site from October 6 through November 2, 2015. Comments from 21 individuals were received during this public comment period; there were no changes made to the report based on these comments.

USPSTF Involvement

The authors worked with four 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 external review of the draft evidence synthesis.

Chapter 3. Results

Key Question 1. What Is the Effectiveness of Screening Programs in Reducing Incidence of and Mortality From CRC?

We included 25 unique fair- to good-quality studies[41,109-132] (published in 47 articles[41,109-154]) to assess the effectiveness or comparative effectiveness of screening tests on CRC incidence and mortality (**Table 4**). We found one cohort study that examined the effectiveness of screening colonoscopy, four RCTs that examined the effectiveness of FS, no studies that examined the effectiveness of CTC, six trials that examined the effectiveness of Hemoccult II gFOBT, and no studies that examined the effectiveness of high-sensitivity gFOBT, FIT, mtsDNA, or blood tests. Additionally, we found 15 comparative effectiveness studies that were primarily designed to assess the relative uptake and CRC yield between different screening modalities. None of these studies provided mortality data and, generally, these studies were not powered to detect differences in CRC detection.

Overall Summary

Well-conducted trial data for one- or two-time FS and stool-based screening programs using Hemoccult II have demonstrated a reduction in CRC mortality and incidence (**Table 5**). Based on four RCTs (n=458,002) that used intention-to-treat analyses, one- or two-time FS consistently decreased CRC-specific mortality compared to no screening at 11 to 12 years of followup (IRR, 0.73 [95% CI, 0.66 to 0.82]). Based on five RCTs (n=404,396) that used intention-to-treat analyses, biennial screening with Hemoccult II resulted in reduction of CRC-specific mortality compared to no screening, ranging from 9 to 22 percentage points after two to nine rounds of screening with 11 to 30 years of followup (relative risk [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). Based on one of these trials, conducted in the United States, annual screening with Hemoccult II after 11 rounds of screening resulted in greater reductions (RR, 0.68 [95% CI 0.56, 0.82]) at 30 years than biennial screening. We found no trials (currently underway) and only one large observational study for the effectiveness of colonoscopy on CRC incidence and mortality. After 24 years of followup, one prospective cohort (n=88,902) found the CRC-specific mortality rate was lower in persons who self-reported at least one screening colonoscopy (multivariate adjusted HR, 0.32 [95% CI, 0.24 to 0.45]) compared to those who had never had screening endoscopy. We could not directly compare the magnitude of benefit in CRC mortality and cancer incidence across tests because of major differences in study design across bodies of literature examining various test types. To date, no CRC screening modality has been shown to reduce all-cause mortality. While no RCTs evaluating the mortality benefit of newer, more sensitive stool testing currently exist, these population-based RCTs of newer stool testing may not be necessary because evidence-based reasoning supports that screening with stool tests with sensitivity and specificity that are as good as, or better than, Hemoccult II would result in CRC mortality reductions similar or better than reductions shown with Hemoccult II.

Comparative effectiveness studies comparing one screening modality to another are limited to

the evaluation of a single round of screening, with low CRC yield (number of cancers detected) and few interval cancers reported. Therefore, these studies do not provide robust direct evidence of comparative benefit on CRC incidence or mortality outcomes.

Based on a single fair-quality prospective cohort study, colonoscopy (as opposed to FS) appears to have mortality benefit for both proximal and distal CRC. Four large FS RCTs confirm that this mortality benefit is limited to distal CRC. Data on subgroups by age and sex are limited and provide mixed findings about possible differential benefit. While one gFOBT trial and three FS trials suggest greater benefits in men than in women, interaction testing for these results was not statistically significant, when reported. The differences in benefit may be due to higher incidence of cancer and cancer-related mortality in men, greater number of proximal cancers in women, or unknown confounders, since randomization in the trials was not stratified by sex.

Detailed Results

Colonoscopy

We found no trials that evaluated the efficacy of screening colonoscopy to reduce CRC and/or mortality. We found one fair-quality prospective cohort study (n=88,902) that evaluated the impact of lower endoscopy on CRC incidence and mortality.[41] Using data from two large cohorts in 1988, the Nurses' Health Study (57,166 women) and the Health Professionals Followup Study (31,736 men), Nishihara and colleagues analyzed the association of screening colonoscopy and FS with the risk of CRC over 22 years and CRC mortality over 24 years. Among this select group of health care professionals, receipt of and reason for endoscopy (e.g., screening) were determined via self-report as part of a questionnaire administered every 2 years. Using a random sample of participants, investigators showed a high concordance of self-report and medical records. Seventy-three percent of endoscopies were performed for screening, including those performed for family history of CRC.

All analyses were stratified by age and sex. Multivariate analyses further adjusted for known or potential risk factors for CRC (i.e., body mass index, smoking status, first-degree relative with CRC, physical activity level, total red meat intake, total calorie intake, alcohol consumption, folate intake, calcium intake, multivitamin use, and regular use of aspirin, nonsteroidal anti-inflammatory drugs, cholesterol-lowering drugs, and hormone replacement therapy). Given the potential selection bias of persons receiving endoscopy versus those who did not, investigators conducted additional CRC incidence analyses adjusting for the propensity scores. Propensity score adjustment analyses were consistent with reported results. Investigators stated that they did not conduct any post hoc analyses. Nonetheless, given the study design, investigators could not address unknown or unmeasured confounders. Other limitations include the measurement of "screening" colonoscopy; thus, it is unclear if the benefit is from a single colonoscopy, multiple colonoscopies, or screening plus surveillance colonoscopies. Because of the nature of this study design, one cannot directly compare the magnitude of effect (association) measured in this observational study with the relative risk reduction measured in the intention-to-treat analyses from RCT trials of other CRC screening tests (i.e., FS, Hemoccult II).

During 24 years of followup, there were 474 deaths due to CRC. The CRC-specific mortality

rate was lower in persons with 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 to those who had never had screening endoscopy. Results were similar for men and women. Outcomes for all-cause mortality were not reported. This study found that screening colonoscopy was 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 FS was not.

During 22 years of followup, there were a total of 1,815 incident cases of CRC. Cancer incidence was lower in persons with self-reported 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 to those who had never had screening endoscopy. Results were similar for men and women. Reduction in cancer incidence was observed across all stages of CRC at presentation. Only negative screening colonoscopy was associated with reduced incidence of proximal CRC (multivariate HR, 0.74 [95% CI, 0.57 to 0.96]).

FS

We found five trials that evaluated the efficacy of screening FS to reduce CRC and/or mortality. We excluded one early pilot trial that was conducted in Norway (n=399 screened, n=400 control) for poor quality because of a number of limitations (e.g., no true randomization, small study sample, potentially nonrepresentative sample, low adherence, and crossover).[17] All four of the fair-quality RCTs (n=458,002) we included were published after the previous USPSTF recommendation (**Table 6**).[109,122,124,143]

Population Characteristics

Only one included trial was conducted in the United States (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCO]);[122,154] the remaining three trials were conducted in Norway (Norwegian Colorectal Cancer Prevention [NORCCAP]),[143] Italy (Screening for Colon Rectum [SCORE]),[124,149] and the United Kingdom (U.K. Flexible Sigmoidoscopy Screening Trial [UKFSST]).[109,133] All trials started in the 1990s and recruited average-risk adults between the ages of 50 and 74 years. The mean age at baseline across three of the trials was 56 to 60 years (PLCO did not report mean age at baseline but included participants ages 55–74 years). Only two trials reported the underlying percent of participants with family history of CRC, which was approximately 10 percent. One trial, UKFSST, explicitly excluded persons with two or more close relatives with CRC.[109] The baseline prevalence of CRC in the trials ranged from 1.4 to 1.6 percent. All trials included an even mix of men and women. Only the U.S. trial, PLCO, reported the race/ethnicity of participants, and this trial included 14 percent nonwhite participants.[122]

FS Protocol

All four included trials evaluated screening FS with a limited bowel preparation (i.e., not a full bowel preparation required for colonoscopy). Two trials used a colonoscope instead of a flexible sigmoidoscope to conduct the FS.[124,143] The screening protocol and criteria for referral to

diagnostic colonoscopy varied between trials. NORCCAP evaluated FS with or without FIT testing (approximately half of the screening arm also received FIT testing).[143] The other trials compared FS to a no-screening control group.[109,122,124] PLCO evaluated screening with followup FS at 3 to 5 years. SCORE and UKFSST evaluated one-time FS.[122] Referral to diagnostic colonoscopy varied across trials and was likely related to referral criteria:

- UKFSST (5.2% referred to colonoscopy), biopsy-based referral criteria: polyp 10 mm or larger, three or more adenomas, or high-risk findings (including tubulovillous or villous histology, severe dysplasia or malignancy, or ≥20 hyperplastic polyps)[109]
- SCORE (8.6% referred to colonoscopy), biopsy-based referral criteria: UKFSST criteria plus adenomas 6–9 mm[124]
- NORCCAP (20.4% referred to colonoscopy), biopsy-based referral criteria: any polyp 10 mm or larger, any adenoma (regardless of size), all CRC, and any positive FIT results[143]
- PLCO (32.9% referred to colonoscopy), visual (without biopsy) referral criteria: any lesion or polyp considered positive, patients referred to their primary care physician for decision on referral to diagnostic colonoscopy[122]

Study Quality

All included trials were very large fair-quality RCTs. Only PLCO had a traditional randomized trial design in which the control group participants gave consent and were enrolled in the trial. In the European trials, the control groups were not contacted and were unaware of their trial involvement. Adherence to screening ranged from about 58 to 83 percent for the initial FS. The highest adherence rate was observed in PLCO; however, adherence to the subsequent FS was much lower, about 54 percent. Only the PLCO trial reported CRC screening in the control group, and a large proportion of the control group (about 47%) was found to have had some type of lower gastrointestinal endoscopy during the screening phase (0–5 years).[122] Details about the number, training, or quality parameters of the endoscopy or endoscopists were not consistently or commonly reported.

Outcomes

Despite some heterogeneity in the FS screening protocols, we found it reasonable to quantitatively pool results for reduction in mortality and cancer incidence because of generally similar study design/methods, population characteristics, and length of followup (median followup, approximately 11–12 years). Based on intention-to-treat analyses across the four trials, one-time FS consistently decreased CRC-specific mortality. The pooled IRR for CRC mortality for FS versus no screening across the four studies was 0.73 (95% CI, 0.66 to 0.82; I^2=0%) (**Figure 3**). The outcome data from NORCCAP used in our meta-analyses differ slightly from that reported in the publication due to our preference for non–age-adjusted data (for consistency) and the primary publication's reporting of age-adjusted results. While three of the four trials defined distal cancers to include the descending colon to the rectum, the UKFSST limited its definition of distal to the sigmoid colon and rectum. The pooled reduction in distal but not proximal CRC mortality was statistically significant (IRR, 0.63 [95% CI, 0.49 to 0.84]; I^2=44.1%) (**Figures 4** and **5**). In NORCCAP, 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] vs. 0.84 [95% CI,

0.61 to 1.17], respectively).[143] In PLCO, initial plus repeat FS at 3 or 5 years was effective in reducing CRC-specific mortality at about 12 years (RR, 0.74 [95% CI, 0.63 to 0.87]).[122]

Three of the four trials that reported relevant results did not find reductions in all-cause mortality (**Figure 6**).[109,124,143] PLCO did not report all-cause mortality outcomes.

Intention-to-treat analyses across the four trials consistently found that screening with FS decreased the incidence of CRC. The pooled IRR for CRC incidence for FS versus no screening was 0.79 (95% CI, 0.75 to 0.85; I^2=0%) (**Figure 7**). Similar to findings on CRC mortality, the reduction in incidence for distal but not proximal CRC incidence was statistically significant (IRR, 0.71 [95% CI, 0.64 to 0.82]; I^2=35.3%) (**Figures 8** and **9**).

Subpopulations

Three trials (NORCCAP, PLCO, and UKFSST) reported CRC mortality estimated separately by age and/or sex (**Table 6**).[109,122,143] All of these trials suggest that the benefit in mortality reduction may be greater for men than for women. PLCO also reported CRC mortality separately by age group. The finding of a greater CRC mortality reduction for older adults than for middle-aged adults, however, was not statistically significant.

All four trials reported CRC incidence separately by age and/or sex.[109,122,124,143] Three of the four trials (NORCCAP, PLCO, UKFSST) estimated greater CRC incidence reduction for men than for women.[109,122,143] Only PLCO reported statistic tests for differential effects of the intervention by sex, and these results showed borderline statistical significance (p=0.052).[122] Two trials (PLCO, SCORE) reported subgroup analyses for older and middle-aged adults but found no statistically significant difference on cancer incidence between these age groups.[122,124] Although trials were not powered to detect differential effects of FS across subgroups, results are suggestive of a stronger benefit in men than in women, which may be due to the fact that women had a lower proportion of screen-detected cancers and a higher proportion of proximal cancers than men. We did not conduct pooled analyses for subgroups, as randomization was not stratified by age or sex, and interaction testing for subgroup analyses was not statistically significant.

CTC

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

Stool Tests

gFOBT

We found six[113,117-119,123,127] fair- to good-quality large population screening trials (reported in 11 articles;[113,117-119,123,127,142,145-147,150] n=525,966) that evaluated the effectiveness of gFOBT, specifically Hemoccult II, on mortality (**Table 7**). While these trials are important for a historical and contextual understanding of CRC screening, our summary of results is brief because Hemoccult II is no longer widely used for CRC screening in the United States. Five of the six

trials (conducted in France, Denmark, Sweden, United Kingdom, and the United States) are older trials with longer-term followup of mortality reported,[113,117,118,123,127] while one newer trial in Finland has not yet reported mortality outcomes.[119]

Trials primarily evaluated biennial testing, although one also evaluated annual testing.[127] Overall, biennial screening with Hemoccult II (k=5; n=404,396) resulted in reduction of CRC-specific mortality, from 9 to 22 percent after two to nine rounds of screening with 11 to 30 years of followup. Trials varied in screening protocols in terms of number of screening rounds, use of rehydrated samples (no longer used in practice), definition of "test positive" (i.e., number of test squares on each slide required to be positive for referral to additional testing), and recommended diagnostic followup for positive results (e.g., FS with or without DCBE, colonoscopy), and had different followup periods and adherence to screening and followup testing. The lowest CRC mortality reduction (RR, 0.91 [95% CI, 0.84 to 0.98] at 19.5 years) was observed in the Nottingham trial (n=151,975), which used three to five rounds of screening that had a higher threshold for test positivity than other gFOBT trials.[123] This trial also had slightly lower adherence to testing after adjustment for nonadherence (of the first test). The RR for CRC mortality was equivalent to other studies (data not shown). The CRC mortality reduction observed in the Göteborg trial (n=68,308), which had two to three rounds of screening, was no longer statistically significant at 17 years of followup when deaths due to complications of CRC treatment were included (RR, 0.89 [95% CI, 0.78 to 1.01]).[118] Since comparable data on treatment-related CRC deaths are not reported in the other trials, and very limited details about the underlying analysis are reported, this finding is difficult to interpret. Only two studies, Funen and Nottingham, reported CRC mortality by cancer location, and neither found a statistically significant difference in mortality reduction by proximal versus distal CRC.[117,123]

The Minnesota Colon Cancer Control Study showed that annual screening with Hemoccult II (n=30,964) resulted in reduction of CRC-specific mortality of 32 percent (RR, 0.68 [95% CI, 0.56 to 0.82]), with 11 rounds of screening and 30 years of followup.[127]

Overall, biennial or annual screening with Hemoccult II did not reduce all-cause mortality. This may be due to the relatively small number of CRC deaths that contribute to overall deaths, limiting the power of screening to affect the all-cause mortality estimates.

In two trials (n=213,908), Funen and Nottingham, CRC-specific mortality reductions were similar for both men and women.[117,123] In the Minnesota trial (n=46,551), however, it appears that men had greater CRC-specific mortality reductions compared to women at 30 years of followup (for biennial: RR, 0.63 [95% CI, 0.48 to 0.82] in men vs. 0.92 [95% CI, 0.72 to 1.18] in women; p=0.04 for interaction).[127]

Other Stool Tests

We found no prospective studies evaluating the effectiveness of high-sensitivity gFOBT or FITs on cancer incidence or mortality.

Comparative Effectiveness of Different Screening Tests

We found 12 fair-quality trials[110,111,116,120,121,125,126,128-132] (published in 16 articles[110,111,116,120,121,125,126,128-132,137,138,148,152]) that examined the comparative effectiveness of different screening tests in average-risk screening populations (**Table 8**). We also found three fair-quality, large prospective cohort studies[112,114,115] in six articles[112,114,115,139-141] that examined the comparative effectiveness of gFOBT versus FIT in average-risk screening populations (**Table 8**).

All studies were conducted in Western European countries. Trials were primarily designed to assess the differential uptake (adherence) of testing and relative detection of colorectal lesions. Although these trials include CRC outcomes, the trials are not powered to detect differences in CRC incidence and/or mortality. For example, 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.

Because these studies are limited to the evaluation of a single round of screening, low CRC yield (number of cancers detected), and few interval cancers reported, they do not provide robust direct evidence of comparative benefit on CRC incidence or mortality outcomes. These studies are not discussed further, but more details are available in **Appendix D**.

Key Question 2. What Are the Test Performance Characteristics of the Different Screening Tests for Detecting CRC, Advanced Adenomas, and/or Adenomatous Polyps Based on Size?

We included 33 unique diagnostic accuracy studies[49-52,155-183] (published in 44 articles[49-52,155-194]) that evaluated CRC screening tests compared to an adequate reference standard (i.e., colonoscopy for adenomas and colonoscopy or robust clinical/registry followup for CRC) (**Table 9**). We found no diagnostic accuracy studies that compared colonoscopy or FS to a colonoscopy reference standard. In order to approximate test performance of screening tests in community practice, we excluded endoscopy studies primarily conducted in single-center research settings or those with a very limited number of endoscopists. We found nine unique studies that evaluated CTC as a screening modality (three of which were included in our prior review). Four of these nine CTC studies provided data on the diagnostic accuracy of screening colonoscopy conducted by more than just a limited number of endoscopists.[50,52,169,183] We found 23 unique studies evaluating high-sensitivity stool-based testing,[49,155-162,164,166-168,171-174,177-182] three evaluating high-sensitivity gFOBT,[155,156,173] 20 evaluating various different FITs,[49,155-162,164,166-168,171-174,177-182] and one evaluating a mtsDNA test, which included a FIT component.[167] In addition, we used a good-quality AHRQ-funded systematic review to summarize older stool-based DNA screening tests,[175] which are no longer available. Finally, we identified only one diagnostic accuracy study that met our inclusion criteria that evaluated m*SEPT9*.[163] All of these studies were designed to evaluate a single application of the screening test, as opposed to a program of screening.

Overall Summary

For this review of screening test accuracy, we primarily focused on the per-person (as opposed to per-lesion) sensitivity and specificity of a single application of each screening test to detect: 1) CRC or advanced neoplasia (a composite outcome of CRC plus advanced adenomas), 2) advanced adenomas (generally defined as adenomas ≥10 mm,with villous components, or with high-grade dysplasia), and 3) adenomatous polyps based on size (e.g., ≥10 or ≥6 mm). Results for adenomas smaller than 6 mm were not commonly reported.

Direct Visualization Tests

Only four fair- to good-quality studies (n=4,821) examined the diagnostic accuracy of colonoscopy generalizable to community practice. Although colonoscopy is considered the criterion standard, it can miss cancers. Based on three studies that compared colonoscopy to CTC or CTC-enhanced colonoscopy (n=2,290), the per-person sensitivity for adenomas 10 mm or larger ranged from 89.1 percent (95% CI, 77.8 to 95.7) to 94.7 percent (95% CI, 74.0 to 99.9), and the per-person sensitivity for adenomas 6 mm or larger ranged from 74.6 percent (95% CI, 62.9 to 84.2) to 92.8 percent (95% CI, 88.1 to 96.0) (**Table 10**).

Based on nine fair- to good-quality studies of screening CTC (n=6,497), test positivity ranged from 10 to 30 percent. Overall, included studies were not powered to estimate test performance to detect cancer because of low numbers of cancers in these studies (range, 0 to 7 cancers). Based on seven studies of CTC with bowel preparation (n=5,328), the per-person sensitivity and specificity to detect adenomas 10 mm or larger ranged from 66.7 percent (95% CI, 45.4 to 83.7) to 93.5 percent (95% CI, 83.6 to 98.1) and 86.0 percent (95% CI, 84.6 to 87.3) to 97.9 percent (95% CI, 95.7 to 99.1), respectively (**Table 10**). Likewise, the per-person sensitivity and specificity to detect adenomas 6 mm or larger ranged from 72.7 percent (95% CI, 58.4 to 84.1) to 98.0 percent (95% CI, 90.9 to 99.8) and 79.6 percent (95% CI, 77.1 to 82.0) to 93.1 percent (95% CI, 89.5 to 95.7), respectively. Only three studies (n=1,044) reported sensitivity to detect advanced adenomas, ranging from 87.5 percent (95% CI, 65.6 to 97.3) to 100 percent (95% CI, 89.3 to 100). Two studies (n=1,169) evaluated CTC without using bowel preparation. Although data are much more limited, it appears that sensitivity of CTC without bowel preparation to detect advanced adenomas, adenomas 10 mm or larger, or adenomas 6 mm or larger is lower than for CTC protocols including bowel preparation (**Table 10**). Although there is some variation in estimates of sensitivity and specificity across included studies, it is unclear if the variation of test performance is due to differences in study design, populations, bowel preparation, CTC imaging, or differences in reader experience or reading protocols.

Stool Tests

Currently available stool tests include high-sensitivity gFOBT, FIT, and mtsDNA (stool DNA plus FIT). Three fair-quality trials of Hemoccult SENSA screening addressed high-sensitivity gFOBT. While all studies followed screen-positive participants with colonoscopy, these studies used different methods to follow screen-negative participants (differential followup). Based on two studies (n=10,170) reporting test performance to detect CRC in the entire colon, the sensitivity for CRC ranged from 61.5 percent (95% CI, 35.0 to 83.5) to 79.4 percent (95% CI,

63.8 to 90.3) and specificity from 86.7 percent (95% CI, 85.9 to 87.4) to 96.4 percent (95% CI, 95.6 to 97.2) (**Table 10**).

We grouped FITs by qualitative (fixed cutoff) and quantitative (adjustable cutoff) test design. We also grouped FITs by study design (i.e., same vs. differential reference standard followup). Fourteen fair- to good-quality studies (n=59,425) that used a colonoscopy reference standard in all participants reported sensitivity and specificity for different qualitative and quantitative FITs; overall the sensitivity for CRC and advanced adenomas varied widely (**Table 10**). Quantitative FITs included an older, discontinued test that resulted in unusually low sensitivity. We focused on FIT performance characteristics of currently available tests (family of tests) evaluated in more than one study. Two tests, OC-Light® (qualitative; k=3; n=25,924) and OC FIT-CHEK® (quantitative; k=5; n=12,794) (Polymedco; Cortlandt, NY), had relatively high sensitivity and specificity and are cleared by the FDA. Lowest sensitivity with accompanying specificity for CRC in these studies using one stool specimen was 73.3 percent (95% CI, 48.3 to 90.2) and 95.5 percent (95% CI, 94.6 to 96.3), respectively. Similarly, the highest sensitivity and paired specificity was 87.5 percent (95% CI, 54.6 to 98.6) and 90.9 percent (95% CI, 89.2 to 92.4), respectively. In the largest studies, sensitivity ranged from 73.8 percent (95% CI, 62.3 to 83.3) for quantitative (n=9,989) to 78.6 percent (95% CI, 61.0 to 90.5) for qualitative (n=18,296) test categories. In one small study (n=770) that tested three stool specimens, sensitivity was 92.3 percent (95% CI, 69.3 to 99.2) and specificity was reduced to 87.2 percent (95% CI, 84.7 to 89.4). Using the same FITs (OC-Light or OC FIT-CHEK), sensitivities for advanced adenoma were as low as 22.2 percent (95% CI, 17.0 to 28.2; specificity, 97.4% [95% CI, 96.6 to 98.0]) and as high as 40.3 percent (95% CI, 29.8 to 51.4; specificity, 91.3% [95% CI, 90.6 to 91.9]). While higher sensitivities for adenoma were obtained for certain other FITs or by using three specimens, corresponding specificities were reduced. In six fair-quality studies of various FITs that used differential reference standard followup, the lowest sensitivity with accompanying specificity for CRC was 68.8 and 94.4 percent, respectively, and the highest sensitivity and paired specificity was 90.9 and 95.6 percent, respectively, for both types of FITs (excluding results from three additional studies for noncomparable study design or few CRC cases).

Only one stool test using stool DNA testing, the mtsDNA assay Cologuard® (Exact Sciences; Madison, WI), is available for clinical use. One fair-quality study (n=9,989) evaluated the mtsDNA assay compared to a commercial FIT and to colonoscopy, finding statistically significant improved performance for detection of CRC and advanced adenoma compared to OC FIT-CHEK. The increased sensitivity for CRC (92.3% [95% CI, 84.0 to 97.0]) and for advanced adenoma (42.4% [95% CI, 38.9 to 45.9]) compared to FIT is accompanied by reduced specificity (84.4% [95% CI, 83.6 to 85.1]) for CRC and 86.6% [95% CI, 85.9 to 87.2] for adenoma) (**Table 10**).

Blood Test

Only one blood test has been prospectively evaluated in a screening population.[163] This test detects circulating methylated *SEPT9* DNA. This test was evaluated through a fair-quality, multicenter diagnostic accuracy study (n=1,516) that found that m*SEPT9* had a relatively low sensitivity to detect CRC (48.2% [95% CI, 32.4 to 63.6]), with a test positivity of 10.1 percent.

Detailed Results

Colonoscopy

We found no tandem colonoscopy studies that met our inclusion criteria of evaluating screening colonoscopy performance representative of community practice. We found seven diagnostic accuracy studies evaluating CTC in screening populations that also reported on sensitivity and/or specificity of colonoscopy against CTC or CTC-enhanced colonoscopy. The majority of CTC studies, however, were single-institution studies that included a very limited number of expert endoscopists. Four of these studies (n=4,821) included a larger number of endoscopists, and have greater applicability to colonoscopy performance in community practice (**Table 11**).[50,52,169,183]

Population Characteristics

All four of the included trials were conducted in the United States. Three of these trials (n=4,369) were multicenter trials.[50,52,183] All studies recruited similar populations of asymptomatic, average-risk adults age 50 years or older. Two studies also included persons age 40 years and older with or without a family history.[52,169] The mean age across studies ranged from 58 to 65 years. The baseline prevalence of cancer in the populations ranged from 0.16 to 1.1 percent. The highest prevalence was in the study by Johnson and colleagues with the highest mean age of 65 years.[169] Two studies included more than 15 percent nonwhite participants.[50,169]

Colonoscopy Details

Only one study actually reported the number of endoscopists (17). The others suggested a large number of endoscopists without reporting the actual number or were conducted in multiple clinical sites, which suggests a large number of endoscopists. All studies stated that colonoscopies were either conducted (or supervised) by an experienced gastroenterologist or surgeon. Only two studies actually reported the cecal intubation rate (both ≥99%).[52,169]

Study Quality

These four studies were all rated as fair- to good-quality studies. 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, adenomas 10 mm or larger, or adenomas 6 mm or larger. Two studies used colonoscopy enhanced with CTC as their criterion standard.[52,183] 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.[50,169] Despite this approach, however, not all the participants recommended 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 persons who were recommended to receive a repeat colonoscopy for lesions detected on CTC actually received the second colonoscopy.[50]

Outcomes

For CRC. In two trials (n=1,685), colonoscopy missed CRCs.[52,169] 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.[169] 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.[52] In this study, index colonoscopy results were compared to colonoscopy with segmental unblinding. Colonoscopy detected one of two CRC cases.

For adenomas by size. Per-person and per-lesion sensitivity and specificity for adenomas did not differ significantly within studies, and per-lesion accuracy was more commonly reported. The per-person sensitivity for adenomas 10 mm or larger ranged from 89.1 percent (95% CI, 77.8 to 95.7)[52] to 94.7 percent (95% CI, 74.0 to 99.9),[183] and the per-person sensitivity for adenomas 6 mm or larger ranged from 74.6 percent (95% CI, 62.9 to 84.2)[183] to 92.8 percent (95% CI, 88.1 to 96.0).[52] The per-lesion (per-person sensitivity not reported) sensitivity of colonoscopy in ACRIN for adenomas 10 mm or larger was 97.6 percent (95% CI, 93.1 to 99.5).[50] Specificity could only be calculated in one of the included studies. This good-quality study (n=605) by Zalis and colleagues observed a per-person specificity for adenomas 10 mm or larger of 88.7 percent (95% CI, 85.8 to 91.1) and 94.2 percent (95% CI, 91.8 to 96.0) for adenomas 6 mm or larger.[183] None of these studies reported sensitivity or specificity for lesions smaller than 6 mm.

FS

We found no studies that evaluated the test performance of FS against a colonoscopy standard in average-risk screening populations. Our previous review included other study designs that provided miss rates (i.e., one tandem FS study that provided miss rates of FS in the distal colon, two studies with repeat FS in 3 years that provided miss rates in the distal colon) or simulated data based on colonoscopy examinations (i.e., six large cohort studies of screening colonoscopy that provided simulated FS performance with or without biopsy).[195-203] None of these studies met the inclusion criteria for our current review.

CTC

We found nine diagnostic accuracy studies[49-52,165,169,170,176,183] in 10 articles[49-52,165,169,170,176,183,193] that evaluated CTC as a screening test in asymptomatic average-risk persons (**Table 12**). Three of these studies were included in the prior review.[52,169,176] Two of the previously included studies were excluded from this review due to use of older, single-detector technology that is no longer applicable to current practice.[204,205]

Population Characteristics

Six (n=5,453) of the nine studies were conducted in the United States.[50,52,165,169,176,183] Three trials (n=4,369) were multicenter trials.[50,52,183] The sample sizes for these nine studies ranged from 68 to 2,531. The largest trial (n=2,531) was a multicenter trial (15 centers), the ACRIN National CT Colonography Trial, conducted in the United States.[50] All nine studies recruited similar populations: asymptomatic, average-risk adults age 50 years or older. Four studies included persons age 40 years and older with or without a family history.[52,165,169,170] The mean age across studies ranged from 55 to 65 years. Only one study (n=452), conducted by Johnson and colleagues, had a mean age of 65 years or older.[169] All trials excluded persons with familial hereditary CRC syndromes. Two trials also explicitly excluded persons with family history of CRC in first-degree relatives.[49,176] The baseline prevalence of cancer in the populations ranged from 0.16 to 1.1 percent. The highest prevalence was in the study conducted by Johnson and colleagues that also had the highest mean age of 65 years.[169] All trials included a reasonably even mix of men and women, except for one small trial (n=68) conducted exclusively in men in a VA medical center setting.[176] Most studies did not report the race/ethnicity of participants. Three studies included more than 15 percent nonwhite participants, two studies were conducted in the United States,[50,169] and one study was conducted in South Korea.[170]

CTC Protocol

All included studies evaluated multidetector CTC using two examinations (supine and prone), although protocols for bowel preparation, imaging, and reading images varied across studies. Seven studies (n=5,328) evaluated CTC with bowel preparation with[50-52] or without fecal tagging,[49,169,170,176] and two more recent studies (n=1,169) evaluated CTC without bowel preparation and with fecal tagging.[165,183] Studies using bowel preparation varied in the type used, from full preparation with polyethylene glycol (PEG) to more limited preparation using only sodium phosphate or sodium picosulfate. Only one study (n=241), conducted by Kim and colleagues, administered intravenous contrast as part of the CTC protocol.[170] There was also variation in the number of detectors, reconstruction interval, collimation, and slice thickness. The number of reading radiologists for each study ranged from one to 15. Seven studies used three or fewer highly trained radiologists,[49,51,165,169,170,176,183] and only one trial (n=2,531), ACRIN, used a larger sample of CTC readers (15 radiologists).[50] While readers generally used a combination of two- and three-dimensional reading strategies, the primary reading strategy varied.

Study Quality

Studies were fair- to good-quality prospective diagnostic accuracy studies evaluating CTC in which all persons also received a colonoscopy. Five studies were good quality.[49,50,52,165,183] Limitations of fair-quality studies included limited reporting on study details (e.g., attrition, exclusions due to inadequate CTC or colonoscopy), small number of included participants, and, in one study, attribution of lesions seen on CTC but not colonoscopy as false-positives. The reasons for attrition were not consistently reported, however, followup (n analyzed/n screened) was generally high (>97%). In at least five studies, it appears that some of the attrition was due to incomplete or nondiagnostic CTC (e.g., nonadherence, issues with preparation or CTC examination, technical error).[50-52,169,183] Only three studies used the best choice of reference

standard (i.e., colonoscopy with segmental unblinding [CTC-enhanced colonoscopy]).[49,52,183] Two studies used colonoscopy plus an optional second/repeat colonoscopy triggered by CTC findings as the reference standard.[50,51] The remaining four studies used a single colonoscopy only as the reference standard.[165,169,170,176] Details about the number, training, or quality parameters of the endoscopists or colonoscopy itself were not consistently or commonly reported.

Outcomes

Commonly reported outcomes of the included studies were per-person and per-lesion sensitivity and/or specificity by type or histology (i.e., CRC, advanced adenomas, nonadvanced adenomas) and size (i.e., 6–9, ≥6, or ≥10 mm). The test positivity for CTC ranged from 10 to 30 percent of persons undergoing screening CTC. Test positivity was defined as having at least one lesion 5 or 6 mm or larger and therefore would have resulted in a followup colonoscopy for polypectomy, or at minimum required surveillance CTC.[50-52,165,169,170,176,183] Three studies reported on detection of lesions smaller than 6 mm.[49,170,176]

Sensitivity and specificity of CTC with bowel preparation.

For CRC. Overall, the number of cancers (20) detected in seven studies that evaluated CTC with bowel preparation (n=5,328) was low, and the actual number of cancers detected ranged from 0 to 7 (**Table 12**). In only one study, ACRIN (n=2,531), was one of the seven cancers missed. This missed cancer was a 10 mm lesion in the low rectum (not visible on a second review of the CTC image).[50]

For advanced adenomas or advanced neoplasia. For the three studies that evaluated CTC with bowel preparation (n=1,044), the per-person sensitivity and specificity to detect advanced adenomas ranged from 87.5 percent (95% CI, 65.6 to 97.3) to 100 percent (95% CI, 89.3 to 100) and 39.4 percent (95% CI, 33.7 to 45.2) to 87.1 percent (95% CI, 83.8 to 89.9), respectively (**Figure 10**).[49,51,170] The per-person sensitivity and specificity for advanced neoplasia was similar because the number of cancers was low (**Table 12**).

For adenomas by size. Across five included studies using bowel preparation (n=4,764), the per-person sensitivity for adenomas 10 mm or larger ranged from 66.7 percent (95% CI, 45.4 to 83.7) to 93.5 percent (95% CI, 83.6 to 98.1).[49,50,52,169,170] Across four studies using bowel preparation (n=4,523), the per-person specificity for adenomas 10 mm or larger ranged from 86.0 percent (95% CI, 84.6 to 87.3) to 97.9 percent (95% CI, 95.7 to 99.1).[49,50,52,169] The pooled estimate for sensitivity was 89.2 percent (95% CI, 82.0 to 96.4; I^2=56.9%) and for specificity was 94.4 percent (95% CI, 88.9 to 1.00; I^2=98.4%) (**Figure 11**).

The per-person sensitivity for adenomas 6 mm or larger across five included studies using bowel preparation (n=4,808) ranged from 72.7 percent (95% CI, 58.4 to 84.1) to 98.0 percent (95% CI, 90.9 to 99.8).[49-52,170] Across four studies using bowel preparation (n=4,567), the per-person specificity for adenomas 6 mm or larger ranged from 79.6 percent (95% CI, 77.1 to 82.0) to 93.1 percent (95% CI, 89.5 to 95.7).[49-52] The pooled estimate for sensitivity was 86.5 percent (95% CI, 77.7 to 95.2; I^2=90.0%) and for specificity was 88.3 percent (95% CI, 82.5 to 94.1; I^2=96.5%) (**Figure 12**).

Only three studies (n=616) reported test accuracy information for lesions smaller than 6 mm.[49,170,176] We could not calculate per-person sensitivity or specificity using reported data. In two studies (n=548), the per-lesion sensitivity for adenomas smaller than 6 mm ranged from 41.0 percent (95% CI, 32.6 to 49.8) to 59.2 percent (95% CI, 51.1 to 66.9).[49,170] In two studies (n=375), the per-lesion sensitivity for any polyp (regardless of histology) smaller than 6 mm ranged from 11.5 percent (95% CI, 5.9 to 20.0) to 38.4 percent (95% CI, 33.0 to 44.1).[170,176]

Clinical and statistical heterogeneity. We caution readers in interpreting pooled point estimates, given the large statistical heterogeneity, particularly around estimates of specificity and test accuracy around smaller adenomas. Instead, we suggest focusing on the 95% CI or range of estimates across the individual studies. However, the high statistical heterogeneity for specificity is in part due to the high degree of precision around estimates from individual studies. As described above, there is variation among CTC imaging and reading protocols, as well as additional 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 the clinical heterogeneity, it is yet unclear what are the key determinants accounting for the variation in test performance. There is some evidence, although not definitive, to suggest that fecal tagging improves sensitivity, from this body of evidence. It is unclear from this body of evidence if primary two- or three-dimensional reading strategy or radiologist choice of primary reading strategies improves sensitivity.

Only three studies reported sensitivity to detect advanced adenomas or advanced neoplasia, and while the sensitivity varied, there were no particular outliers.[49,51,170] Only two studies reported specificity to detect advanced adenomas or advanced neoplasia.[49,51] One study in particular, conducted by Graser and colleagues, observed a very low specificity for advanced adenoma or advanced neoplasia.[49] This good-quality study employed a limited number of CTC readers using a primary three-dimensional reading strategy against a criterion standard of colonoscopy with segmental unblinding. The CTC protocol did not use fecal tagging. Although the specificity for advanced neoplasia was low, this study showed a relatively high specificity for adenomas 10 mm and 6 mm or larger. This study also showed relatively high corresponding sensitivities for the detection of all types of lesions. Identification of more subcentimeter lesions, which will necessarily have a lower prevalence of advanced histology, resulted in lower specificity for advanced neoplasia.

For adenomas 10 mm or larger, one study conducted by Johnson and colleagues observed lower sensitivity than in the other studies.[169] This fair-quality study was conducted in a somewhat older population (mean age, 65 years) with a higher prevalence of cancer, using a limited number of CTC readers using a primary three-dimensional reading strategy. The CTC protocol did not use fecal tagging. The authors reported that the CTC examinations were conducted prior to standard fecal tagging and insufflation practices. For adenomas 6 mm or larger, the sensitivity was more variable compared to larger or more advanced lesions; however, there were no specific outliers. Two studies that employed a larger number of CTC readers found lower specificities for adenomas 10 mm or larger[50] and those 6 mm or larger.[52] The lower specificities did not correlate with higher sensitivities in these studies. Both of these studies used fecal tagging and primary three-dimensional reading strategies. Given the heterogeneity in these studies, it is inconclusive if the lower specificities observed were due to the greater number of CTC readers.

Subpopulations. Four studies of CTC with bowel preparation reported on the distribution of lesions in the colon.[49-52] 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.[49] This good-quality study (n=307), conducted by Graser and colleagues, evaluated CTC with bowel preparation and without fecal tagging against colonoscopy with segmental unblinding. The sensitivity for advanced adenomas did not vary significantly by location (proximal, 88.9% [95% CI, 58.6 to 98.8] vs. distal, 91.7% [95% CI, 75.9 to 98.2]). One study, ACRIN,[50] reported post hoc analyses for sensitivity and specificity by age in a subsequent publication.[193] This study (n=2,531) evaluated CTC with bowel preparation and fecal tagging against colonoscopy (with an option for a second-look colonoscopy if indicated). This study found nonstatistically significant lower per-person sensitivities for the detection of adenomas or cancers in persons age 65 years and older (n=477) compared to 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 to middle-aged adults was 82.1 percent (95% CI, 64.4 to 94.4) and 91.5 percent (95% CI, 83.7 to 96.7), respectively. Likewise, the per-person sensitivity for adenomas or cancers 6 mm or larger in older adults compared to middle aged adults was 71.5 percent (95% CI, 56.5 to 85.4) and 81.3 percent (95% CI, 74.5 to 88.2), respectively. No tests for interaction were reported for these subgroup analyses. The authors noted that there were differences in bowel preparation and distention by age group.

Sensitivity and specificity of CTC without bowel preparation. Only two studies (n=1,169) evaluated CTC performance without bowel preparation but with fecal tagging (**Table 12**).[165,183] Both studies were good-quality and conducted in the United States. Neither study was designed to estimate the diagnostic accuracy to detect CRC, as the total number of CRC cases was very low (4 cancers). One study (n=564), conducted by Fletcher and colleagues, reported a per-person sensitivity and specificity for detection of adenomas 10 and 6 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).[165] In the second study (n=605), conducted by Zalis and colleagues, 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]).[183] 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 if 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.

High-Sensitivity gFOBT

Study Details

Three fair-quality trials (n=15,969) reported results of high-sensitivity gFOBT (Hemoccult SENSA) in adults at average risk for CRC (**Table 13**).[155,156,173] Two of these studies were included in the previous systematic review.[155,156] Two were multicenter studies[155,173] and one was conducted at a single medical center.[156] Two studies were conducted in the United States[155,156] and one was conducted in Israel.[173] Two studies followed gFOBT-positive patients with

colonoscopy and all studies followed screen-negative patients over 2 years using registry data. In one study, gFOBT-positive patients were followed by sigmoidoscopy and, if positive, colonoscopy.[156] In another study, gFOBT-negative patients were recommended to have sigmoidoscopy.[155] Mean or median age was not reported, but studies included individuals age 50 years or older; 50 to 60 percent of the enrolled population were women in two reporting studies.[155,156] The prevalence of CRC ranged from 0.3 to 0.55 percent across studies. Allison and colleagues reported results only for distally located lesions (results not shown in **Table 13**).[155]

Outcomes

Levi and colleagues, with a total of 13 CRC cases, reported a sensitivity of 61.5 percent (95% CI, 35.0 to 83.5) and a specificity of 96.4 percent (95% CI, 85.9 to 87.4) for CRC (**Table 13**).[173] Allison and colleagues had a total of 34 CRC cases and reported a sensitivity of 79.4 percent (95% CI, 63.8 to 90.3) and a specificity of 86.7 percent (95% CI, 85.9 to 87.4) for CRC.[156] The 95 percent CIs for sensitivity overlapped across the two studies. In a later study and for the subset of distal lesions only, Allison and colleagues reported a sensitivity of 64.3 percent (95% CI, 38.4 to 84.8) and a specificity of 90.1 percent (95% CI, 89.3 to 90.8).[155]

FIT

The analysis of FIT studies is limited by several sources of heterogeneity, including the reference standard used to follow screening results and various attributes of FIT tests. In addition, study populations varied widely within FIT test categories. For these reasons, we decided against quantitative pooling of diagnostic accuracy results and instead qualitatively examined study results according to appropriate categories (see the Methods section). Briefly, we focused first on study designs that follow FIT screening with colonoscopy for all study participants, regardless of FIT result; then we evaluated studies with differential followup. For each study design, we examined categories of included FIT assays broadly by qualitative and quantitative methods and more specifically by test "family" (**Table 14**).

Studies With Colonoscopy Followup for All

We found 14 diagnostic accuracy studies[49,157,160,162,164,166,167,172,174,177,178,180-182] (published in 20 articles[49,157,160,162,164,166,167,172,174,177,178,180-182,184,186,187,189,191,194]) that evaluated FIT as a screening test in asymptomatic, average-risk persons and followed all screenees (both screen-negatives and screen-positives) with a diagnostic colonoscopy (**Table 15**). Three of these studies were included in the previous review.[160,177,178] We excluded one of the previously included studies from this review because the study was conducted in high-risk patients.[206] One study (Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung [BliTz]) is discussed twice in the results because the authors published a set of articles with a subsample and different FITs than the most recent publication.[157,186]

Population characteristics. Of the 14 included studies of FITs, eight were conducted in Asia (Japan, Taiwan, Hong Kong, or South Korea),[160,162,172,177,178,180-182] four were conducted in Europe (Germany, the Netherlands),[49,157,164,166] one was conducted in the United States,[174] and one, which compared a FIT to the mtsDNA test (includes a FIT), was conducted in the United

States and Canada.[167] Five of these studies were single-center studies,[160,162,177,180,182] six were multicenter studies,[157,164,166,167,172,181] and three studies did not provide sufficient description.[49,174,178] Overall, study sample size ranged from 285 to 21,805. Participants were described as asymptomatic and at average risk for CRC or as volunteers in general health or CRC-specific screening programs. The age threshold for participant enrollment was most often 50–55 years, but when reported, was 40 years in two studies.[174,178] Reported mean age varied from 46.8 to 64.2 years. The proportion of women enrolled in these studies ranged from about 40 to 60 percent, except for 28 percent in one study.[177] Baseline prevalence of cancer ranged from 0.15 to 1.7 percent and appeared to be poorly correlated with mean or median age. Most studies did not report race/ethnicity of participants, including seven conducted in Asia. Two studies reported less than 10 percent nonwhite participants, one in the Netherlands and one in the United States,[164,174] and one study (conducted in the United States and Canada) reported 16 percent nonwhite participants.[167]

FITs. Results from 19 FIT families (hereafter referred to as FITs) were reported in the included studies (**Table 15**). Some FITs were utilized in different versions (e.g., manual vs. various options for automation) or in combination with assays for other analytes. Not all FITs have been reviewed or cleared for marketing in the United States by the FDA, and some FITs have since been discontinued by the manufacturer. One study (BliTz, in multiple publications) compared multiple FITs across the same participant population (**Table 15**),[157,186] one study utilized four different FITs over time in different study subgroups,[174] and one study compared a FIT to the mtsDNA assay, which includes a FIT (see "Stool-Based DNA and mtsDNA Tests" section).[167] The number of patient samples analyzed by any one FIT ranged from 44 to 21,805.

Study quality. In this category of diagnostic accuracy or screening program studies, in which all participants received a colonoscopy, five studies were rated good-quality[49,157,162,164,166] and nine studies were rated fair-quality.[160,167,172,174,177,178,180-182] Limitations of fair-quality studies included incomplete reporting, potential selection bias, thresholds for a positive FIT result tested and selected after results were evaluated, and substantive or inappropriate exclusion of participant results from analysis. In one study, 58 percent of participants were younger than age 50 years and the study enrolled 2.5 times as many men as women, making the study less representative.[177] In another study, only 78 percent of enrolled participants had results that were evaluable.[167] In general, details about the number, training, or quality parameters of the endoscopists or colonoscopy itself were not consistently or commonly reported across all studies.

Outcomes. We grouped the most commonly reported outcomes as CRC, advanced neoplasia (CRC and advanced adenoma), and advanced adenoma. Although the definition of advanced adenoma varied somewhat across studies, variation was limited. A few studies reported results for all adenomas. No studies reported results by adenoma or polyp size categories. Five studies reported results by location (distal, proximal) but did not do so consistently for the same outcome.[157,162,167,177,186] Three studies reported results by sex[157,177,182] and two studies by age groups.[177,182] Subgroup results by sex, age, and location in colon are briefly discussed but data are sparse.

Sensitivity and specificity of qualitative FIT for CRC. Four studies (n=34,857), each of which utilized one of three FDA-cleared qualitative FITs (OC-Light, Hemosure® [Irwindale,

CA], MonoHaem® [Merck Millipore, Billerica, MA]), reported diagnostic accuracy for CRC outcomes (**Table 16**).[160,162,178,180] CRC prevalence ranged from 0.15 to 0.48, and the number of CRC cases detected ranged from 16 to 28. Across studies, the highest sensitivity for CRC, along with concordant specificity, was 88.9 percent (95% CI, 68.9 to 97.6) and 93.1 percent (95% CI, 92.4 to 93.8), respectively (**Figure 13**). The lowest sensitivity with paired specificity was 54.5 percent (95% CI, 32.3 to 73.7) and 89.4 percent (95% CI, 88.4 to 90.2), respectively (**Figure 13**). Sensitivity results for CRC were not clearly associated with assay cutoff value and may have been confounded by differing numbers of stool samples tested. The best results for an FDA-cleared, one-sample FIT were obtained with OC-Light (assay cutoff, 10 µg Hb/g feces), at a sensitivity of 87.5 percent (95% CI, 65.6 to 97.3) and specificity of 91.0 percent (95% CI, 90.3 to 91.6),[160] although another study using the same assay reported somewhat poorer sensitivity at 78.6 percent.[162] CIs were widely overlapping between the two studies. The lowest sensitivity was for Hemosure (assay cutoff, 50 µg Hb/g feces), for a manufacturer-recommended single sample. The MonoHaem FIT had the highest sensitivity in this group, even though it has the highest cutoff (about 1,000 µg Hb/g feces) due to the manufacturer's recommendation of testing three different stool samples. MonoHaem sensitivities for CRC using one- and two-stool samples were 55.6 and 83.3 percent (data not shown).

Sensitivity and specificity of qualitative FIT for advanced adenomas. Four studies (n=31,576) using eight qualitative FITs (OC-Light, Hemosure, bioNexia® FOBplus and bioNexia Hb/Hp Complex [bioMérieux, Marcy-l'Étoile, France]; FOB Advanced [ulti med, Ahrensburg, Germany]; immoCARE-C [CAREdiagnostica, Voerde, Germany]; PreventID® CC [Preventis GmbH, Bensheim, Germany]; QuickVue® [Quidel, San Diego, CA]) reported diagnostic accuracy outcomes for advanced adenoma (**Table 16**).[160,162,180,186] Two of these studies utilized OC-Light.[160,162] One study (BliTz) compared six FITs within the same population.[186] Cutoff values across FITs, where reported, ranged from 10 to 50 µg Hb/g feces. Advanced adenoma prevalence ranged from 1.0 to 9.8 percent across studies; lowest prevalence was associated with lowest mean age. Among tests with cutoff values reported in µg Hb/g feces, sensitivity for advanced adenoma was highest at 56.2 percent (95% CI, 47.6 to 64.5), with accompanying specificity of 67.9 percent (95% CI, 65.2 to 70.5). Lowest sensitivity was 25.4 percent (95% CI, 18.5 to 33.3), with specificity of 96.4 percent (95% CI, 95.2 to 97.3). Variation in results was not clearly related to cutoff value (**Figure 14**).

Sensitivity and specificity of qualitative FIT for advanced neoplasia. Six studies (n=36,808) that assessed 11 qualitative FITs (Clearview® iFOB Complete [cassette] and Clearview ULTRA iFOB [test strip] [Alere, Waltham, MA]; OC-Light; QuickVue; Hemosure; bioNexia FOBplus; bioNexia Hb/Hp Complex; FOB Advanced; immoCARE-C; PreventID CC; MonoHaem) with cutoff values ranging from 6 to 50 µg Hb/g feces reported diagnostic accuracy results for advanced neoplasia (**Table 16**).[160,162,174,178,180,186] Six of these FITs have been cleared by the FDA. Among FITs with cutoff values reported in µg Hb/g feces, sensitivity was highest at 61.5 percent (95% CI, 51.3 to 71.0), with accompanying specificity of 93.9 percent (95% CI, 93.2 to 94.6), and lowest at 5.0 percent (95% CI, 0 to 26.0), with specificity of 99.0 percent (95% CI, 96.0 to 100.0) (**Figure 15**). The lowest sensitivities were obtained in a study with very small sample sizes for a succession of four FITs.[174] Brenner and colleagues compared six FITs within a screening program (n=1,330).[186] Of the FDA-cleared tests in these rare FIT comparison studies, the highest and most consistent sensitivities were obtained by QuickVue (50.0% [95% CI, 1.0 to

99.0] and 59.6% [99% CI, 51.3 to 67.4]) but at a loss of corresponding specificity (88.0% [95% CI, 76.0 to 95.0] and 69.6% [95% CI, 66.9 to 72.1]). In two larger studies, OC-Light had variable sensitivities of 30.2 percent (95% CI, 26.7 to 33.7) and 48.4 percent (95% CI, 38.4 to 58.5), with accompanying specificities of 93.6 percent (95% CI, 93.2 to 93.9) and 91.3 percent (95% CI, 90.6 to 91.9).[160,162] The narrow range of FIT cutoff values was not helpful in explaining variability in this group of studies and for this outcome.

Sensitivity and specificity of quantitative FIT for CRC. Nine studies (n=42,310) that evaluated seven quantitative FITs (OC FIT-CHEK/OC-Sensor MICRO/OC-Sensor; RIDASCREEN® Haemoglobin and RIDASCREEN Haemo-/Haptoglobin Complex [R-Biopharm, Darmstadt, Germany]; FOB Gold® [Sentinel Diagnostics, Milan, Italy]; MagStream 1000/HemSp® [Fujirebio, Tokyo, Japan]; OC-Hemodia [Eiken Chemical, Tokyo, Japan]; Hemo Techt NS-Plus [Alfresa Pharma, Osaka, Japan]) reported diagnostic accuracy for CRC outcomes (**Table 17**).[49,157,164,166,167,172,177,181,182] CRC prevalence in these studies ranged from 0.3 to 1.7 percent and the number of CRC cases detected ranged from 1 to 79. Five studies used a version of the FDA-cleared OC FIT-CHEK assay.[157,164,167,181] FIT cutoff values ranged primarily from 2 to 20 μg Hb/g feces, with the exception of the MagStream 1000 assay (cutoff, about 100–200 μg Hb/g feces). The best results for these tests were seen with the OC FIT-CHEK family of assays, with sensitivities in studies testing one stool sample as low as 73.3 percent (95% CI, 48.3 to 90.2), with corresponding specificity of 95.5 percent (95% CI, 94.6 to 96.3), to as high as 87.5 percent (95% CI, 54.6 to 98.6), with specificity of 90.9 percent (95% CI, 89.2 to 92.4). These results are comparable to the best results obtained using qualitative FITs. Sensitivity to detect CRC was higher using lower cutoff values. The best sensitivity for the OC FIT-CHEK (92.3% [95% CI, 69.3 to 99.2]) was obtained by testing three consecutive stool samples in one small study but resulted in a loss of specificity (87.2% [95% CI, 84.7 to 89.4]).[181] Other assays generally had lower sensitivities (or were tested on few cancer cases) and are either discontinued or otherwise not available in the United States.

Sensitivity and specificity of quantitative FIT for advanced adenomas. Six studies (n=18,329) using six quantitative FITs (OC FIT-CHEK/OC-Sensor/OC-Sensor MICRO; RIDASCREEN Haemoglobin; RIDASCREEN Haemo-/Haptoglobin Complex; FOB Gold; OC-Hemodia) reported diagnostic accuracy outcomes for advanced adenoma (**Table 17**).[49,157,164,167,172,181,182] Four of these studies used OC FIT-CHEK (on different or unspecified automated analyzers).[157,164,167,181] Cutoff values ranged from 2 to 20 μg Hb/g feces, where reported. Where reported, adenoma prevalence ranged from 1.8 to 9.3 percent across studies; the lowest prevalence appeared associated with lowest mean age. The study with the lowest prevalence of advanced adenoma (1.8%) used the now discontinued OC-Hemodia and reported the lowest sensitivity of 6.0 percent (no corresponding specificity reported).[182] Excluding this study, the lowest sensitivity among single-sample, FDA-cleared FITs used in four studies was 22.2 percent (95% CI, 17.0 to 28.2), with corresponding specificity of 97.4 percent (95% CI, 96.6 to 98.0), and the highest was 33.6 percent (95% CI, 25.6 to 42.4) with specificity of 89.8 percent (95% CI, 87.4 to 91.9). A higher sensitivity (44.1% [95% CI, 31.9 to 56.8]) was obtained using this FIT in a small study that tested three stool samples and used a lower cutoff value.[181]

Sensitivity and specificity of quantitative FIT for advanced neoplasia. Nine studies (n=42,310) that used seven quantitative FITs (OC FIT-CHEK/OC-Sensor/OC-Sensor MICRO;

RIDASCREEN Haemoglobin; RIDASCREEN Haemo-/Haptoglobin Complex; FOB Gold; OC-Hemodia; MagStream 1000/HemSp; Hemo Techt NS-Plus) with cutoff values ranging from 2 to 100 µg Hb/g feces reported diagnostic accuracy results for advanced neoplasia (**Table 17**).[49,157,164,166,167,172,177,181,182] Only one of the FITs (OC FIT-CHEK family) is currently available and cleared by the FDA. For this FIT, the highest sensitivity using a single stool sample was 37.8 percent (95% CI, 29.5 to 46.7), with specificity of 93.3 percent (95% CI, 91.8 to 94.6), and the lowest sensitivity was 25.7 percent (95% CI, 20.3 to 31.7), with specificity of 97.4 percent (95% CI, 96.6 to 98.0). Sensitivity to detect advanced neoplasia was higher using lower cutoff values. A higher sensitivity of 52.8 percent was obtained for this same FIT using three stool samples and a lower cutoff value in a small study.[181] Overall, the highest sensitivity for advanced neoplasia (76.2%) was obtained using Hemo Techt NS-Plus, a FIT that is not available in the United States.

Subpopulations. Only a small number of studies reported FIT results by population subgroups and for various outcomes. In general, FIT sensitivities sometimes appeared higher for distal than for proximal lesions, but differences were not consistently apparent or statistically significant. Sensitivities for the reported outcomes tended to be higher in men than in women. Little data were reported for age subgroups.

Two studies of qualitative FITs reported subgroup results.[162,191] Chiu and colleagues reported no statistically significant difference in OC-Light sensitivity for CRC by distal (82.3%) versus proximal (72.7%; p=0.44) location.[162] The difference was statistically significant, however, for advanced adenoma, with a sensitivity for distal versus proximal lesions of 31.6 versus 22.5 percent, respectively (p<0.001). The BliTz study evaluated six qualitative tests, two of which are cleared by the FDA (immoCARE-C, QuickVue iFOB). Neither FIT showed a significant difference in sensitivity for any adenoma by location.[186,191] None of these studies reported statistical testing for interaction.

Three studies of quantitative FITs reported subgroup results (one study, BliTz,[157,186,187,189,191] is presented twice since it has a subsample of the population with different FITs).[177,182,194] Morikawa and colleagues reported FIT (MagStream 1000/HemSp) sensitivity for advanced adenoma in the distal location of 26.1 percent compared to 11.2 percent in the proximal location (p<0.001).[194] The pattern was similar for advanced neoplasia in this and one other study (BliTz), where the reported FIT (RIDASCREEN Haemoglobin) sensitivity was higher for distal (43.9%) than for proximal (29.6%) lesions (p=0.04).[189] The latter study also reported a sensitivity for advanced neoplasia that was higher in men (47.7% [95% CI, 40.0 to 55.6]) than in women (30.7% [95% CI, 21.8 to 40.8]).[187] Morikawa and colleagues reported that FIT sensitivity for advanced adenoma was higher in men (23.9%) than in women (16.7%) but an estimate of statistical significance was not available.[194] There were no obvious differences in FIT sensitivity by age. Sohn and colleagues reported FIT (OC-Hemodia) sensitivity by sex and age categories, but the specific FIT used had poor sensitivity in general and was discontinued, and results were inconclusive.[182] Again, none of the studies reported tests of interaction for included subgroup analyses.

Studies With Differential Colonoscopy or Registry Followup

Nine diagnostic accuracy studies (n=873,663)[155,156,158,159,161,168,171,173,179] in 10 articles[155,156,158,159,161,168,171,173,179,188] evaluated FIT as a screening test in asymptomatic, average-risk persons and followed screen-positive participants with diagnostic colonoscopy (or FS plus barium enema[161]), but followed screen-negative participants for interval cancers for 1–3 years by administrative database or cancer registry (**Table 18**). In one study that reported results only for distally located lesions, participants who screened negative by FIT were followed with FS, and all participants were followed for 2 years by administrative database.[155] Because participants received different followup depending on the results of their screening tests (test-referral bias), these studies as a group are considered lower quality and were not rated higher than fair quality.

Results from seven FITs were reported in the nine differential followup studies (**Table 18**).[155,156,158,159,161,168,171,173,179] Four studies were conducted in Asia (Japan, Taiwan),[159,161,168,179] two were conducted in Europe (France, Italy),[158,171] two were conducted in the United States by the same group,[155,156] and one study was conducted in Israel.[173] Five studies reported results from screening programs,[158,159,161,168,179] three from multicenter designs,[155,171,173] and one from a single medical center.[156]

Because participants who screened negative were followed via administrative database or cancer registries for cancer outcomes in most studies, only CRC outcomes were considered for this group of studies. Three studies (n=38,361) utilized qualitative FITs[156,158,179] (**Table 19**), which were OC-Hemodia and HemeSelect® (Beckman Coulter), both now discontinued, and MonoHaem (available and cleared by the FDA). Sensitivities for CRC using qualitative assays and 2-year followup for interval cancers ranged from 80.7 percent (95% CI, 70.6 to 88.6) to 83.3 percent (95% CI, 51.6 to 97.9), omitting results from the discontinued HemeSelect, which also has a high cutoff value (300 μg Hb/g feces[179]). Specificity ranged from 94.4 to 96.3 percent across all tests. Allison and colleagues reported sensitivity (81.8%) and specificity (96.9%) only for distal CRC using FlexSure OBT (Beckman Coulter), with an assay cutoff of 300 μg Hb/g feces (n=5,356) (data not shown).[155]

Five studies (n=82,840) utilized quantitative FITs (**Table 20**).[159,161,168,171,173] Three of these studies used the FDA-cleared OC FIT-CHEK family of FITs;[159,161,173] one of these studies compared OC FIT-CHEK to HM-JACK (A. Menarini Diagnostics, Firenze, Italy) in the context of a nationwide screening program linked to a cancer registry.[161] A third study used OC-Hemodia (discontinued).[168] All of these FITs have cutoffs in the range of 10–20 μg Hb/g feces. A fourth study used the MagStream 1000 (not cleared by the FDA) with a cutoff of 100–200 μg Hb/g feces.[171] Three studies followed FIT screen-negative participants for 2 years using cancer registries or an administrative database; these studies reported only on evaluable participants and excluded those without appropriate followup.[168,171,173] Chen and colleagues[159] reported on a community-based screening program with staggered entry and variable, minimum 1-year followup. Participants who initially screened positive by FIT but refused followup by colonoscopy were included in diagnostic accuracy calculations. Thus, study design may at least partly explain the low sensitivity of 45 percent for OC-Sensor. Two other studies reported sensitivities of about 86 percent and specificities of about 95 percent for two FITs.[168,171] Chiang and colleagues reported sensitivities of 77.1 and 73.7 percent, with corresponding specificities of

96.4 and 96.3 percent, for OC-Sensor and HM-JACK, respectively.[161] Levi and colleagues, also using OC-Sensor but evaluating three stool samples, detected all of the CRC cases (n=6) in their study.[173]

Stool-Based DNA and mtsDNA Tests

In 2012, we published a systematic review on stool-based DNA testing to screen for CRC in average-risk adults.[175] We rated the 2012 systematic review good-quality according to the methods of the current review. We found one diagnostic accuracy study for a mtsDNA test published after this review.[167] Our 2012 AHRQ-funded systematic evidence review used similar inclusion criteria and quality assessment as this review, and found only three studies that evaluated the performance of stool-based DNA tests in asymptomatic persons.[185,190,192] Because the stool-based DNA tests evaluated in these studies are no longer offered by the manufacturer, we describe results here briefly. The best evidence came from two studies (n analyzed=5,004) that evaluated a multimarker stool-based DNA test, a prototype to a later version that was clinically available as PreGen-Plus™ (Exact Sciences).[185,192] The sensitivity to detect CRC for this prototype was discordant between the two studies (25% [95% CI, 5 to 57] vs. 51.6% [95% CI, 34.8 to 68.0]), although the CIs overlapped. Sensitivity for advanced adenomas was similarly poor in both studies (19% [95% CI, 5 to 42] and 15.1% [95% CI, 12.0 to 19.0]). Between-study differences, such as differences in study populations, do not clearly account for the differences in test sensitivity. Specificity for advanced neoplasia ranged from 93.6 percent (95% CI, 92.9 to 94.3) to 96 percent (95% CI, 95 to 97) (**Table 21**). From that review we concluded that there was insufficient evidence regarding the clinical accuracy of stool-based DNA tests in persons at average risk for CRC.

The same manufacturer (Exact Sciences) of stool-based DNA tests included in the prior review reconfigured one of its tests to include assays to detect hypermethylation of the promoter regions of the *BMP3* and *NDRG4* genes, point mutations in the *KRAS* gene, and the beta-actin gene (used as a reference gene for quantity of human DNA), as well as a FIT for human hemoglobin.[167,207] The quantitative results for each DNA marker and FIT are incorporated into a logistic-regression algorithm that has been validated for a cutoff value of 183 to designate a positive result. This mtsDNA assay, Cologuard, is substantially different from previous stool-based DNA tests by this manufacturer.

One fair-quality diagnostic accuracy study (evaluable n=9,989) conducted at 90 clinical sites in the United States and Canada compared the results of the mtsDNA test to colonoscopy and a commercially available FIT (OC FIT-CHEK) (**Tables 15** and **17**).[167] Participants were asymptomatic adults ages 50 to 84 years at average risk for CRC and scheduled to undergo screening colonoscopy. Overall, the cancer prevalence in this study was 0.65 percent and advanced adenoma prevalence was 6.9 percent. Enrollment was weighted toward those age 65 years and older and, as a result, 63 percent of the evaluable participants were in this age category. Of the participants who originally consented to the mtsDNA study, 13.8 percent could not be evaluated because they withdrew consent (3.6%), did not have colonoscopy (9.1%), or did not submit a stool sample (1%). Of the remaining evaluable participants, 6.25 percent lacked mtsDNA test results because of specimen leakage or lack of a necessary repeat specimen (4.3%) or had technical failure (1.9%). In comparison, 0.3 percent of evaluable participants were

excluded because the sample had insufficient hemoglobin for FIT detection. In response to a letter, the authors of the study note that the collection device seal has been improved to prevent leakage.[208] Other limitations included unclear lack of independence of interpretation of the index and reference tests and slight differences between the evaluable and nonevaluable populations. mtsDNA testing detected 60 of 65 patients with cancer who were identified by colonoscopy. The sensitivity of the mtsDNA test for CRC was statistically significantly improved compared to the FIT (92.3% [95% CI, 84.0 to 97.0] vs. 73.8% [95% CI, 62.3 to 83.3], respectively; p=0.002) (**Table 17**).[167] Specificity for CRC, however, was statistically significantly lower for the mtsDNA test than for the commercial FIT (84.4% [95% CI, 83.6 to 85.1] vs. 93.4% [95% CI, 92.9 to 93.9], respectively), indicating a higher false-positive rate with mtsDNA. The pattern of results was similar for advanced adenoma (**Table 17**), with noticeably improved sensitivity for mtsDNA but a consequent reduction in specificity.

m*SEPT9* DNA Test

We found only one study that evaluated the test performance of a blood test to screen for CRC in asymptomatic, average-risk adults. This fair-quality multicenter prospective nested case-control study (Prospective Evaluation of Septin 9 or PRESEPT), evaluated the m*SEPT9* marker using the first generation of a commercially available polymerase chain reaction assay, Epi proColon® (Epigenomics, Germantown, MD).[163] The assay was designed to detect circulating methylated *SEPT9* DNA as a marker for CRC (not precursors of CRC).

This study initially included 7,920 asymptomatic adults from 32 clinical sites in the United States and Germany who met inclusion criteria, were age 50 years or older, and had an average risk for CRC. This study excluded persons with previous colonoscopy, previous cancer or adenomas, iron deficiency anemia, blood in stool, or family history of CRC. Eighty-seven percent of persons were available for analyses, with attrition mainly due to incomplete data or inadequate sample quality. Of the participants available for analyses (n=6,874), the mean age was 61 years, 55 percent were women, and the prevalence of underlying CRC was 0.8 percent. Participants had their blood drawn for the m*SEPT9* assay at least 1 day before the colonoscopy bowel preparation, with an average of 14 days prior to preparation. All patients included in the analyses had colonoscopies performed by board-certified endoscopists at the respective clinical site. The overall adenoma detection rate was 44.8 percent. It is assumed but not reported that the endoscopist was blinded to m*SEPT9* assay test results. Interpretation of the m*SEPT9* assay was independent of colonoscopy and pathology findings.

For the analyses, study investigators identified a subset of persons (n=1,516) using random sampling stratified by colonoscopy findings, including all 53 cancers, 315 of the 666 advanced adenomas, 210 of the 2,359 nonadvanced adenomas, and 938 of the 3,796 persons without evidence of disease. The test positivity rate in this subset was 10.1 percent (153/1,510). Weighted sensitivity and specificity of the m*SEPT9* assay to detect CRC calculated from this subset was 48.2 percent (95% CI, 32.4 to 63.6) and 91.5 percent (95% CI, 89.7 to 93.1), respectively. Test sensitivity to detect CRC increased with increasing CRC tumor stage. Sensitivity for distal (53.3% [95% CI, 34.7 to 72.4]) and proximal CRC (39.4% [95% CI, 14.2 to 68.2]) was not statistically significantly different (p=0.28). Test sensitivity to detect advanced adenomas was 11.2 percent (95% CI, 7.2 to 15.7); however, the assay was not designed to detect

advanced adenomas.

Key Question 3. What Are the Adverse Effects of the Different Screening Tests? Do Adverse Effects Vary by Important Subpopulations?

We included 98 fair- to good-quality studies[48-52,111,113,120-122,128,131,147,149,160,162,165,169,170,175,176,180,183,209-282] (in 113 articles[17,33,48-52,111,113,118,120-122,127,128,131,133,136,147,149,153,160,162,165,169,170,175,176,180,183,209-282]) that evaluated the harms of CRC screening (**Table 22**). This group included 14 studies that evaluated a screening program (stool testing or FS and subsequent diagnostic colonoscopy harms), 55 studies that evaluated screening colonoscopy, 18 studies that evaluated screening FS, and 15 studies that evaluated CTC in asymptomatic adults. In addition, 12 CTC studies provided estimates of radiation exposure per examination, and 21 CTC studies reported information on extracolonic findings. Although extracolonic findings can be either a benefit or harm, a summary is included in this section. While we found no additional studies examining the harms of stool testing, we did not hypothesize any harms for these noninvasive tests other than diagnostic inaccuracy (i.e., false-positive or false-negative testing) or downstream harms of diagnostic followup seen in "program of screening." We also found no empirical studies that directly addressed issues of harms related to overdiagnosis. Although we address the diagnostic (in)accuracy of a single test application in Key Question 2 (i.e., sensitivity [false-negatives] and specificity [false-positives]), our review did not specifically address harms around missed or interval cancers.

Overall Summary

Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons is estimated at 4 perforations (k=26) (95% CI, 2 to 5) and 8 major bleeds (k=22) (95% CI, 5 to 14) per 10,000 procedures. Serious adverse events from screening FS are even less common, with a pooled estimate of 1 perforation (k=17) (95% CI, 0.6 to 3) and 3 major bleeds (k=11) (95% CI, 1 to 9) per 10,000 procedures. FS, however, may require followup diagnostic or therapeutic colonoscopy. From six FS screening trials, the pooled estimate was 14 perforations (95% CI, 9 to 26) and 34 major bleeds (95% CI, 5 to 63) per 10,000 followup colonoscopy procedures for positive screening FS. While we found no studies addressing serious harms of stool-based (or blood/serum-based) tests, patients with false-positive test results also experience the risk of serious adverse events associated with diagnostic colonoscopy. The rate of perforation for followup colonoscopies for stool-positive testing may be higher—the pooled estimate was 8 perforations (k=6) (95% CI, 2 to 32) per 10,000 diagnostic colonoscopy procedures.

Other serious harms from endoscopy are not routinely reported or defined. Very few studies of endoscopy harms reported rates of adverse events in nonendoscopy comparator arms. Only two studies compared harms other than perforation and bleeding in a control group; both of these studies did not find a statistically significantly higher risk of serious harms due to colonoscopy (including myocardial infarction [MI], cerebrovascular accident [CVA], other cardiovascular events, and mortality). Because of reporting bias around serious harms other than perforation and

bleeding, as well as the lack of evidence for other serious harms attributable to colonoscopy in limited studies with control groups (k=2), we did not quantitatively pool these rates of serious harms.

Eighteen studies provided analyses of differential harms of colonoscopy by age (groups). These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding. Only one study provided data on differential harms of FS by age, and this study did not find an increased risk of serious adverse events with increasing age.

Based on 15 studies, there is little to no risk of serious adverse events (e.g., symptomatic perforation) for screening CTC. While CTC may also require followup diagnostic 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, 1 to 7 mSv). CTC also detects extracolonic findings, which could be a benefit or harm. Extracolonic findings are very common and are estimated to occur in 41 to 69 percent of examinations, although approximately 5 to 37 percent of examinations have extracolonic findings that necessitate actual diagnostic followup. An even smaller proportion of examinations have findings that require any type of definitive treatment (≤3%). From empirical evidence to date, it remains unclear if detection of extracolonic findings represents a net benefit or harm.

Detailed Results

Screening Programs

gFOBT or FIT

Based on included studies for Key Question 1 and reported harms from national stool testing–based CRC screening programs, the main source of serious harms comes from diagnostic colonoscopies conducted after gFOBT or FIT positive results (**Table 23**). Only one included study was conducted in the United States, the Minnesota Colon Cancer Control Study, which evaluated Hemoccult II.[147] Studies had varying number of rounds of screening (range, 1 to 11). Based on seven CRC screening studies (five trials and two cohort studies), the test positivity for stool testing ranged from 1.5 to 4.1 percent for gFOBT and 3.2 to 6.9 percent for FIT. Given the limited number of included studies (k=6), the estimates of harms are imprecise; nonetheless, the pooled estimate was 8 perforations (95% CI, 2 to 32; I^2=60%) (**Figure 16**) and 1.9 major bleeds (95% CI, 5 to 64; I^2=83%) (**Figure 17**) per 10,000 followup diagnostic colonoscopy procedures. From a single round of stool-based screening, assuming a 5 percent test positivity rate and 100 percent adherence to recommended followup colonoscopy, 1 to 16 persons would have a perforation and 2 to 32 persons would have major bleeding per 100,000 persons screened. Other types of serious harms were not commonly reported. No included studies reported differential diagnostic colonoscopy harms by age (groups).

FS

Screening programs of FS can accrue harms from either the screening FS or followup diagnostic or therapeutic colonoscopy. For harms of screening attributed to FS alone, please see the section

below. Five included trials for Key Question 1 evaluating FS screening reported harms from followup colonoscopy (**Table 23**). Only one trial, PLCO, was conducted in the United States.[122] This was also the only trial that evaluated more than a single round of screening. Based on these trials, 5 to 33 percent of participants received diagnostic or therapeutic colonoscopy. Again, given the limited number of studies (k=5), the estimates of harms are imprecise. The pooled estimate was 1.4 perforations (95% CI, 9 to 26; I^2=0%) (**Figure 18**) and 3.4 major bleeds (95% CI, 5 to 63; I^2=8%) (**Figure 19**) per 10,000 followup colonoscopy procedures after positive screening FS. Therefore, from one round of FS screening, assuming a 25 percent referral rate to colonoscopy and 100 percent adherence to recommended followup, approximately 22 to 65 persons would have a perforation and 12 to 158 persons would have major bleeding per 100,000 persons screened; this is in addition to harms accrued directly from FS (6 to 30 perforations and 10 to 90 major bleeds) (see below). Other reported serious harms included hospitalizations, MI, and syncope, but because these were not commonly reported, we do not provide a summary estimate of their likelihood of occurrence. No included studies reported differential diagnostic or therapeutic colonoscopy harms by age (groups).

FS

We found 18 fair- or good-quality studies[111,121,122,126,131,133,149,235,238,243,250,255,269,276,278,279,283,290] (in 21 articles[17,33,111,121,122,126,131,133,149,235,238,243,250,255,269,276,278,279,283,284,290]) that evaluated serious harms from screening FS in a general-risk population (**Table 24**). Five of these studies were retrospective cohort studies designed to assess for harms of screening FS;[238,243,250,276,278] the remaining 13 were prospective.[111,121,122,126,131,133,149,235,255,269,279,283,290] Five studies were conducted in the United States.[122,238,250,276,279] The length of followup to determine harms was not commonly reported, but when reported, was approximately 1 month. Despite some clinical heterogeneity, given the stringency of our inclusion criteria, and focusing on estimates of harms in the community practice setting, we quantitatively combined rates for commonly reported serious harms (i.e., perforation and bleeding). Other serious harms (e.g., hospitalization, MI, syncope, serious gastrointestinal conditions other than perforation/bleeding) were not commonly or consistently defined and/or reported.

Based on 16 studies (n=329,698),[121,122,126,131,133,149,235,238,243,250,269,276,278,279,283,290] we found that perforations from FS in average-risk screening populations were relatively uncommon, with a pooled point estimate of 1 perforation per 10,000 procedures (95% CI, 0.4 to 1.4; I^2=18.4%) (**Figure 20**). Based on 10 studies (n=137,987),[111,121,131,133,149,235,238,250,278,279] we found that major bleeding episodes from FS were also relatively uncommon, with a pooled point estimate of 2 major bleeding episodes per 10,000 procedures (95% CI, 0.7 to 4; I^2=52.5%) (**Figure 21**). Because of limitations in reporting, it is unclear if perforation and bleeding result from FS with biopsy. Exploratory meta-regressions were limited because of the number of included studies; nonetheless, none of the study-level characteristics investigated appeared to significantly affect estimates of FS harms.

No studies reported serious harms (other than mortality) as compared to a nonscreened group. There was no difference in all-cause mortality between screened and unscreened groups. Average age in these studies was not commonly reported. No studies appeared to be conducted in exclusively older adults. Only one study provided information on differential harms by age,

and found that age (50–59, 60–69, and 70–79 years) was not a significant predictor of risk for serious adverse events due to FS.[250]

Colonoscopy

We found 55 fair- or good-quality studies that evaluated serious harms from colonoscopy (**Table 25**).[48,50,120,128,160,162,180,183,209,210,212,214-217,221-224,226,232,234,236,239,240,242,243,247,248,251,252,254-256,263-266,268-271,273-276,280,281,291213,219,245,249,267,282] Twenty-four studies were conducted explicitly and exclusively in screening populations (or reported harms specific to the screening subgroup);[48,50,120,128,160,162,180,183,210,214,217,223,224,242,248,255,256,263,269,273-275,281,282] five studies were conducted in asymptomatic (but not necessarily screening) populations[213,219,245,249,267] and 26 studies were conducted in mixed populations (including nonscreening colonoscopies).[209,212,215,216,221,222,226,232,234,236,239,240,243,247,251,252,254,264-266,268,270,271,276,280,291] Thirty-one of these 54 studies were retrospective cohort studies,[209,212,214-216,221,222,224,226,232,234,236,239,240, 243,247-249,252,254,265-268,271,273,274,276,280-282] while the other 24 were prospective study designs.[48,50,120,128,160,162,180,183,210,213,217,219,223,242,245,251,255,256,263,264,269,270,275,291] Twenty-six studies were conducted in the United States.[50,183,209,212,214,215,219,221,222,226,232,239,242,245,247-249,256,264,266,267,276,280-282,291] The length of followup to determine harms was not commonly reported, but when reported ranged from 3 days to almost 2 years (most commonly approximately 30 days or 1 month). Despite the clinical heterogeneity, we quantitatively combined rates for commonly reported serious harms (i.e., perforation and bleeding), given the stringency of our inclusion criteria, and focused on estimates of harms in the community practice setting. Other serious harms (e.g., hospitalization, emergency department visits, MI, syncope, infection, other severe gastrointestinal symptoms, other cardiopulmonary events, splenic injury, acute kidney injury) were not consistently defined and/or reported.

Based on pooling 26 studies (n=3,414,108) in screening or generally asymptomatic persons,[48,50,120,128,160,162,180,183,213,214,217,219,223,224,242,245,249,256,263,267,269,273-275,281,282] we found that perforations from colonoscopy were relatively uncommon, with a point estimate of 4 per 10,000 procedures (95% CI, 2 to 5; I^2=86%) (**Figure 22**). Based on 22 studies (n=3,347,101),[50,120,128,160,180,183,213,214,217,219,223,224,245,249,256,263,267,273-275,281,282] we found that the risk of major bleeding from colonoscopy was 8 per 10,000 procedures (95% CI, 5 to 14; I^2=97%) (**Figure 23**). Statistical heterogeneity was very high for all of these pooled analyses. We conducted exploratory meta-regressions to determine if certain a priori identified study level characteristics would affect estimates of harms for colonoscopy. Indication of colonoscopy (i.e., screening or asymptomatic, mixed population [asymptomatic and symptomatic], followup FOBT positive, and followup FS) affected estimates of perforation. As a result, we stratified results by indication. Retrospective study designs with mixed populations appeared to have statistically (but not clinically) significantly lower estimates of major bleeding.

Only eight studies (n=204,614) explicitly reported if perforation or major bleeding was related to polypectomy or biopsy.[48,50,128,213,251,266,270,271] Based on this limited subset of studies reporting adequate information, many of the perforations and most of the major bleeding may be from polypectomy—about 36 percent (15/42) of perforations and about 96 percent (49/51) of major bleeding. Only four studies reported risk of perforation or bleeding in a control group (persons without colonoscopy).[120,212,273,280] The risk of perforation and bleeding was statistically significantly higher in the colonoscopy group in three of the four studies.[120,212,280]

Serious harms other than perforation or major bleeding were not routinely reported, including MI, diverticulitis, and mortality. About half of these studies (28 of 55) reported any harm other than bleeding or perforation. Furthermore, the types of additional serious harms (e.g., cardiopulmonary and gastrointestinal events) were not consistent. Most importantly, since the vast majority of studies had no comparator arm (nonscreened group), it is unclear if many of the additional serious harms that were reported can be related to the receipt of colonoscopy. Only two studies compared harms (other than perforation and bleeding) in persons who had a colonoscopy versus those who did not.[273,280] Both of these studies did not find a statistically significant higher risk of serious harms due to colonoscopy (including MI, CVA, other cardiovascular events, and mortality). A few studies were designed to examine specific harms—splenic injury (k=1)[239] and comparative harms of different bowel preparations (k=2).[234,248] Splenic injury (rupture) is a rare but serious event previously described as case reports following colonoscopy. A large retrospective study found splenic injury in 0.002 percent (7/296,248) of colonoscopies, only one of which happened during a screening colonoscopy.[239] Two studies that assessed harms compared PEG versus sodium phosphate bowel preparation and found greater risk of serious harm, including acute kidney injury, with PEG than with sodium phosphate, especially in older adults (age ≥65 years).[234,248]

Nineteen studies provided differential harms of colonoscopy by age (groups) (**Appendix E**).[48,209,212,215,216,221,222,224,232,245,247,249,252,254,263,265,267,280,282] Only two studies provided differential harms limited to screening populations, one in Australia (n=44,350)[48] and another in the United States (n=55,423).[282] The Australian study found that cardiopulmonary adverse events increased with age, from 0.05 percent in ages 50–60 years to 0.25 percent in ages 70–80 years (p<0.001), whereas bleeding events were similar (p=0.23).[48] The U.S. study in a Medicare population found that increasing age was associated with higher odds of serious bleeding, perforation, other gastrointestinal events, and cardiovascular events from either colonoscopy (n=54,039) or CTC (n=1,384), although only cardiovascular events were statistically significant.[282] The remaining 17 studies were large studies of colonoscopy harms in mixed populations (n>10,000), including but not limited to screening colonoscopy. Serious adverse events were not reported by age for the screening subgroups in these studies. In general, studies of colonoscopy performed for mixed indications found increasing risk of serious adverse events with increasing age, including bleeding, perforation, and serious 30-day serious adverse events,. Seven studies reported increasing age as a risk factor for serious adverse events after adjusting for potential confounders.[215,216,221,222,245,267,280] Only two studies explicitly included indication for colonoscopy as a confounder in their multivariate analyses; both found increased harms with increasing age after adjusting for confounders, including indication for colonoscopy.[215,267] We also used study-level age in our exploratory meta-regressions for our meta-analyses, and it did not appear to affect estimates of perforation or major bleeding. However, average age was not always reported, and only six studies were exclusively conducted in older adults (age ≥65 years) or had a mean age of 65 years or older.[222,226,234,263, 273,280]

CTC

Serious Adverse Events

We found 15 fair- to good-quality studies that addressed serious adverse effects of screening

CTC (**Table 26**).[49-51,128,165,170,183,211,228,237,242,255,262,272] Eleven of these were prospective studies that were restricted to screening populations, three were large retrospective studies conducted in mixed populations (including but not limited to screening examinations),[237,262,272] and one was a retrospective study conducted in a mixed population that presented screening results separately.[282] The most commonly reported serious adverse event was perforation, which can happen due to insufflation. Other nonserious adverse events included gastrointestinal symptoms such as abdominal pain, due to either the bowel preparation or the CTC examination, and vasovagal syncope or presyncope. The mean age ranged from 51 to 77 years, although age was not routinely reported.

Overall, the risk of perforation for screening CTC was less than 0.02 percent (2 per 10,000 CTC procedures). There were no perforations reported in 11 prospective studies (n=10,272) limited to screening populations.[49-51,128,165,170,183,211,228,237,242,255,262,272] Evidence of any clinically significant adverse effects primarily came from four retrospective studies (n=65,082), which included both asymptomatic and symptomatic populations.[237,262,272] These four studies suggested an increased risk of perforation in symptomatic compared to asymptomatic persons. Three of these studies specified perforation rates in the screening CTC subgroup.[262,272,282] No perforations were reported in one study's screening subgroup of 11,707 procedures.[262] In the study by Sosna and colleagues, there was 1 screening-related perforation in 11,870 procedures (number of CTC screening procedures not reported).[272] In one small study using Medicare claims data, 1 perforation was found among 1,384 screening CTC examinations.[282] While there were 7 perforations in 40,121 procedures in a fourth study, the author states that none were due to mechanical insufflation, and five of the seven perforations occurred in persons who also had colonoscopy within 2 weeks.[237] Results were not reported for screening-only examinations in this study. Limited data suggest that not all CTC-detected perforations are symptomatic or require any clinical management. In the study by Sosna and colleagues, for example, six of the seven perforations were detected only on CTC (number of symptomatic perforations not reported), and only four of the seven perforations required surgical intervention.[272] In the study by Pickhardt and colleagues, only one of the two perforations was clinically symptomatic and required treatment.[262]

We found no studies that reported on the differential risk for serious harms of CTC by age. However, one study, ACRIN, noted that hospitalizations following both CTC and colonoscopy were greater in persons older than age 65 years.[50]

Radiation exposure per examination. Many of the CTC diagnostic accuracy studies in this review did not report actual radiation exposure or provide sufficient information to calculate it (**Table 27**). Based on four included diagnostic accuracy studies of CTC (published between 2008 and 2013), however, the estimated radiation dose for one full-screening CTC examination (dual positioning supine and prone) was about 4.5 to 7 mSv.[49,50,165,183] Based on three additional recent CTC screening studies (2004–2008), the estimated radiation dose has decreased to a range of 1 to less than 5 mSv.[211,228,255] A recent survey of academic and nonacademic institutions (62 of 109 responding) found that the median radiation dose per screening CTC examination was 4.4 mSv.[292] In contrast, two older reviews provided estimates of radiation exposure and found a dose range per CTC examination (not limited to screening examinations) of 1.6 to 24.4 mSv, with a median dose estimate of 8.8 or 10.2 mSv.[293,294] Overall, the body of evidence reflects a decrease

in radiation exposure for CTC examinations over time due to newer multidetector scanners and protocols. Based on survey data and included studies, however, radiation exposure has not decreased significantly from 2007 to 2011.[292]

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.

Extracolonic findings. Incidental extracolonic findings detected on CTC can be a benefit or a harm, depending on the finding. The CT Colonography Reporting and Data System (C-RADS) is a well-recognized standard for reporting CTC findings. Under C-RADS, extracolonic findings are categorized into five categories: E0=limited examination, E1=normal examination or normal variant, E2=clinically unimportant finding in which no workup is required, E3=likely unimportant or incompletely characterized finding in which workup may be required, and E4=potentially important finding requiring followup.[295] Some studies examining extracolonic findings do not use the C-RADS classification system but instead a classification 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, aneurysms of the splenic or renal arteries, adenopathy >1 cm). Findings of "moderate" clinical significance do not require immediate medical attention but would 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.

We found 21 studies (n=38,293)[50,52,128,183,218,220,227,229-231,233,242,244,253,257,259-261,277,285,288] (seven studies with overlapping populations reported different extracolonic findings) in 22 articles[50,52,128,183,193,218,220,227,229-231,233,242,244,253,257,259-261,277,285,288] reporting on extracolonic findings in asymptomatic persons, 16 studies (n=35,409) in screening populations,[50,52,128,183,220,227,229,242,244,257,259-261,277,285,288] and five studies (n=2,884) in mixed asymptomatic populations (including those undergoing surveillance, those with positive stool testing or iron deficiency anemia, and those with family history) (**Table 28**).[218,230,231,233,253] The number of examinations in these studies ranged from 75 to 10,286. The largest study (n=10,286) represented persons included in other studies but focused on different extracolonic malignancies only.[260] In general, studies that reported extracolonic findings varied greatly in their ability to accurately assess followup and the duration of followup. The longest duration of followup was 5 years, but was often not reported. Thus, none of these studies are able to articulate the true net health benefit or harm due to extracolonic findings for persons undergoing CTC.

Overall, extracolonic findings were common among screening or surveillance CTC examinations and ranged from 27 to 69 percent for any extracolonic findings. Similarly, available studies suggested a very wide range of findings needing additional workup; 5 to 37 percent had E3 or E4 category findings and 1.7 to 12 percent had E4 category findings. Because E3 or E4 findings, as well as those of "moderate" or "high" clinical significance, generally require medical followup, the potential for significant additional morbidity and cost, as well as benefit, remains. Among the studies that also reported medical followup of extracolonic findings, between 1.4 and 11 percent went on to diagnostic evaluation, which closely mirrors the prevalence of E4 category

findings. Among studies adequately reporting subsequent treatment, only a minority of findings (≤3%) required definitive medical or surgical treatment. Extracolonic cancers were not common and occurred in only 0.5 percent of persons undergoing CTC examinations. In the largest series of examinations (n=10,286), with about 4 years of followup, 36 (0.35%) examinations found an extracolonic malignancy, 32 of which received definitive treatment.[260] Abdominal aortic aneurysm occurred in up to 1.4 percent of persons.

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 persons. Extracolonic findings, however, 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.[218,285] Two studies compared extracolonic findings in persons younger than age 65 years to those age 65 years and older.[50,253] Both studies found a higher prevalence of both any extracolonic finding and extracolonic findings that warranted further workup (E3/E4).[50,253]

Chapter 4. Discussion

Summary of Evidence

Overall

We conducted this review to support the USPSTF in updating its recommendation on screening for CRC. Since its previous recommendation was published in 2008,[87] we have included 95 new studies. They include 24 studies that assessed the impact of screening on CRC incidence and mortality, 19 new studies that assessed the diagnostic accuracy of screening tests, and 70 new studies that assessed harms.

A number of tests have been studied for their use in screening for CRC in average-risk adults, including colonoscopy, FS, CTC, high-sensitivity gFOBT, various qualitative and quantitative FITs, and mtsDNA test (which includes FIT) (**Table 29**). These test options have different levels of evidence to support their use, different test performance to detect cancer and precursor lesions, and different risk of serious adverse events. At this time, comparative studies of the different screening tests are limited in their study design and power to detect cancers (and missed/interval cancers), mortality, or serious harms. Therefore, they cannot answer questions of the relative benefit and harms (tradeoffs) between the tests. Taking this in consideration, this systematic review of the available evidence may be used in tandem with microsimulation modeling conducted by CISNET, which addresses issues around the comparative performance, benefit, and harms of available tests, as well as decisions around screening intervals and age to start/stop screening. Additionally, choice of screening test and implementation of screening programs within health systems will depend on a number of factors (not covered in this report) in addition to the comparative performance, including patient preference and available resources (including but not limited to cost).

To date, no CRC screening modality has been shown to reduce all-cause mortality. Robust data from well-conducted, population-based screening RCTs demonstrate that both Hemoccult II and FS can reduce CRC mortality. However, FS data are limited to one or two rounds of screening. In addition, Hemoccult II and FS are no longer widely 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 RCTs of newer stool tests may not be necessary, as evidence-based reasoning supports that screening with stool tests with sensitivity and specificity that are as good as, or better than, Hemoccult II would result in CRC mortality reductions similar or better than reductions shown in existing trials.[296] Based on our review, there are a number of newer stool tests available that meet those requirements, including single-sample testing with OC-Light or OC FIT-CHEK. Stool tests that maximize sensitivity, such as mtsDNA, multisample FITs, or quantitative FIT using lower cutoffs, have lower specificity and therefore need new trials or modeling exercises to understand the tradeoff of more false-positives. Although imperfect, colonoscopy remains the criterion standard for assessing the test performance of other screening tests; however, its superiority in a program of screening has not been established. To date, no trials have reported on the mortality benefit of

colonoscopy. Furthermore, colonoscopy is significantly more invasive, with greater accompanying harms (and potential harms of overdiagnosis and/or unnecessary polypectomy/surveillance) than other available testing. Evidence continues to accrue for CTC that suggests 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. Although a blood test would undoubtedly increase screening rates, the Epi proColon test for circulating m*SEPT9* has worse test performance for the detection of CRC than other noninvasive testing.

Stool Tests

gFOBT

We updated and confirmed that Hemoccult II is the only stool CRC screening test that has been shown to significantly 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 to no screening in large, well-designed RCTs. Hemoccult II screening did not affect all-cause mortality. These results are in general agreement with the Cochrane Colorectal Cancer Group update on CRC screening using Hemoccult testing. In this review, overall reduction in CRC mortality across four RCTs was 16 percent (RR, 0.84 [95% CI, 0.78 to 0.90]) at 12–18 years.[297]

Hemoccult SENSA has replaced Hemoccult II because of its improved sensitivity to detect CRC. Based on three diagnostic accuracy studies, Hemoccult SENSA (three samples) sensitivity ranged from 61.5 to 79.4 percent. The specificity, however, was reported as low as 86.7 percent.

FIT

In the United States, many health systems and coordinated screening programs now use FITs, as opposed to gFOBT, to screen for CRC.[298-302] FIT testing usually requires only one sample and eliminates dietary and medicinal restrictions, which generally improves ease of and adherence to testing.[303,304]

No included studies addressed the impact of FIT on CRC mortality. We excluded one large (n=192,261) RCT conducted in rural China that compared single FIT screening to no screening because of the setting (i.e., our inclusion criteria was limited to countries with a “very high” Human Development Index).[305] 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. In trials or cohort studies in which Hemoccult II was compared to various FIT assays, test positivity and CRC detection with FIT was consistently higher, although not always significantly so. Patient adherence to FIT was also consistently higher than to gFOBT. Given at least equal and likely better CRC detection and patient adherence, FITs are preferable to gFOBT.
FITs are not a class of tests, however, and assay differences result in tests with different diagnostic performance. FIT sensitivity varied considerably across different qualitative and quantitative assays in the included diagnostic accuracy studies. The qualitative OC-Light

(n=25,707) and the quantitative OC FIT-CHEK (n=15,029) tests, both available in the United States and cleared by the FDA, performed well in more than one study. Although quantitative FITs are cleared only for qualitative or dichotomous use in the United States, they maintain the advantage of a flexible assay cutoff value (to adjust desired performance characteristics) and potential for automation in high-volume settings. Qualitative assays designed for manual use are ideal for low-volume settings where flexibility is not required. Based on a single stool sample for OC-Light or OC FIT-CHEK, the test performance to detect CRC ranged from 73.3 percent sensitivity and 95.5 percent specificity to 87.5 percent sensitivity and 90.9 percent specificity. In the largest studies, sensitivity to detect CRC was 73.8 percent (95% CI, 62.3 to 83.3) for quantitative OC FIT-CHEK (n=9,989) and 78.6 percent (95% CI, 61.0 to 90.5) for qualitative OC-Light (n=18,296). For these FITs, the sensitivity was higher in small studies that either tested three stool samples (sensitivity, 92.3% [95% CI, 69.3 to 99.2]; specificity, 87.2% [95% CI, 84.7 to 89.4]) or lowered the assay cutoff value (sensitivity, 87.5%; specificity, 90.9%). Specificity decreased with increasing sensitivity. The range of sensitivity and specificity estimates for these selected FITs is similar to the results of a meta-analysis of all FIT types, in which estimated sensitivity was 0.79 (95% CI, 0.69 to 0.86) and estimated specificity was 0.94 (95% CI, 0.92 to 0.95).[306]

mtsDNA (Stool DNA Plus FIT)

The mtsDNA test (Cologuard), concurrently approved by the FDA for marketing and by CMS for coverage in August 2014, combines the results of a FIT and DNA marker assays. It is the most expensive of the stool tests, reimbursed by CMS at $493 per test.[307] In comparison, the cost of FITs is generally much lower, with a CMS reimbursement of $23 and a mean commercial reimbursement of $21 per test.[308] In one large study (n=9,989), mtsDNA was statistically significantly more sensitive for CRC (92.3%) than OC FIT-CHEK (73.8%) using a recommended single stool sample for each test. In other included FIT studies, OC FIT-CHEK had higher estimated sensitivity when multiple samples or lower assay cutoffs were used. However, comparison of test performances across studies is difficult due to differences in study design and population characteristics. In all cases, increasing sensitivity was accompanied by decreasing specificity. Specificity for the mtsDNA test (84.4%), for example, was lower than for all FIT assays, resulting in the highest false-positive rate.

The high rate of unsatisfactory samples for the mtsDNA test (6.25%) was concerning when compared to the rate for FITs (0.3%). Excluded samples in this study were in part due to leakage in shipping, which the manufacturer reported has since been fixed, as well as a study quality control measure that authors indicate would not be encountered in clinical practice.[208] At a programmatic level, information is lacking on patient adherence and the appropriate screening interval, as well as the impact of false-positives as a result of lowered specificity.[309]

Harms of Stool Testing

There are no hypothesized serious adverse events from noninvasive stool testing other than the risk of missed cancers (false-negatives). However, serious adverse events may result from followup diagnostic colonoscopy for positive stool testing. Based on six trials, the rate of perforation in colonoscopies for positive stool testing may be higher than for colonoscopies in

average-risk screening populations (see below); the pooled estimate was 8 perforations (95% CI, 2 to 32) per 10,000 diagnostic colonoscopies.

Endoscopy

FS

Four large RCTs evaluating screening FS have been published since the previous USPSTF recommendation on CRC screening. These trials showed that one-time FS (or two rounds of FS in the PLCO trial) consistently reduced CRC-specific mortality compared to no screening at 11 to 12 years of followup (IRR, 0.73 [95% CI, 0.66 to 0.82]). This reduction in mortality, however, was limited to distal CRC, and there was no decrease in all-cause mortality. Our meta-analyses produced similar findings to those from another meta-analysis including the same four trials.[310] Despite this robust evidence, recent utilization data in the United States suggest that FS (in combination with stool testing) is very uncommon (<1%).[70] Public and clinician perceptions of accuracy of colonoscopy versus FS, given the reach of endoscopy, also play an important role in this issue.[83]

We found no studies estimating the diagnostic accuracy of FS compared to a colonoscopy reference standard. To date, 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] The sensitivity and specificity for CRC (and advanced adenomas) depend on whether the screening FS used biopsy and the referral criteria used for diagnostic or therapeutic colonoscopy. Screening FS with biopsy does not appear to be commonplace in U.S. practice. 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.

Colonoscopy

One fair-quality large cohort study using data from the Nurses' Health Study and the Health Professionals Followup Study found that persons who self-reported screening colonoscopy had a lower CRC-specific mortality rate than persons who never had a screening endoscopy (adjusted HR, 0.32 [95% CI, 0.24 to 0.45]) at 24 years of followup. This reduction in CRC-specific mortality was greater for distal than proximal cancer but statistically and clinically significant for both types. Although this study adjusted for known confounders, the magnitude of association should be interpreted with caution and cannot be compared to the CRC mortality reduction observed in intention-to-treat analyses of FS and Hemoccult II RCTs. Three large RCTs of screening colonoscopy in average-risk adults that examine the long-term outcomes of CRC incidence and mortality are underway. The first is the Northern European Initiative on Colorectal Cancer trial comparing screening colonoscopy to usual care in Norway, Sweden, Poland, and the Netherlands.[311] The remaining two trials are comparing screening colonoscopy to FIT; COLONPREV is comparing colonoscopy to biennial FIT in Spain[120,312,313] and CONFIRM is comparing colonoscopy to annual FIT in the United States.[302]

We found a limited number of studies examining the test performance of screening colonoscopy

in a community setting. Only four studies, which were primarily designed to evaluate screening CTC and in which colonoscopy was conducted by more than a handful of expert endoscopists, reported sufficient data to determine the sensitivity and specificity of screening colonoscopy. In these studies, colonoscopy was compared to a criterion standard or CTC or CTC-enhanced colonoscopy. However, none of these trials were designed to estimate the test performance for detecting 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. Test performance of screening colonoscopy will vary in clinical practice because of bowel preparation and colonoscopist performance/experience. 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.[314,315]

Most studies evaluating the test performance of colonoscopy are small studies that employed a limited number of expert endoscopists. Additionally, most of these studies were not conducted in screening populations. One review conducted by VanRijn and colleagues to assess miss rate determined by tandem colonoscopy (k=6; n=465) found that colonoscopy rarely misses adenomas 10 mm or larger (2.1% [95% CI, 0.3 to 7.3]) but the miss rate increases with smaller-sized adenomas (5–10 mm, 15% [95% CI, 8.0 to 18] and 1–5 mm, 26% [95% CI, 27 to 35]).[316] These studies were not conducted in screening populations, however, and were thus excluded from our review. We also excluded a growing body of literature addressing technological advancements in colonoscopy to improve adenoma detection, namely chromoendoscopy or digital/virtual chromoendoscopy (e.g., narrow band imaging, flexible spectral imaging color enhancement, iScan) or endoscopic technologies to increase mucosal surface area inspection (e.g., wide-angle lens or full-spectrum endoscopy, cap-fitted colonoscopy, through-the-scope retrograde viewing device). The vast majority of the studies that evaluated these technological advancements were small, single-center studies that employed a small number of expert endoscopists. Multicenter trials of back-to-back colonoscopy evaluating the Third Eye® Retroscope® (Avantis Medical Systems, Sunnyvale, CA) or wide-angle lens endoscopy demonstrate fewer missed adenomas with enhanced technologies.[317,318] To date, based on very limited multicenter randomized trials, it appears that technological advancements (i.e., chromoendoscopy, narrow band imaging, Third Eye Retroscope) can improve detection but data are limited to support widespread adoption in screening or average-risk populations.[319-321]

Harms of Endoscopy

Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons are relatively uncommon, with a pooled estimate of 4 perforations (k=26) (95% CI, 2 to 5) and 8 major bleeds (k=22) (95% CI, 5 to 14) per 10,000 procedures. Based on 18 studies, the risk of serious harms following colonoscopy, including perforation and bleeding, is higher with increasing age. Serious adverse events from screening FS are even less common, with a pooled estimate of 1 perforation (k=17) (95% CI, 0.6 to 3) and 3 major bleeds (k=11) (95% CI, 1 to 9) per 10,000 procedures. In addition, FS may require followup diagnostic or therapeutic colonoscopy. The pooled estimate from six FS screening trials was 14 perforations (95% CI, 9 to 26) and 34 major bleeds (95% CI, 5 to 63) per 10,000 followup colonoscopy procedures for

positive screening FS. Other serious harms (e.g., cardiopulmonary and other gastrointestinal events) were not consistently reported, and two studies evaluating harms in persons 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.

Case reports of fatal or near-fatal outcomes in average-risk persons undergoing routine colonoscopy include splenic rupture,[322,323] retroperitoneal or intra-abdominal hemorrhage,[324,325] retroperitoneal gas gangrene,[326,327] bowel infarction or ischemic colitis,[241,328,329] small bowel perforation,[330] colonic gas explosion with electrocautery,[331] and appendicitis or appendiceal abscess.[332] In addition, there have been case reports of transmission of communicable diseases (i.e., hepatitis C virus, human papillomavirus) using unsanitized colonoscopes[333-335] and chemical colitis from glutaraldehyde, which is used to disinfect endoscopes.[336]

Harms of Bowel Preparation

Common bowel preparation agents for FS include enemas and occasionally oral laxatives. Common bowel preparation agents for colonoscopy or 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 distension/bloating, anal irritation, headache, dizziness, electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, hyper- or hypophosphatemia), and poor sleep.

Serious adverse events (e.g., severe dehydration, symptomatic electrolyte abnormalities) are generally limited to persons with major predisposing illnesses.[337,338] In clinical practice, sodium phosphate use is generally avoided in persons with renal impairment (such as older patients with reduced glomerular filtration rates), cardiovascular impairment (e.g. congestive heart failure, recent MI), major upper or lower gastrointestinal motility disturbances, gastrointestinal malabsorption, pre-existing electrolyte abnormalities, restricted oral intake (inability to rehydrate), and ascites.[337] We found no evidence of clinically significant adverse effects due to bowel preparation that required hospitalization in average-risk screening populations preparing for FS, colonoscopy, or CTC, except for one person with "water intoxication" due to "over anxious bowel cleansing" in preparation for FS[17] and another person with severe diarrhea.[290] Two included studies that compared PEG versus sodium picosulphate bowel preparation found greater risk of serious harm, including acute kidney injury, for PEG versus sodium picosulphate, especially in older adults (age ≥65 years).[234,248] In one recent large population-based retrospective cohort of older adults that we excluded from our review, sodium picosulphate was associated with an increased risk of hospitalization for hyponatremia compared to PEG in adults older than age 66 years.[339] Overall, existing systematic reviews on bowel preparation for endoscopy suggest similar tolerability based on number of minor adverse events, no difference in efficacy of preparation, and no clinically significant adverse events from PEG or sodium phosphate.[340,341] Low-volume PEG (2 L) with bisacodyl may be better tolerated than full-volume PEG (4 L), with no difference in efficacy.[342] Case reports of serious adverse events from bowel preparation in average-risk persons undergoing colonoscopy include acute renal failure and acute phosphate nephropathy in persons who received bowel preparations with sodium phosphate or PEG,[337,343-345] one person with ischemic colitis with sodium phosphate,[337]one person with symptomatic hypokalemia with sodium phosphate,[337] one person with Boerhaave syndrome

(barogenic esophageal rupture) with PEG,[346] and one person with a seizure secondary to hyponatremia with PEG.[347]

CTC

While we found no studies examining the impact of screening CTC on cancer incidence or mortality, there is a growing body of evidence evaluating the test performance of screening CTC in average-risk adults. None of these studies (k=9) were designed to estimate test performance to detect cancer, as the number of cancers in these studies was low (range, 0 to 7 cancers). Based on studies of CTC with bowel preparation (k=7), 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. The per-person sensitivity and specificity of CTC with bowel preparation to detect adenomas 6 mm or larger ranged from 72.7 to 98.0 percent and 79.6 to 93.1 percent, respectively. Only three studies reported sensitivity to detect advanced adenomas, ranging from 87.5 to 100.0 percent. Based on very limited data (k=2), it appears that sensitivity of CTC without bowel preparation to detect advanced adenomas, adenomas 10 mm or larger, or adenomas 6 mm or larger is lower than for CTC protocols including bowel preparation. Our findings are consistent with an existing systematic review by de Haan and colleagues of five prospective CTC screening studies in average-risk adults, which found that the per-person sensitivity and specificity for large adenomas (>10 mm) was 83.3 to 87.9 percent and 97.6 to 98.7 percent, respectively.[348] However, per-person sensitivity and specificity for smaller adenomas (≥6 mm) was lower, at 75.9 to 82.9 percent and 91.4 to 94.6 percent, respectively.

It is unclear if 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 ACR and the International Collaboration for CT Colonography Standards have recommended practice guidelines and quality metrics, as well as specification for training and certification.[349-351] In practice, the standard appears to be a dry preparation (sodium phosphate, magnesium citrate, bisacodyl) rather than a wet preparation (PEG) because of patient preferences and because PEG can leave liquid in the colon that can potentially obscure lesions.[352] 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 soft tissue density 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 choice for which to use is largely based on local experience. Current practice uses multidetector row CT scanners, using much thinner slices with faster scan times, resulting in better imaging and decreased radiation dose. Finally, there are differences in reading software. Currently, V3D® software by Viatronix (Stony Brook, NY) is the only software cleared by the FDA for CTC screening for CRC.[353] Commonly used reading software allows for both two- and three-dimensional display. The choice of primary method used appears to depend on radiologist (personal) preference.

Other practice variation that influences 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) 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 ACR states that persons with lesions of 6–9 mm should be offered colonoscopy and lesions smaller than 5 mm need not be reported.[295,349,354,355] Ultimately, referral and/or surveillance criteria should depend on the risk of indwelling cancer in and the natural history of (still uncertain) small and diminutive lesions. 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.

Harms of CTC

Immediate serious adverse events from screening CTC appear to be rare. Based on 14 studies, the risk of perforation with screening CTC was less than 2 perforations per 10,000 examinations. However, perforations were detected radiographically (not symptomatic) and sustained by room-air manual insufflation (no longer used in practice). CTC may also require followup diagnostic or therapeutic colonoscopy, and we did not find sufficient evidence to estimate serious adverse events from colonoscopy followup procedures. There was one case of acute appendicitis in an average-risk adult undergoing routine screening.[356]

Potential harms from CTC include exposure to radiation, especially if used in a program of screening that requires repeated examinations. Although radiation exposure from screening CTC appears to be decreasing over time due to technological and protocol advancements, the exposure still ranges up to 7 mSv per examination (dual positioning). For radiation produced in CT scanners, the effective dose equivalent (Sv) is the same as absorbed dose (Gy) (i.e., 1 mSv=1 mGy).[192] Given that the average amount of radiation exposure from background sources in the United States is about 3.0 mSv per year,[357] ionizing radiation from a single CTC examination is low. Even low doses of ionizing radiation, however, may convey a small excess risk of cancer.[358,359] 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."[357] Data are inadequate to quantify whether there is risk for noncancer diseases with low-dose radiation exposure.

Most experts in radiation exposure consider the abovementioned report from the National Research Council to be the definitive resource on radiation risk.[357] Based on this report, the Council predicts that approximately 1 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 two or three cannot be excluded.[357] 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.[360] 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.[359,361]

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.[362]

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 are estimated to occur in 41 to 69 percent of examinations. Despite this, only approximately 5 to 37 percent of examinations have extracolonic findings that necessitate actual diagnostic followup. An even smaller proportion of examinations has findings that 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.[363,364] It remains unclear if detection of extracolonic findings represents a net benefit or harm based on empirical evidence.

Contextual Issues

Adherence

In clinical practice, uptake and adherence to CRC screening appears to be improving but remains suboptimal. Adherence to screening and followup testing varies widely. Preference for choice of screening test is multifactorial, based on the individual 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, and the screening frequency (interval of testing).[365] Several patient factors may affect uptake and adherence to screening, including age, sex, socioeconomic status/education, race/ethnicity, acculturation, access to care, health status, risk for cancer, risky

health behaviors, and psychosocial factors (including but not limited to patient knowledge, attitudes, and beliefs).[366]

Recent estimates of prevalence of CRC screening in the United States, based on Behavioral Risk Factor Surveillance System survey data, show that the overall proportion of adults who were "up to date" on CRC screening increased from 54 percent in 2002 to 65 percent in 2010.[70] About 28 percent of U.S. adults, however, still had never been screened. Colonoscopy remains the most commonly used screening test (about 62%) followed by stool tests (about 10%). As such, other screening modalities are not commonly used.[70] Analyses of large insurance databases confirm that colonoscopy is the most commonly used screening test among commercially insured persons in the United States.[308] Additionally, uptake may be higher in health systems, particularly health systems with robust information technology infrastructure. In the Veterans Health Administration, for example, 80 percent of patients were "up to date" on CRC screening in 2008–2009.[367] Uptake of CRC screening also appears to be higher in the United States than in most European countries, such that it may not be valid to extrapolate from CRC screening studies conducted outside the United States. Based on comparative utilization data across 11 European countries (i.e., Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, Switzerland) in 2004 to 2005, the overall proportion of adults who were "up to date" on CRC screening using endoscopy varied from 6 to 25 percent, and using stool tests ranged from 4 to 61 percent.[368]

In general, adherence to screening varies by screening test (and over time), and adherence to screening tests and subsequent colonoscopy (if necessary) is suboptimal. Based on existing systematic reviews and included studies in this review, there appears to be greater adherence to FIT than to gFOBT, greater adherence to single application of stool-based testing than to a single application of endoscopy, and greater adherence to FS than to colonoscopy. Data to estimate adherence to CTC compared to other screening tests are limited; however, these data suggest that adherence to CTC may be greater than to colonoscopy. Overall, there are very limited data on adherence within U.S.-based screening programs and adherence to repeated screening over subsequent screening rounds. Additionally, tests other than colonoscopy may require followup diagnostic or therapeutic colonoscopy, and adherence to followup colonoscopy also varies and is suboptimal.

Adherence to Screening

We can estimate adherence to initial screening and subsequent testing in the United States from several types of study designs, including screening trials, studies of interventions to improve screening adherence, and description of existing screening (programs) in clinical practice. Most CRC screening trials were conducted outside the United States; only two have been conducted in the United States.[122,127] One of these, 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), which was higher than adherence in Hemoccult II trials conducted outside the United States (range, 60% to 70%) (**Table 7**). The other, the PLCO trial of screening FS, had 84 percent adherence in the first round and 54 percent in the second round, which was higher than in the FS trials conducted outside the United States (range, 58% to 67% in the first round). None of the comparative effectiveness screening trials designed to evaluate comparative adherence were

conducted in the United States (**Appendix D**). Based on trials conducted in Western European countries, adherence to a single round of gFOBT ranged from 32 to 59 percent, from 32 to 65 percent for FIT, from 28 to 47 percent for FS, from 20 to 39 percent for FS plus stool testing, from 17 to 27 percent for colonoscopy, and approximately 34 percent for CTC. One Dutch trial found greater adherence to CTC than to colonoscopy.[128] However, estimates of adherence to colonoscopy and CTC are based on a limited number of studies, again none of which were conducted in the United States. We found no studies comparing the relative adherence of FIT versus mtsDNA testing.

Our findings are consistent with existing systematic reviews of adherence in screening trials. The most comprehensive existing review of adherence included 100 prospective studies of CRC screening, only 10 of which were conducted in the United States.[369] This review by Khalid-de Bakker and colleagues included a meta-analysis to determine a pooled estimate of adherence to first-time invitation of screening across a wide range of studies spanning 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. One review of screening trials (k=14), again most of which were not conducted in the United States, found that the overall adherence to testing was about 33 percent, adherence to FIT was higher than for gFOBT (k=5; RR, 1.16 [95% CI, 1.03 to 1.3]), and adherence to endoscopy was lower than for stool tests (k=10; RR, 0.67 [95% CI, 0.56 to 0.80]). When considered by type of endoscopy, adherence to FS was not statistically significantly lower than for stool tests (RR, 0.78 [95% CI, 0.59 to 1.04]), and adherence to stool tests was higher than for colonoscopy (RR, 0.57 [95% CI, 0.42 to 0.78]).[370] Another existing systematic review of 14 FS studies confirmed that the uptake of FS was lower than for stool-based testing (i.e., gFOBT or FIT).[371] One comprehensive systematic review conducted by Holden and colleagues on enhancing the use and quality of CRC screening found a wide variation in adherence to screening in studies designed to improve adherence to CRC screening.[366] Adherence in the usual care group (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. Overall, interventions to improve screening rates vary in their effectiveness but can improve adherence from a few percentage points up to 42 percentage points.

We found very sparse data on adherence to screening over time (i.e., subsequent rounds of screening) in U.S. practice. We did not find published adherence rates for Hemoccult II testing over the multiple rounds of screening in the Minnesota trial. In the United Kingdom, adherence to initial gFOBT was 57 percent in the National Health Service Bowel Cancer Screening Programme but only 44 percent completed all three screening rounds.[372] One study of adherence to stool testing within an integrated U.S. health system, Kaiser Permanente, showed that the initial adherence to FIT was 47 percent but only 24 percent adhered to annual testing over four rounds.[373] A retrospective analysis of Veterans Health Administration medical centers also demonstrated low adherence over multiple rounds, with only 14 percent receiving at least four stool tests over 5 years.[374] Another study comparing the adherence of colonoscopy versus gFOBT in the United States found that 85 percent received a one-time colonoscopy compared to 41 percent who adhered to three rounds of screening with gFOBT.[375] We found even less data on adherence to followup screening colonoscopy. One small study from the Veterans Health Administration during the 1990s demonstrated that 57 percent of persons with a normal

screening colonoscopy returned for a repeat screening colonoscopy (at 5.5-year interval).[376] We found no data on adherence to multiple rounds of other screening modalities, including FS, FS plus stool testing, CTC, or mtsDNA.

Adherence to Followup Colonoscopy

Screening tests other than colonoscopy may require followup diagnostic or therapeutic colonoscopy, which is not always completed. From the Minnesota trial, for example, authors reported that on average 10 percent of participants had positive Hemoccult II tests and 83 percent underwent a diagnostic evaluation (which most often was colonoscopy). Likewise, in the PLCO trial, 33 percent of persons with screening FS were recommended to follow up with colonoscopy and 77 percent actually received this followup colonoscopy. One current prospective study (n=2,410) in VA patients age 70 years or older found that only 42% of those who had a positive stool test (9%) received a complete colon evaluation within 1 year.[377] Of those who did not receive followup testing, however, 38 percent had documentation that comorbidity and preferences did not permit followup (were classified as inappropriate to screen initially). One existing review found that adherence to followup colonoscopy for positive stool testing (within 1 year) in integrated health systems ranged from 44 to 86 percent.[366] This review also found that three older single-institution studies from the 1980s to 1990s had similar findings of incomplete followup.

Differential Adherence by Age, Sex, and Race/Ethnicity

Based on an existing systematic review, national U.S. survey data, and national Medicare data, it appears that uptake in CRC screening varies by age and race/ethnicity, so that older patients are more likely to be screened than younger patients, until age 80 years, and whites are more likely to be screened than blacks or Latinos.[366,378,379] Once adjusted for other factors (e.g., income, insurance, education), however, there was no difference in uptake between whites and blacks. Health insurance coverage and access to care is a major explanatory factor in the United States and often explains observed racial/ethnic differences in screening uptake.[380] Additionally, data were much more limited for Asians. Based on one recent study using California Health Interview Survey data, Asians had lower screening uptake than whites, and disaggregated data showed a wide variation in uptake among the different ethnic groups, such that Chinese and Koreans but not other groups had much lower uptake than whites.[381] Fewer studies actually directly compared adherence to screening by age or race/ethnicity. One comprehensive existing review focusing on adherence to screening (mainly stool testing) found no consistent pattern or difference by age but did not examine race/ethnicity.[369] One recent cluster RCT (n=997) found that adherence to gFOBT and colonoscopy or choice of gFOBT or colonoscopy increased with age and was higher in Latinos and Asians compared to blacks.[382] One VA study found overall high adherence to CRC screening, and although blacks had slightly lower adherence (72%) compared to whites (77%), the disparity was attenuated (compared to national averages) and was accounted for by confounders of being unmarried and having lower levels of education.[383] Very little data exist to understand disparities in adherence to followup colonoscopy by subgroups. Based on the PLCO trial, however, it appears that blacks had lower adherence (63%) to followup diagnostic colonoscopy after screening FS compared to whites (72%).[384]

The data are mixed for differences in uptake by sex, such that there does not appear to be a consistent pattern or difference in men versus women.[366] However, one recent study using 2007 data from the California Health Interview Survey found that women were less likely to undergo CRC screening than men.[385] Uptake was about 26 percent in men versus 24 percent in women for FOBT, 18 percent in men and 15 percent in women for FS, and 50 percent in men and 48 percent in women for colonoscopy. One recent study using Medicare data from 2001–2005 also found lower colonoscopy screening uptake in women.[386] One comprehensive existing review focusing on adherence to screening (mainly stool testing) found no consistent pattern or difference by sex.[369] Another meta-analysis of FIT screening studies demonstrated lower uptake in men than in women.[387]

Targeted or Tailored Screening

Current CRC screening recommendations are made for all adults, except for differentiation based on age and family history. Those without a family history are recommended to begin CRC screening at age 50 years, the age at which CRC incidence begins to substantially increase. The concept of further customizing CRC screening recommendations has become more compelling as we have learned more about differences by age, sex, and race/ethnicity in the epidemiology of precancerous lesions and CRC.[59,388-390] Targeted screening recommendations could potentially address the timing of screening initiation, preferred screening method(s), or both. In theory, tailoring screening recommendations has the potential to improve patient health outcomes, although no empirical data to support this exist at this time. Modeling exercises may be helpful in understanding the net benefit of earlier screening or different preferred screening modalities by age, sex, race/ethnicity, or combinations thereof.

Despite the large range in risk and known risk factors for CRC, risk prediction for CRC is suboptimal, and to date, there is no accepted risk assessment tool to help tailor CRC screening.[69] Based on the higher incidence of CRC in blacks (and Native Americans and Alaskan Natives, based on less data), the American College of Gastroenterology and other experts have advocated to consider screening in blacks beginning at age 45 years.[391,392] One microsimulation model evaluated tailored screening by race/ethnicity and sex and found that earlier screening in black men and women (age 47 vs. 53 years in whites) could marginally improve life expectancy.[393]

Others have advocated for different preferred screening methods in blacks and women due to a higher prevalence of proximal cancers. Colonoscopy, as opposed to FS, is associated with a decreased CRC mortality for both proximal and distal cancers, albeit somewhat attenuated for proximal cancers.[38-42,394] FS is no longer commonly used in the United States, however, and there is currently no evidence to demonstrate that colonoscopy is more sensitive than stool-based testing or CTC for the detection of proximal cancers. Based on limited/sparse data, both gFOBT and FITs may have higher sensitivity for distal versus proximal CRC,[162,186,191,395,396] but results are mixed and there is evidence to suggest that FITs are equally as sensitive for distal and proximal CRC.[164] Even less data exist for CTC, as screening CTC studies were not designed or powered to evaluate detection of CRC. One small study (n=307) did not find any variation in sensitivity to detect advanced adenomas by location in colon.[49]

Overall CRC incidence, and for proximal cancers specifically, is more common with advancing

age. Evidence from our review, as well as others, however, that colonoscopy has increasing serious harms with advancing age. The greatest evidence for harms and inadequate bowel preparation is in the very old (age ≥80 years).[397] The optimal screening modality for older adults and age to stop screening are beyond the scope of this review. Again, modeling exercises may be helpful in understanding the tradeoff between the different screening modalities as both cancers and harms from colonoscopy become increasingly common with aging. Modeled data show that the net benefit of screening diminishes with age due to competing comorbidity, harms associated with screening, and natural life expectancy.[397-399] In 2008, the USPSTF considered modeled data showing that while increases in life expectancy were considerably lower in adults age 75 years and older,[398,400] the number and severity of comorbid medical conditions (or comorbidity index) were equally important factors influencing the decision on when to stop screening, as these comorbid conditions adversely affect one's prognosis after discovery of CRC (e.g., competing source of mortality, worse survival after cancer treatment).[397]

Limitations of the Review

Our review focused on the benefit of CRC screening on mortality, the diagnostic performance of generally available CRC screening tests, and the potential serious harms of these screening tests in average-risk adults. Because of limitations in resources, our review addressed some important contextual issues related to screening (e.g., adherence to testing) but could not address several other important issues, including: screening in high-risk adults (those with known family history of CRC), risk assessment to tailor screening, test acceptability, availability/access to screening tests, methods to increase screening adherence, potential harms of overdiagnosis or unnecessary polypectomy, overscreening or misuse of screening, and surveillance after screening. Our review was commissioned along with microsimulation decision models from CISNET, which address ages to start and stop screening, intervals of screening, and targeted/tailored screening. Given our audience, 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.

When appropriate, we conducted quantitative analyses. In many instances these analyses were limited by a relatively small number of studies (<10) and/or by high statistical heterogeneity, despite limited clinical heterogeneity allowing for pooled analyses. In synthesizing the evidence on FITs, we, unlike others, did not conduct quantitative analyses due to the very limited number of studies evaluating like FITs using similar study designs. We specifically compared similar tests, as FITs are not a class of tests, with similar assay cutoff values. Finding cutoff values expressed in units comparable across studies (μg Hb/g feces), however, was often difficult. Ultimately, we found that assay cutoff value expressed in μg Hb/g feces did not consistently predict assay performance. This deviated from the conclusions of a meta-analysis of all FIT types,[306] likely due to the difference in included studies (we excluded four studies included by Lee and colleagues and included an additional seven studies) and our inability to verify a few of the cutoff values in μg Hb/g feces reported by Lee and colleagues. Last, to illustrate range of performance of FITs, our synthesis included FITs that are now discontinued and several that are not available in the United States and not cleared by the FDA. Additional limitations for each body of evidence are detailed in our summary of evidence table (**Table 29**).

Emerging Issues and Future Research Needs

Screening for CRC is a complex and active area of research. Unlike other routinely recommended/conducted cancer screening, there are multiple viable options for CRC screening, with varying levels of evidence to support their use; aim to detect cancers, potential precursor lesions, or both; test acceptability and adherence; intervals of time to repeat screening; need for followup testing (including surveillance incurred); associated serious harms; availability in practice; cost; and advocacy for their use. The best quality evidence, in terms of robust study design and reduction in mortality, is limited to modalities that are no longer routinely used for screening in the United States. Several ongoing trials may fill this evidence gap for currently used tests (**Appendix F**). This complexity is compounded by technological advancements over time (i.e., to existing tests such as colonoscopy or CTC, and development of new stool or blood tests). Modeling exercises can provide valuable insight into the comparative net benefit of tests in the face of this complexity and (rapid) technological advancements over time. Models 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 different target populations (e.g., average and high risk). Models can, and should, incorporate best evidence about the operating characteristics of new tests. However, because models are based on best available evidence and understanding of disease, they also reflect limitations in our understanding of disease processes. For example, important evidence gaps include our understanding of the clinical importance of smaller lesions (<10 mm), the role of sessile serrated polyps in both the natural history of disease and the performance of screening tests, variation in the disease process across the large intestine (rectum, distal and proximal colon), and variation in the disease process across individuals by age, sex, and race/ethnicity.

We need empirical studies, trials, or well-designed cohort studies in average-risk populations to evaluate the effects of programs of screening using colonoscopy, the best-performing FITs, and CTC on cancer mortality and incidence. These studies should report (if applicable) on the number of screening rounds, intervals of testing, test positivity (with explicit criteria or cutoff values used to define test positivity), adherence to screening and followup, and harms or other burdens of testing incurred. In addition, we need diagnostic accuracy studies to confirm the screening test performance of promising stool tests based on high sensitivity to detect CRC and/or advanced adenomas (e.g., MonoHaem [three stool samples], QuickVue, Hemosure, bioNexia, immoCARE-C, PreventID CC, Hemo Techt NS-Plus, and HM-JACK) with thus far limited reproducibility (i.e., only one study). Likewise, additional diagnostic accuracy studies of screening tests incorporating new technologies with a limited evidence base (e.g., mtsDNA, serum m*SEPT9*) is also needed, with reporting of percent inadequate or indeterminant results. It is also important that we 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 identification of extracolonic findings remains unknown. More complete and consistent reporting of the downstream benefits and harms from 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 2008 USPSTF recommendation, we have more evidence on 1) the effectiveness of FS on reducing CRC mortality, 2) the test performance of screening CTC and decreasing radiation exposure from CTC, and 3) the test performance of a number of promising FITs, including one FIT plus stool DNA test, that are available in the United States and approved by the FDA for screening. Currently used screening modalities, including colonoscopy, FS, CTC, and various high-sensitivity stool-based tests each 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 different screening tests cannot answer questions of the relative benefit and harms (tradeoffs) between the tests. 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. Actual implementation of recommendations will depend on a number of additional factors, including patient preference and available resources.

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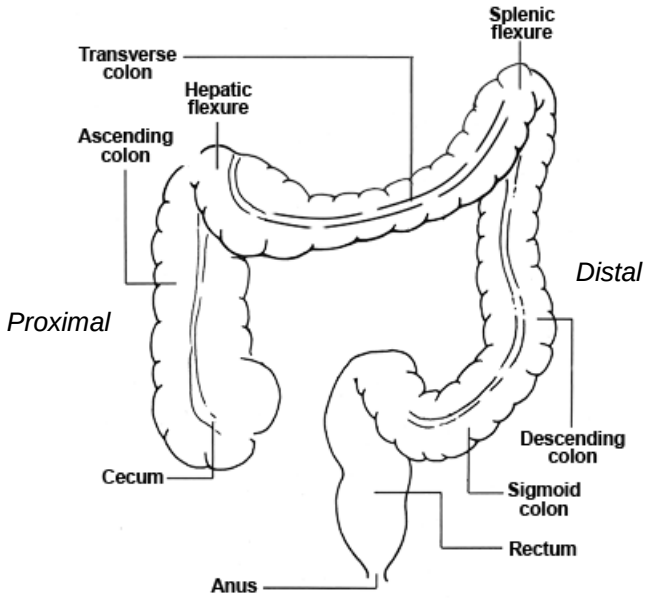
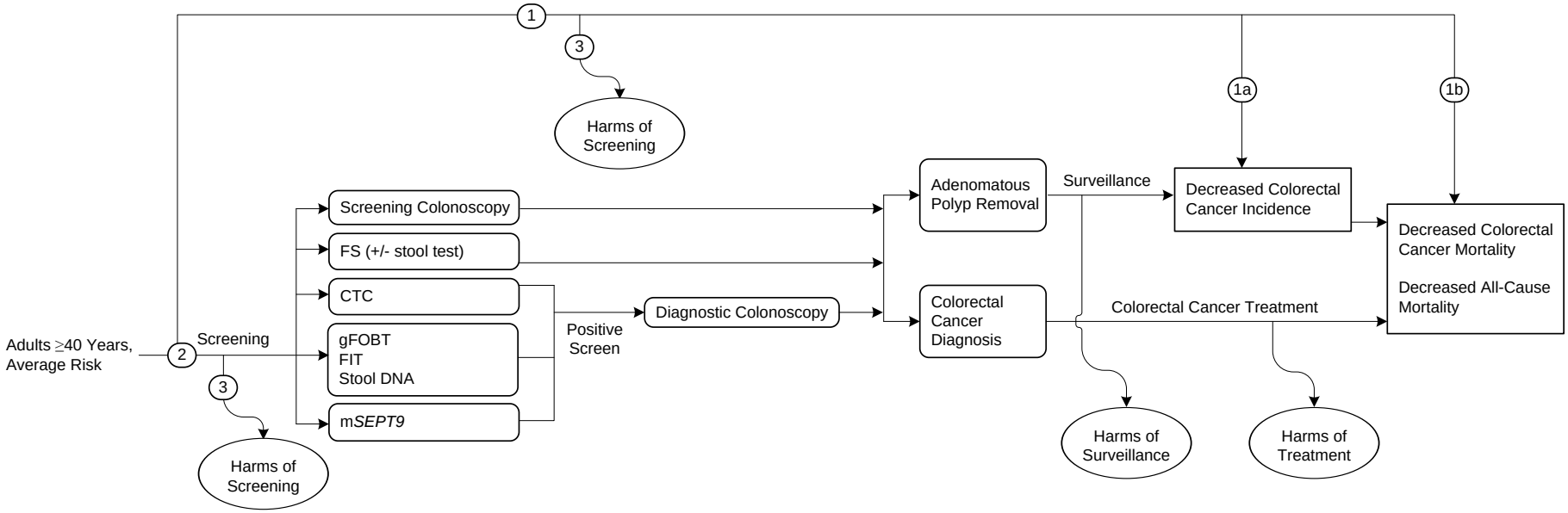
Figure 1. Locations in the Large Intestine: Proximal Colon (Cecum, Ascending, Hepatic Flexure, and Transverse Colon), Distal Colon (Splenic Flexure, Descending, Sigmoid Colon, and Rectum)



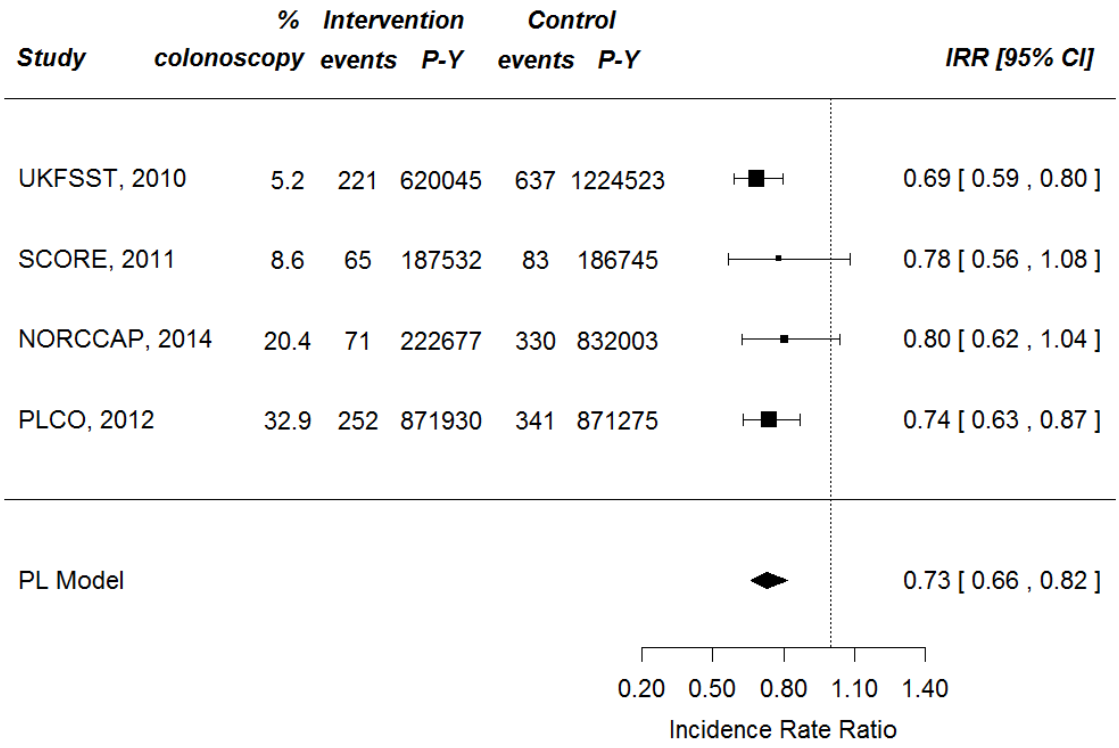
Source: http://cisnet.cancer.gov/projections/colorectal/screening.php

Figure 2. Analytic Framework



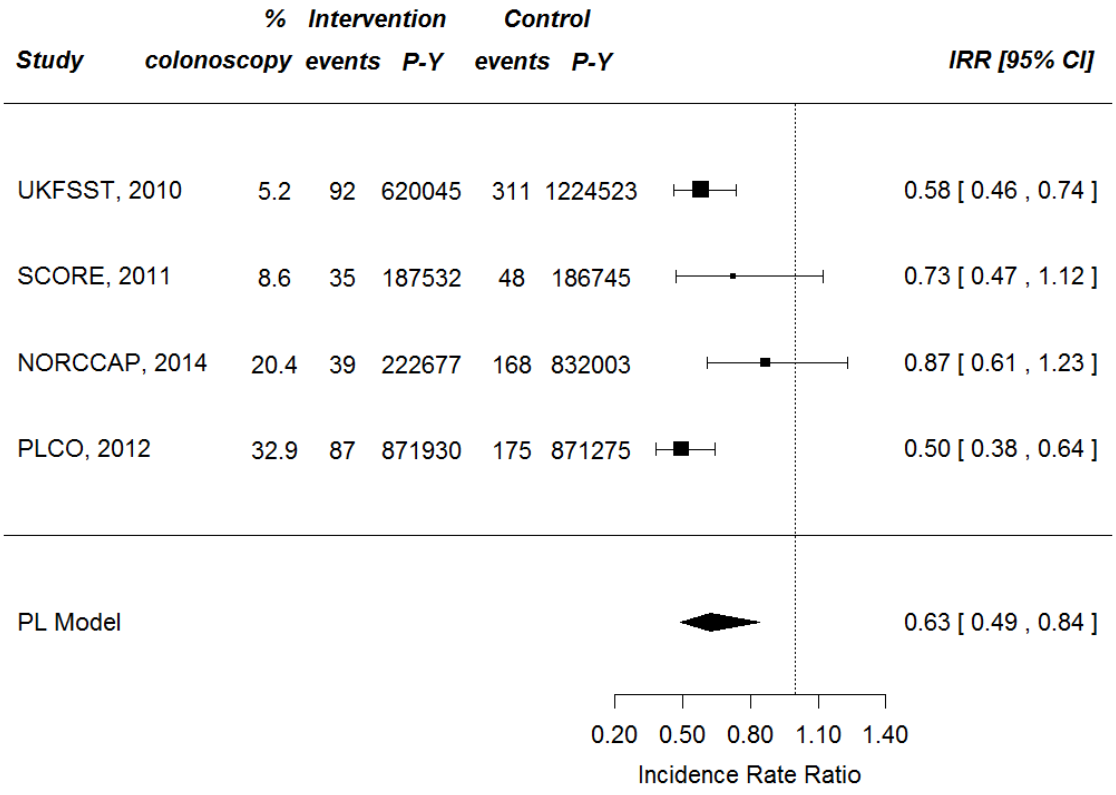
Abbreviations: CTC = computed tomographic colonography; DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid

Figure 3. Key Question 1: Forest Plot of FS Screening on Colorectal Cancer Mortality



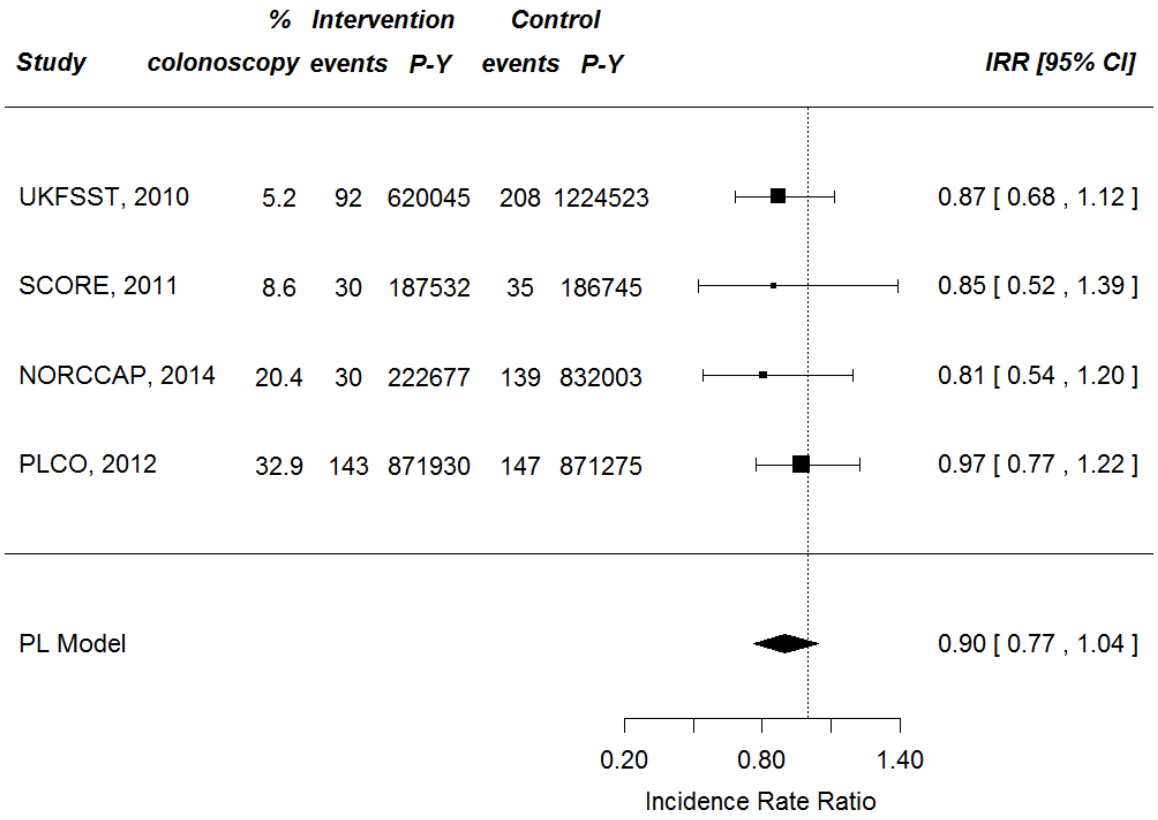
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; p-y = person-years; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I^2 = 0%

Figure 4. Key Question 1: Forest Plot of FS Screening on Distal Colorectal Cancer Mortality



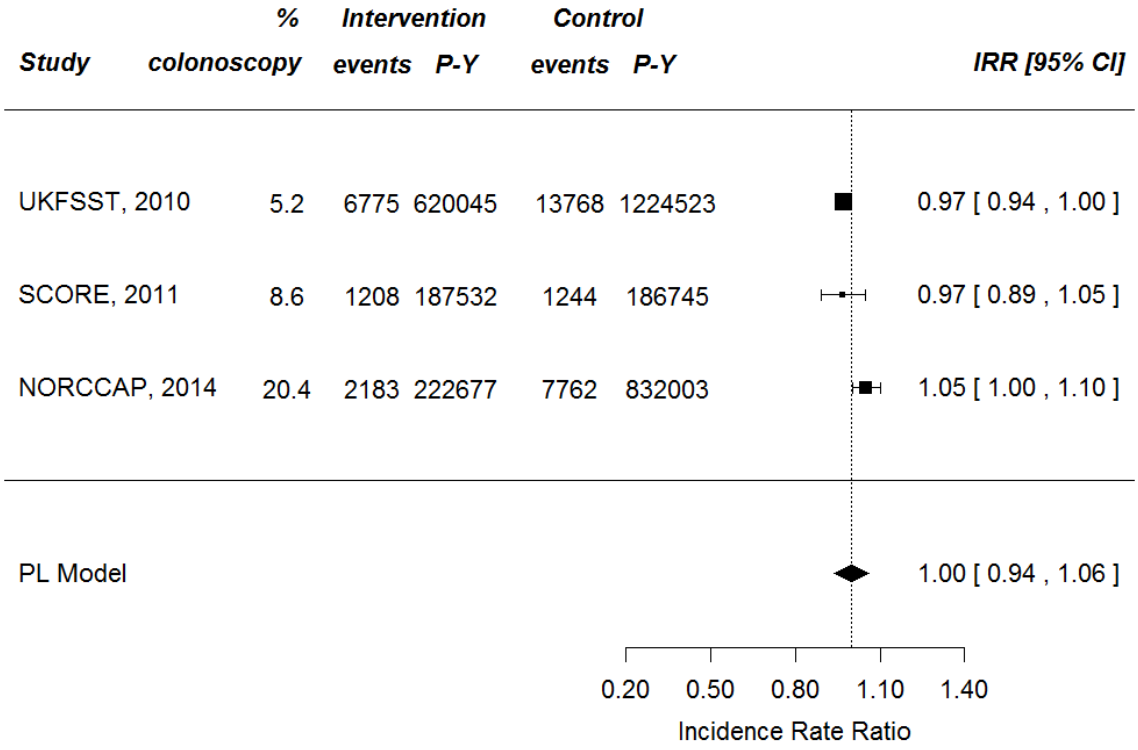
Abbreviations: CI = confidence interval; c-scopy = colonoscopy; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I^2 = 44.1%

Figure 5. Key Question 1: Forest Plot of FS Screening on Proximal Colorectal Cancer Mortality



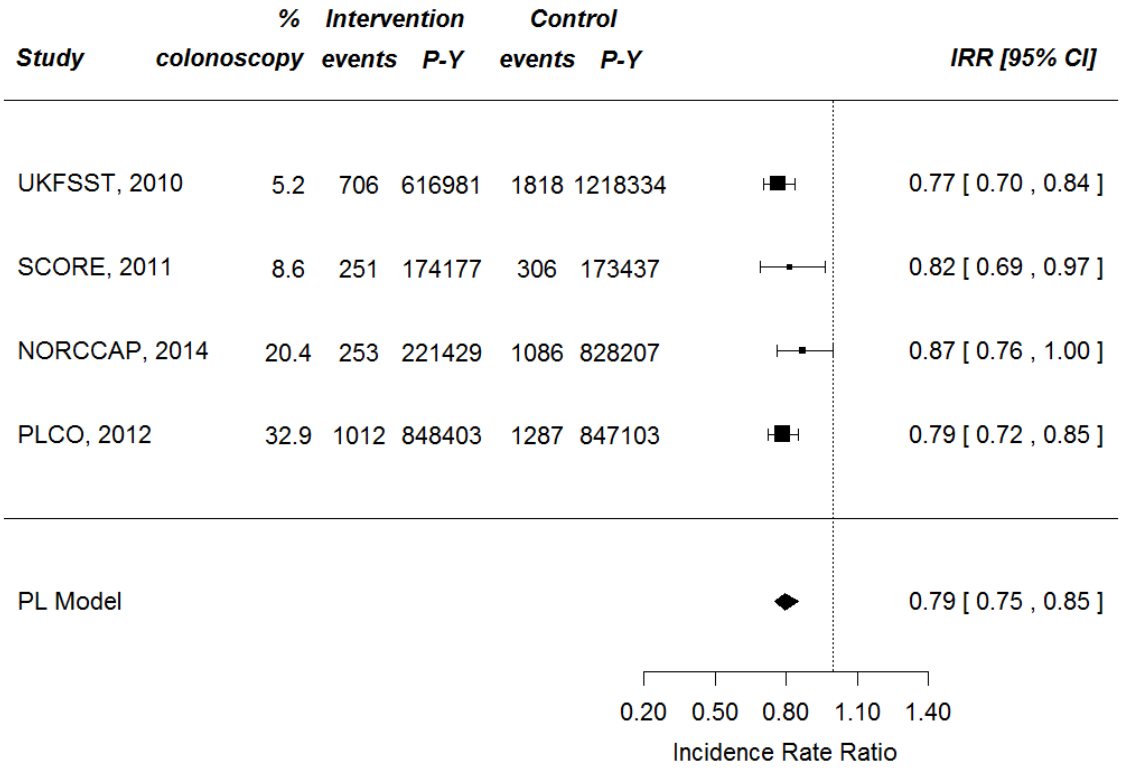
Abbreviations: CI = confidence interval; c-scopy = colonoscopy; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* $I^2 = 0\%$

Figure 6. Key Question 1: Forest Plot of FS Screening on All-Cause Mortality



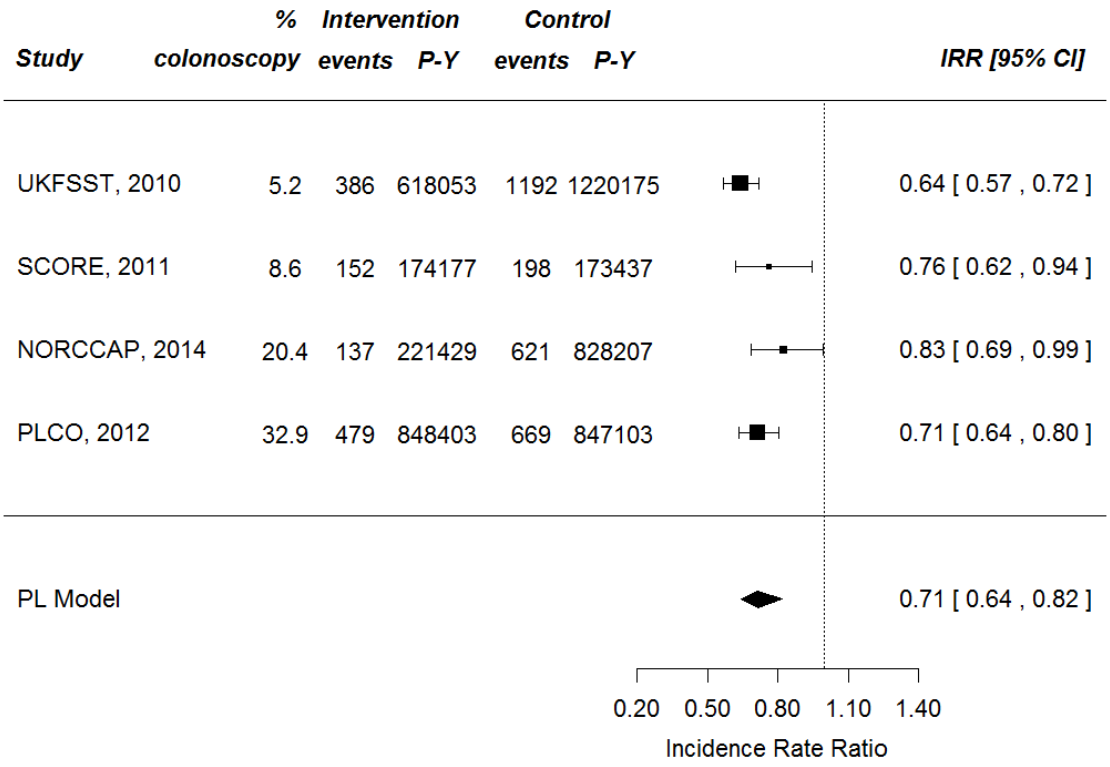
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; p-y = person-years; RE = restricted maximum likelihood; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I^2 = 59.8%

Figure 7. Key Question 1: Forest Plot of FS Screening on Colorectal Cancer Incidence



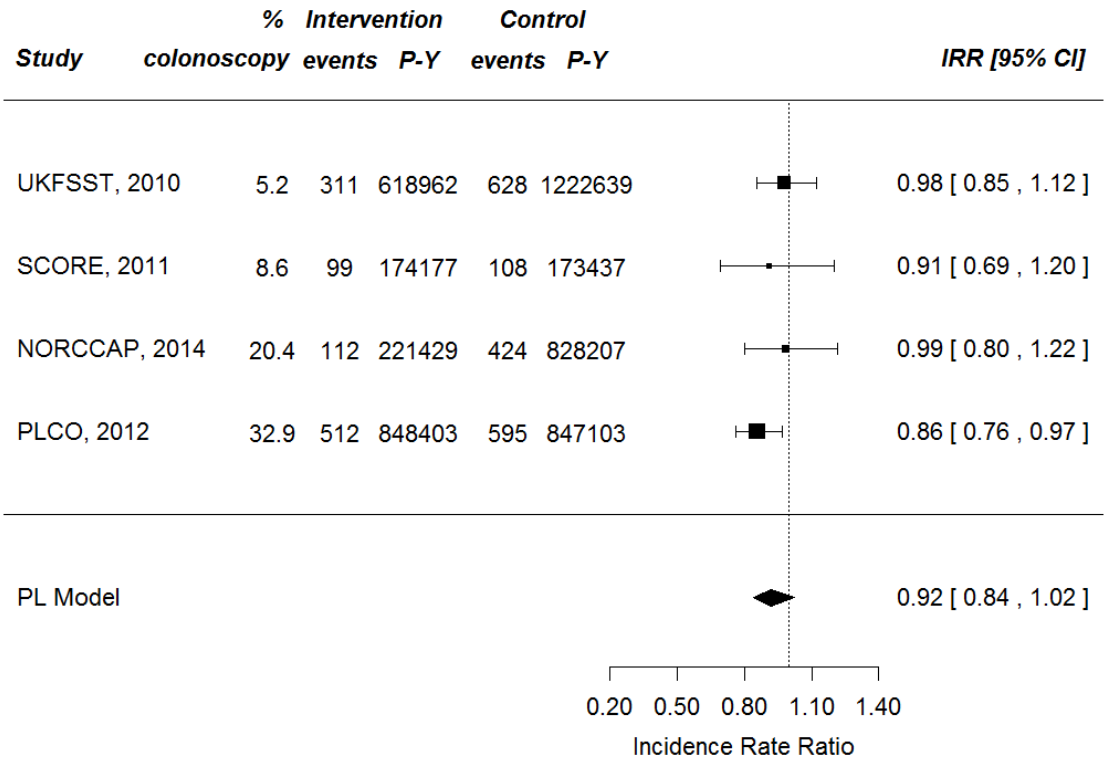
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; RE = restricted maximum likelihood; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* $I^2 = 0\%$

Figure 8. Key Question 1: Forest Plot of FS Screening on Distal Colorectal Cancer Incidence



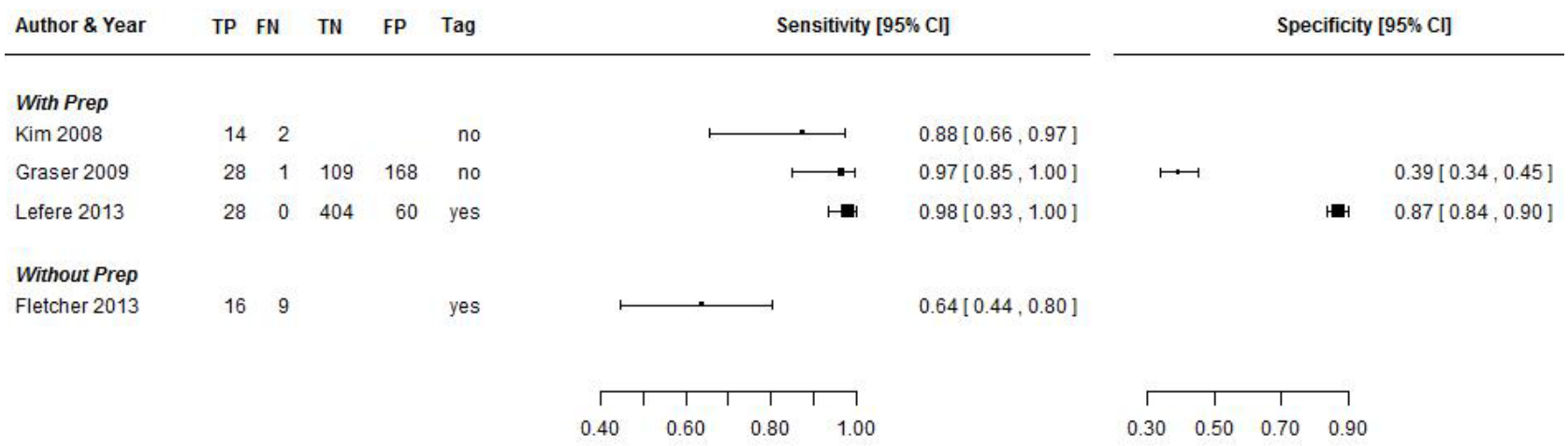
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I^2 = 35.3%

Figure 9. Key Question 1: Forest Plot of FS Screening on Proximal Colorectal Cancer Incidence



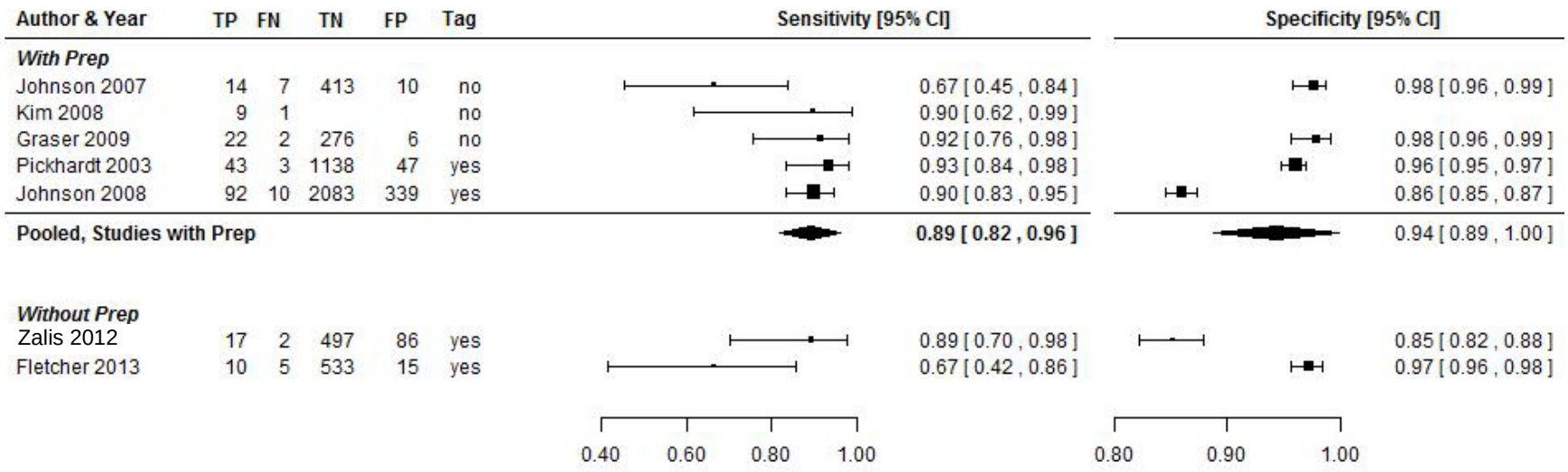
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I^2 = 0%

Figure 10. Key Question 2: Forest Plot of CT Colonography Sensitivity and Specificity for Advanced Adenomas



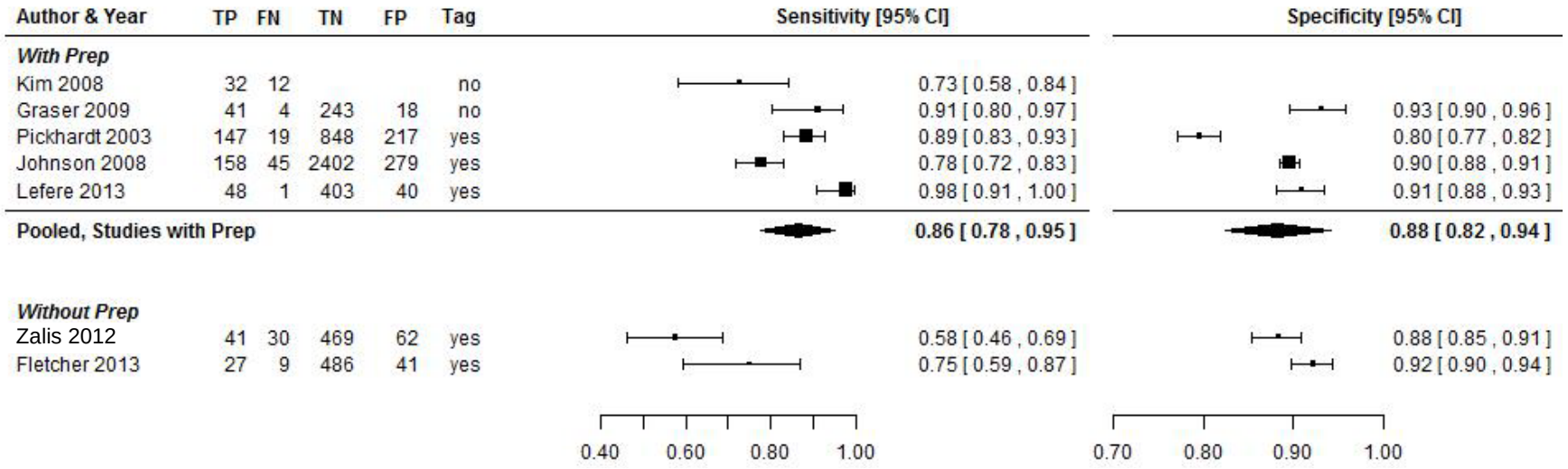
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

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



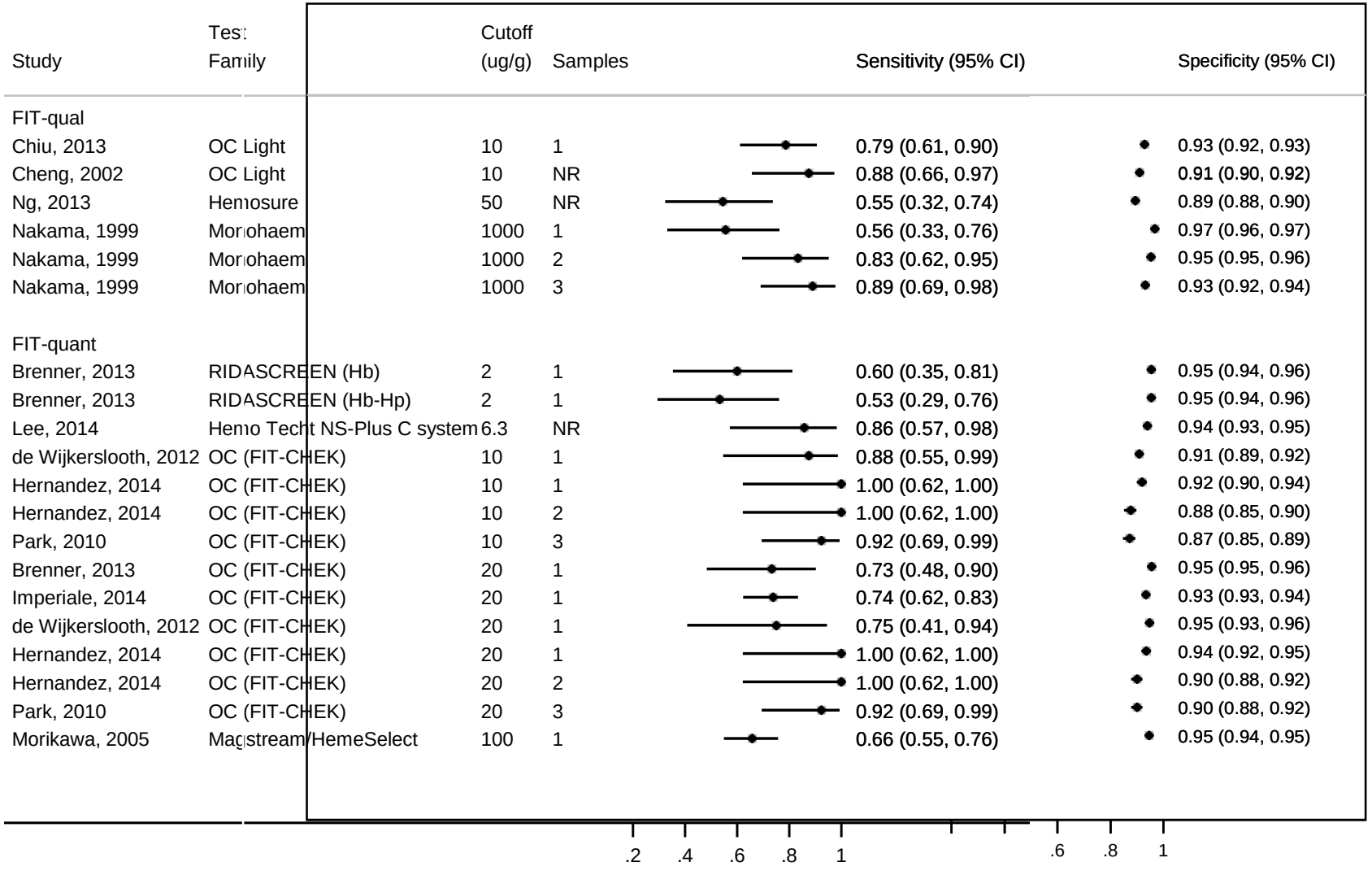
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

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



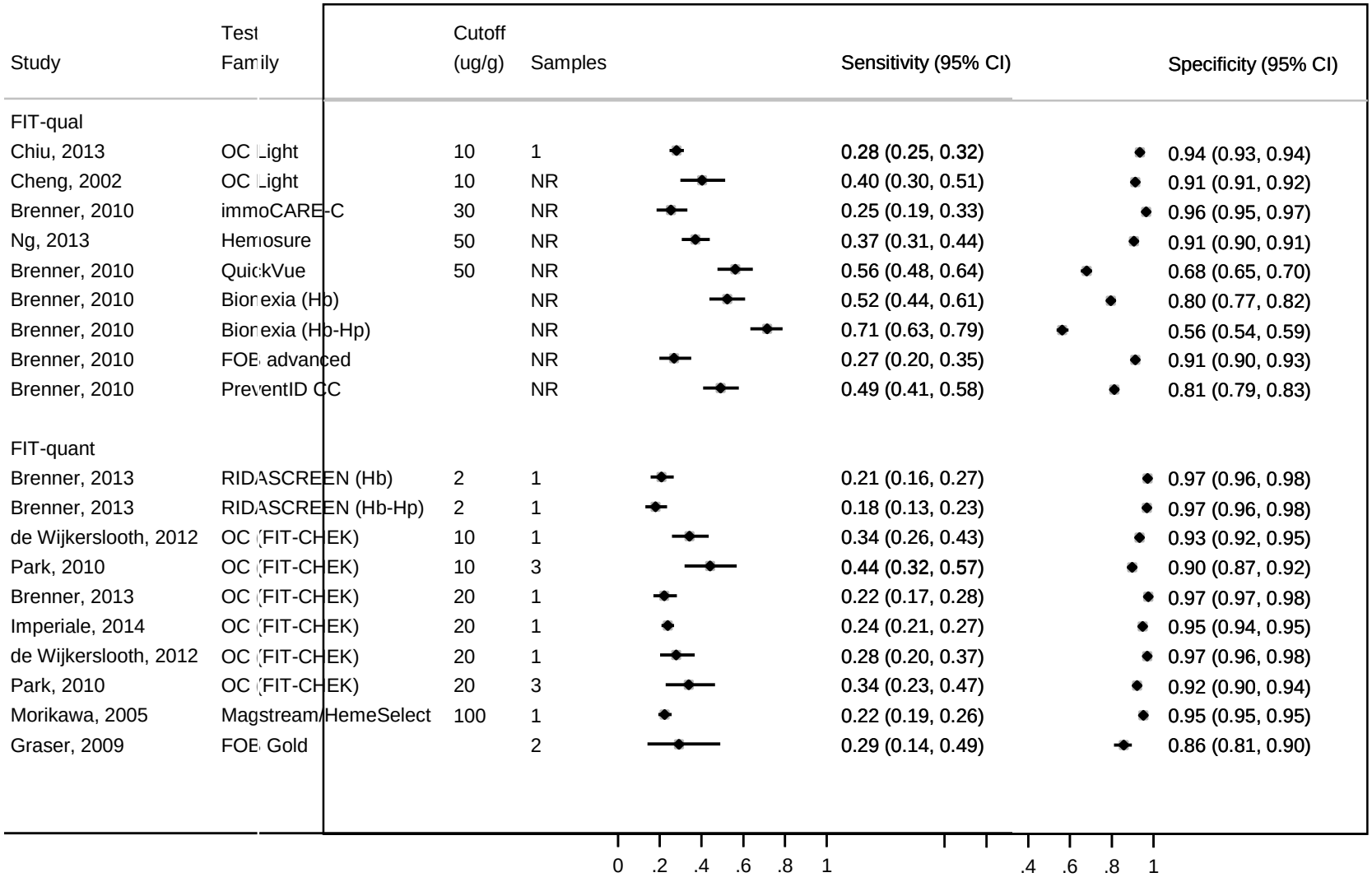
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

Figure 13. Key Question 2: Forest Plot of FIT Sensitivity and Specificity for Colorectal Cancer



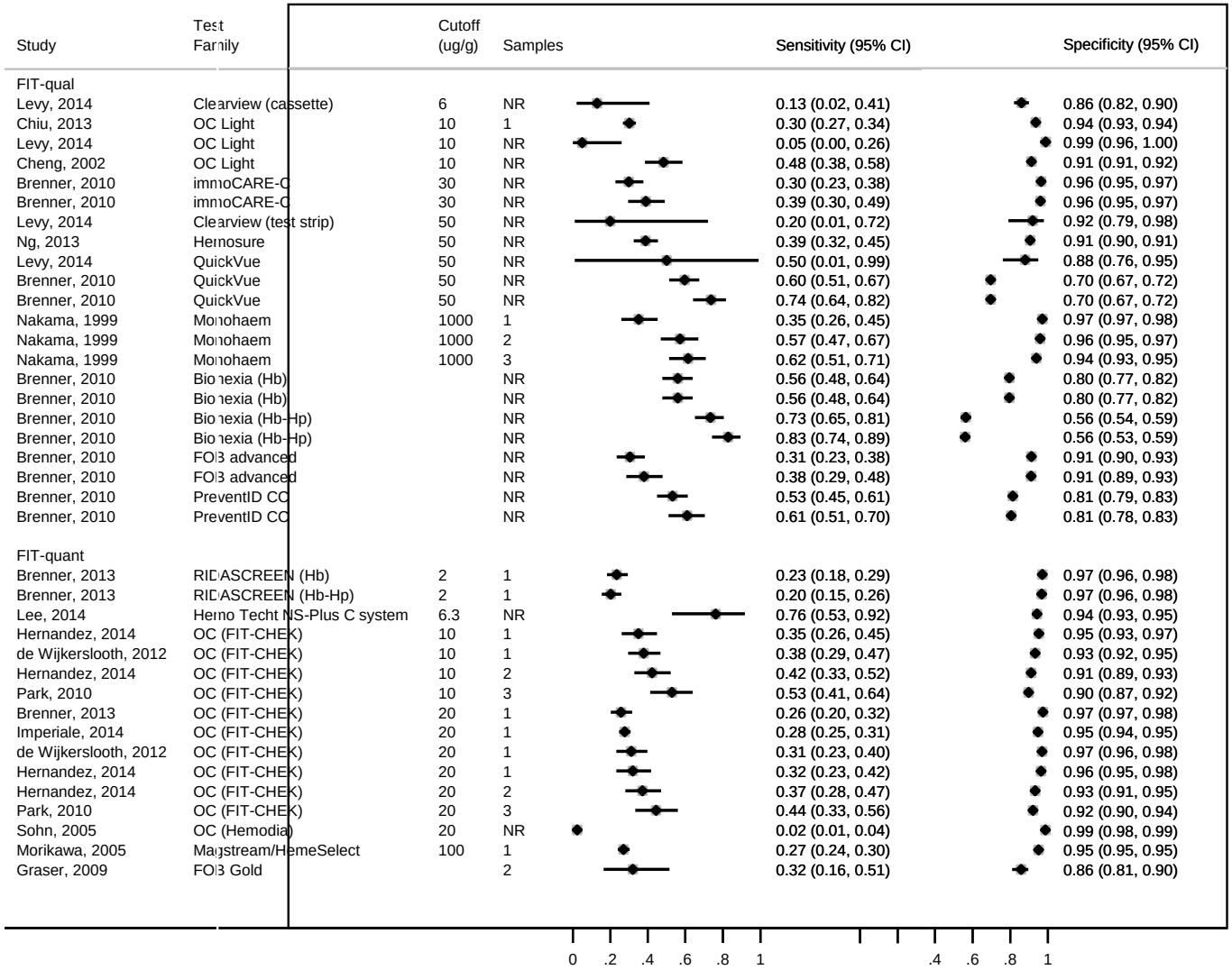
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

Figure 14. Key Question 2: Forest Plot of FIT Sensitivity and Specificity for Advanced Adenomas



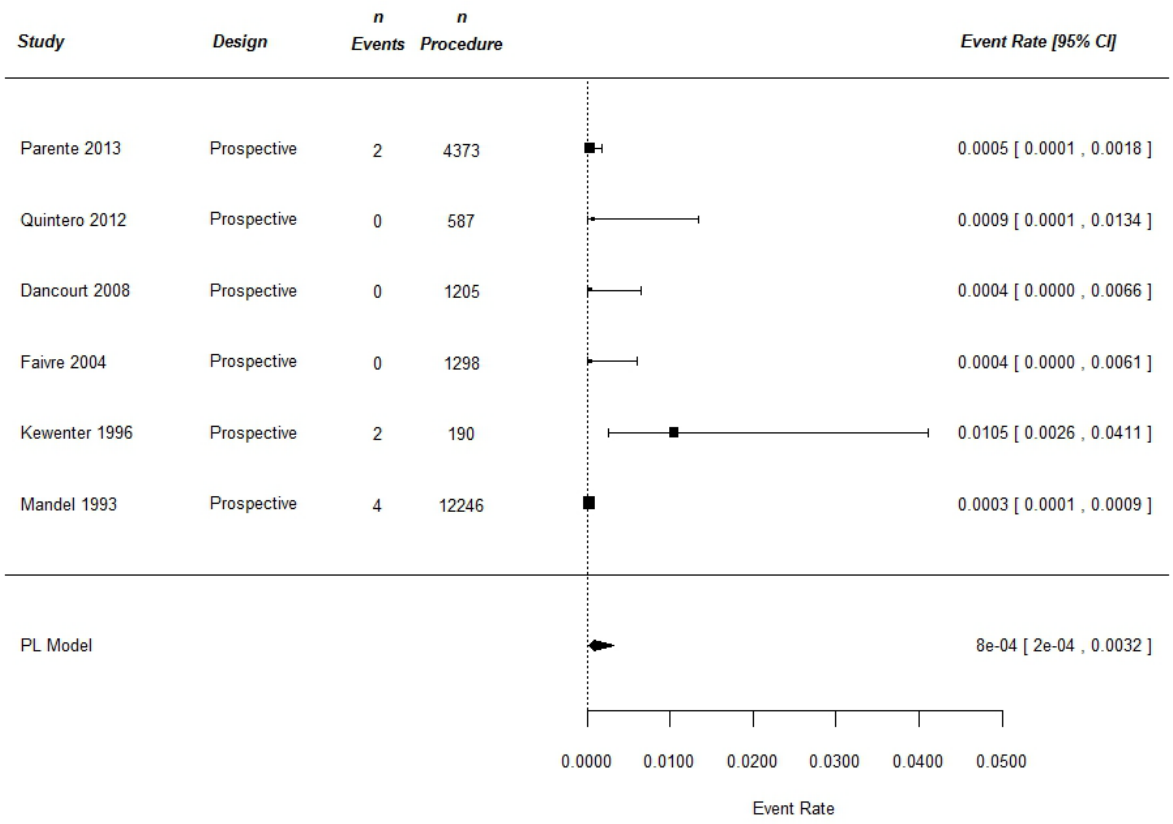
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

Figure 15. Key Question 2: Forest Plot of FIT Sensitivity and Specificity for Advanced Neoplasia



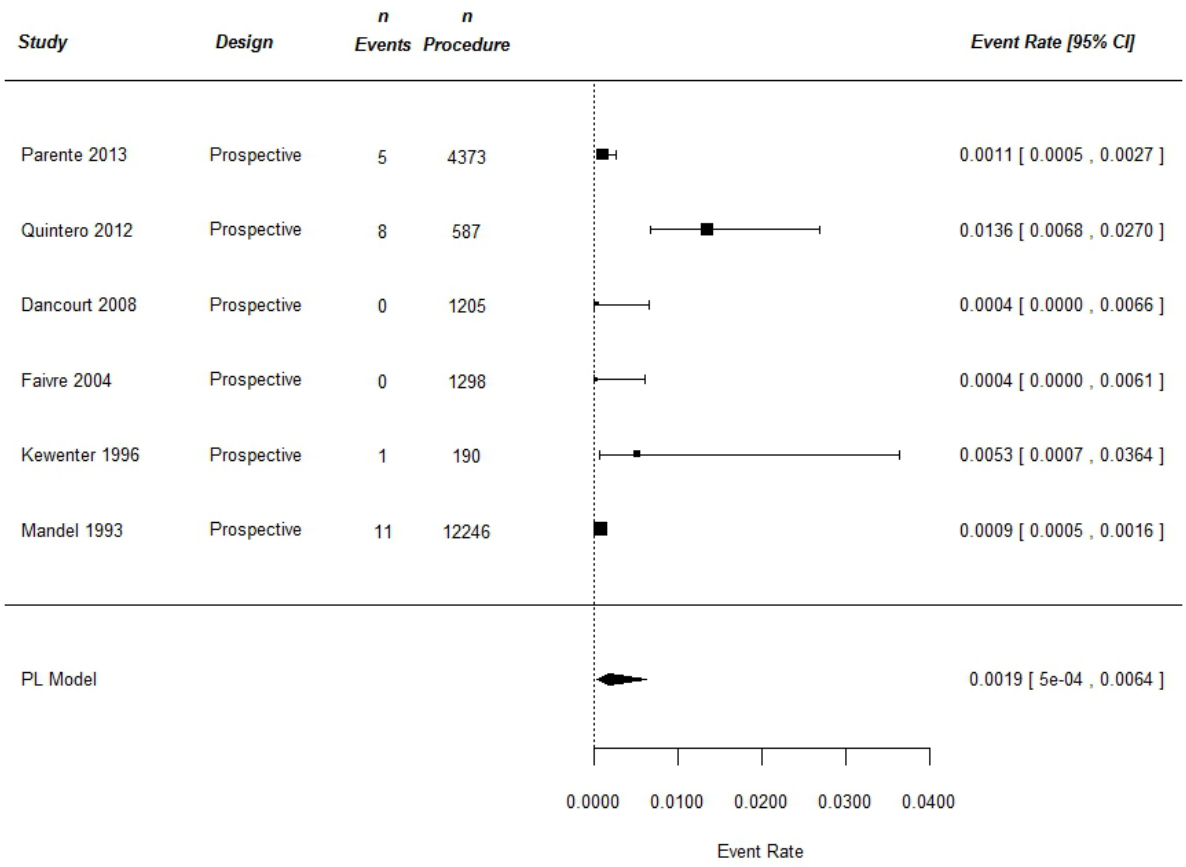
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

Figure 16. Key Question 3: Forest Plot of Perforations From Followup Diagnostic/Therapeutic Colonoscopy, Post Fecal Occult Blood Test*



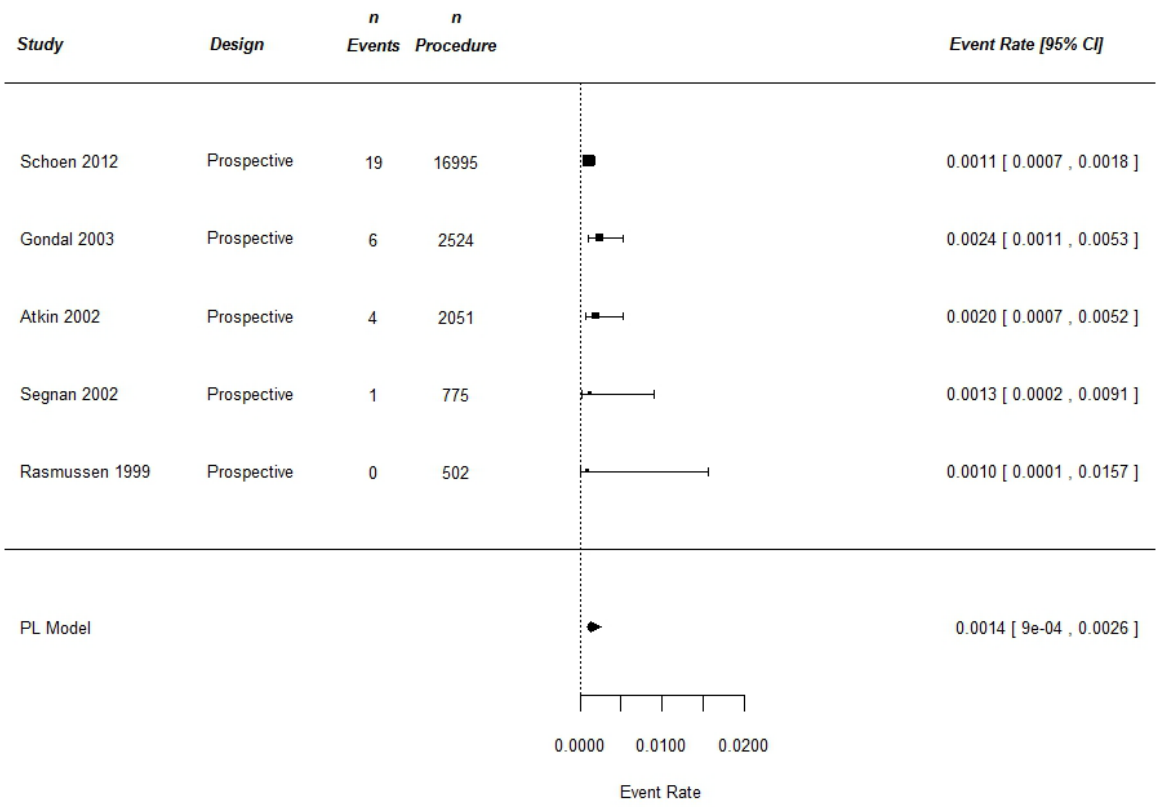
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* I^2 = 60.04%

Figure 17. Key Question 3: Forest Plot of Major Bleeding From Followup Diagnostic/Therapeutic Colonoscopy, Post Fecal Occult Blood Test*



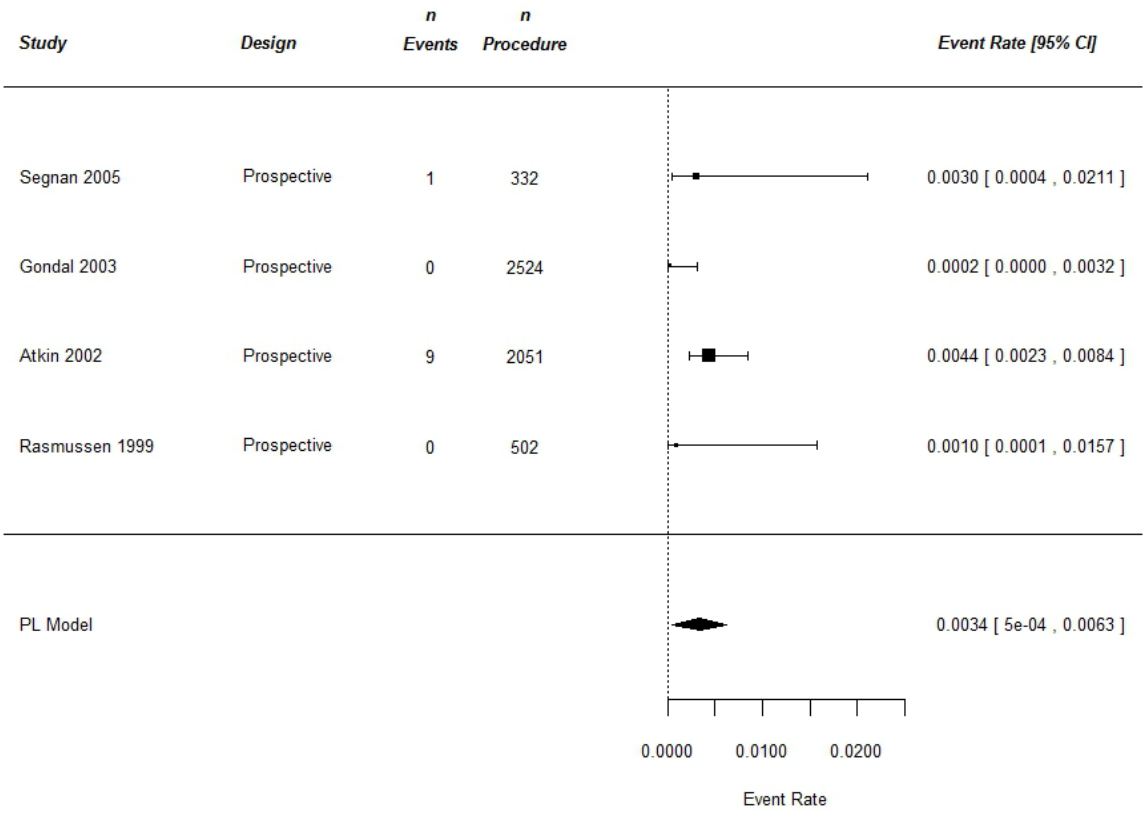
Abbreviations: CI = confidence interval; PL = Profile Likelihood
I^2 = 83.02%

Figure 18. Key Question 3: Forest Plot of Perforations From Followup Diagnostic/Therapeutic Colonoscopy, Post Flexible Sigmoidoscopy*



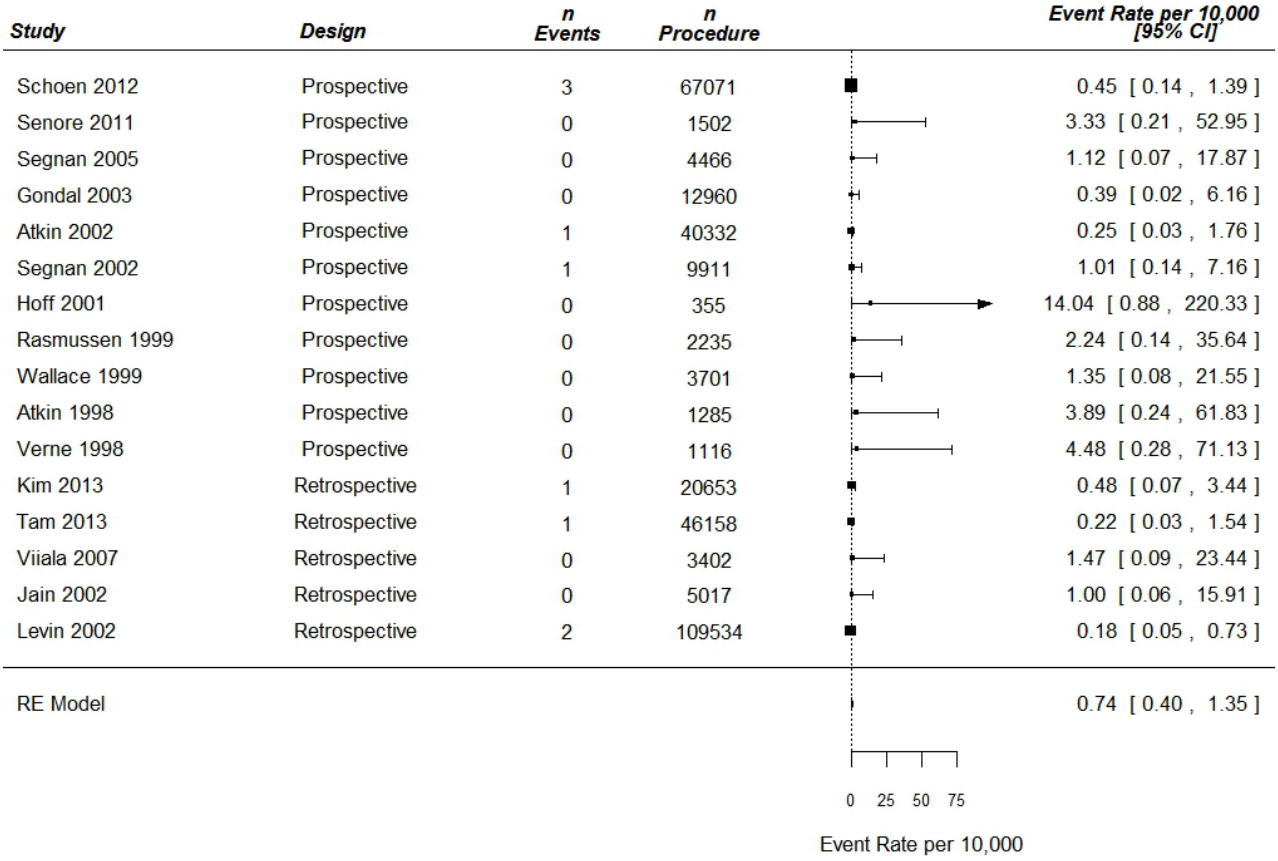
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* $I^2 = 0\%$

Figure 19. Key Question 3: Forest Plot of Major Bleeding From Followup Diagnostic/Therapeutic Colonoscopy, Post Flexible Sigmoidoscopy*



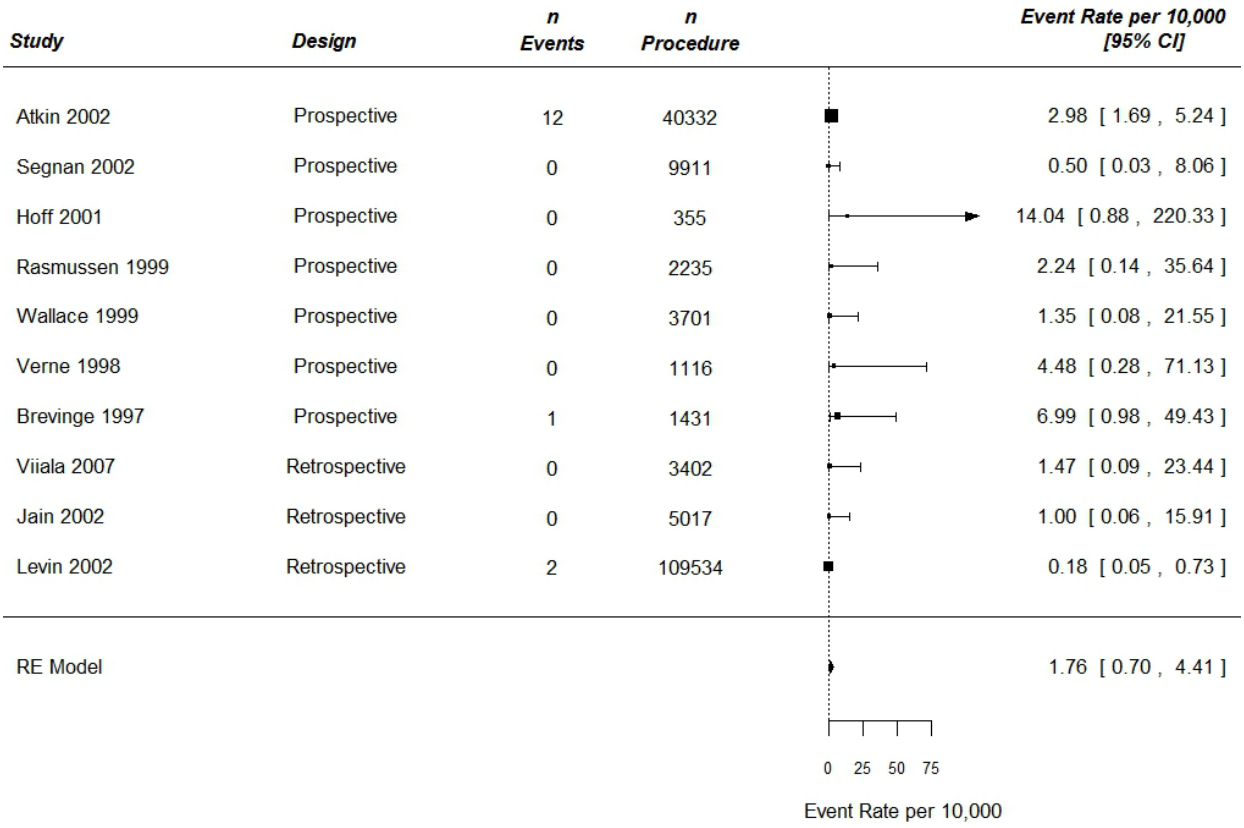
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* I^2 = 7.57%

Figure 21. Key Question 3: Forest Plot of Perforations From Flexible Sigmoidoscopy* **



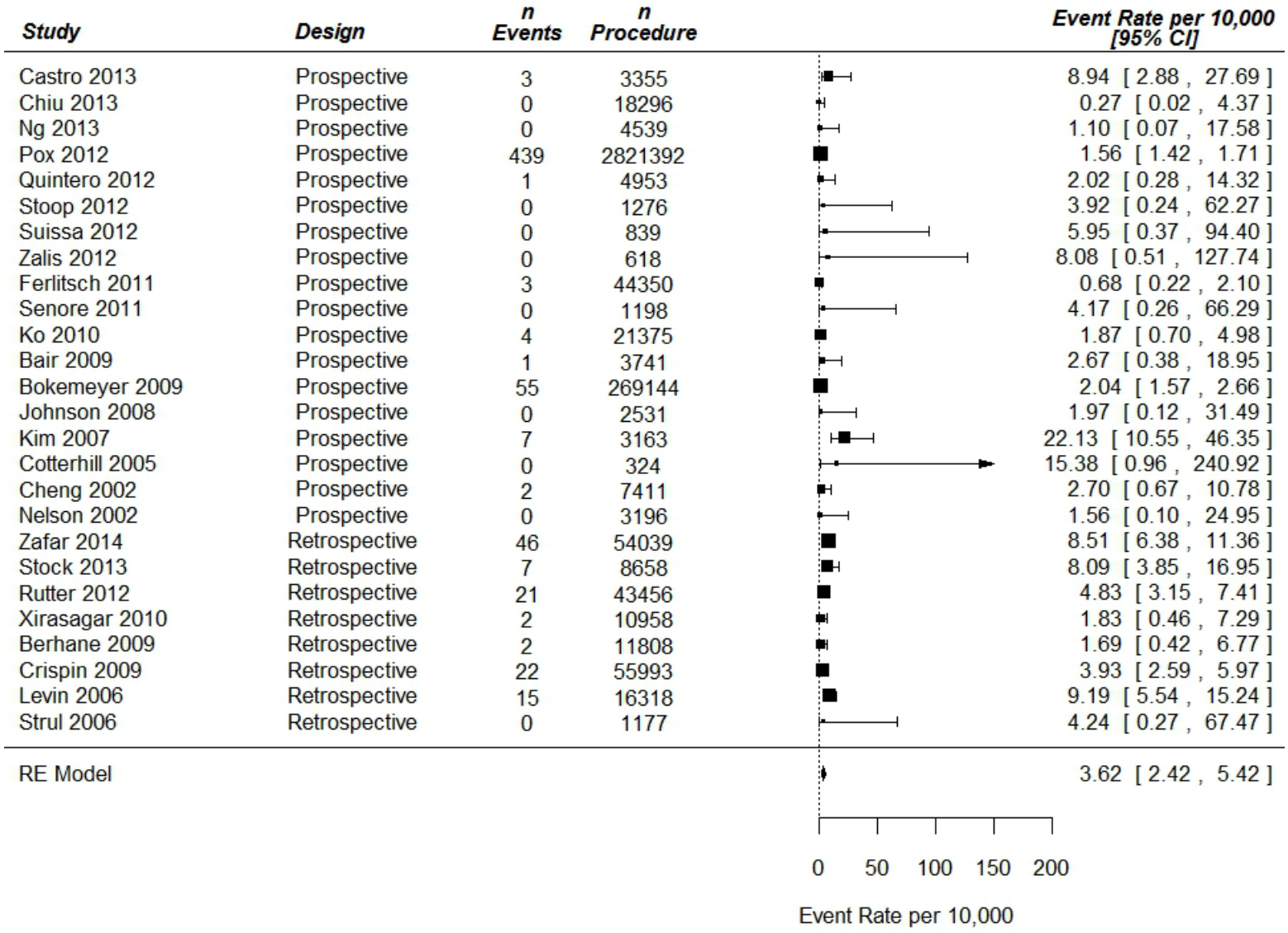
Abbreviations: CI = confidence interval; n = number; RE = restricted maximum likelihood;
* I^2 = 18.39%
** One trial has been excluded from the meta-analysis due to very small n (n=52).[255] There were no episodes of serious bleeding or perforation in the study.

Figure 21. Key Question 3: Forest Plot of Major Bleeding From Flexible Sigmoidoscopy* **



Abbreviations: CI = confidence interval; n = number; RE = restricted maximum likelihood;
* $I^2 = 52.52\%$
** One trial has been excluded from the meta-analysis due to very small n (n=52).[255] There were no episodes of serious bleeding or perforation in the study.

Figure 22. Key Question 3: Forest Plot of Perforations From Colonoscopy, Asymptomatic Population* **

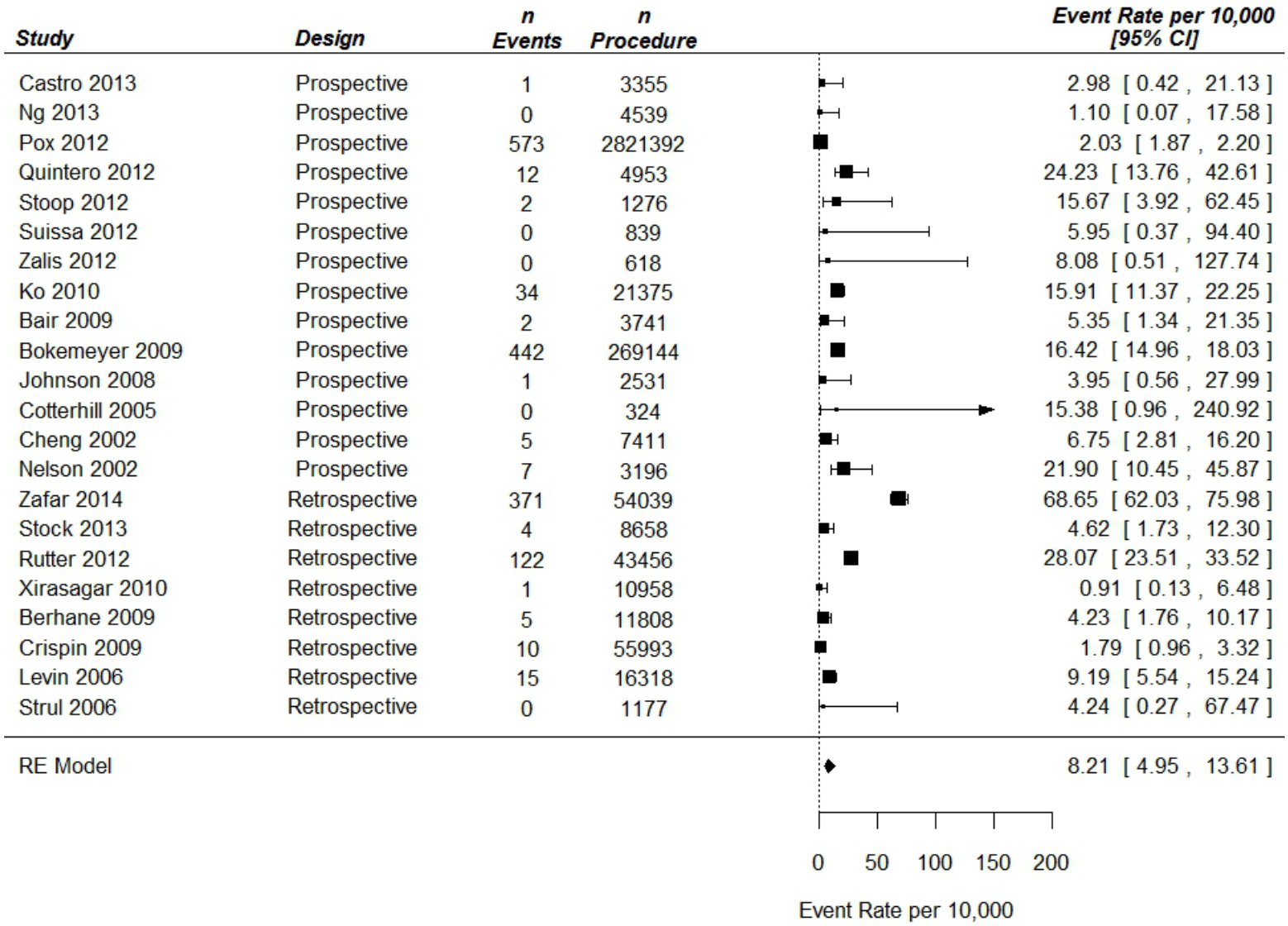


Abbreviations: CI = confidence interval; n = number; RE = restricted maximum likelihood

* I^2 = 88.25%

** One trial has been excluded from the meta-analysis due to very small n (n=63).[255] There were no episodes of serious bleeding or perforation in the study.

Figure 23. Key Question 3: Forest Plot of Major Bleeding From Colonoscopy, Asymptomatic Population* **



Abbreviations: RE = restricted maximum likelihood; CI = confidence interval; n = number
* I^2 = 98.34%
** One trial has been excluded from the meta-analysis due to very small n (n=63).[255] There were no episodes of serious bleeding or perforation in the study.

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

Term	Definition
Adenoma	Benign tumor
Advanced adenoma*	Benign tumor ≥1 cm or with (at least 25%) villous features, or high-grade dysplasia
High risk adenoma*	Advanced adenoma or 3 or more adenomas
Carcinoma in situ	Severe dysplasia limited to the mucosa, Stage 0 colorectal cancer
Adenocarcinoma	Malignant tumor that invades the muscularis mucosa, Stage 1-4 colorectal cancer
Advanced neoplasia	Advanced adenoma and all stages of cancers

* Exact definitions may vary slightly

Table 2. Age-Specific Colorectal Cancer Incidence Rates per 100,000 by Race/Ethnicity, United States, 1999–2011

Sex	Age	All Races	White	Black	Asian/PI	AI/AN	Hispanic*
Men and Women	40–44	17.8	17.4	19.4	14.1	13.2	13.3
	45–49	29.8	28.5	36.5	24.1	26.2	23.2
	50–54	54.4	51.1	70.5	48.7	35.1	45.8
	55–59	65.9	62.2	89.3	54.4	46.9	59.2
	60–64	88.7	83.8	122.0	75.2	77.9	86.6
	65–69	129.0	124.3	169.7	98.3	114.9	124.4
	70–74	172.2	169.9	194.9	131.4	149.1	161.2
	75–79	216.8	215.2	235.5	172.3	136.2	193.1
	80–84	262.2	262.1	258.8	222.2	155.8	223.2
	85+	291.1	290.3	294.0	234.9	186.5	255.5
Women	40–44	16.2	15.8	17.7	14.1	13.0	12.4
	45–49	26.9	25.6	32.4	24.3	24.3	20.5
	50–54	48.0	44.1	66.4	44.5	35.4	41.1
	55–59	54.3	50.4	78.7	46.3	31.7	50.4
	60–64	73.5	69.5	104.5	53.5	60.7	67.7
	65–69	104.4	100.0	140.7	77.8	99.6	96.2
	70–74	145.7	144.7	157.8	111.2	124.7	123.2
	75–79	188.4	187.3	203.4	142.4	123.4	148.5
	80–84	239.0	239.9	230.4	195.2	148.0	192.1
	85+	270.9	270.4	273.6	207.6	165.4	233.1
Men	40–44	19.3	19.0	21.4	14.0	13.4	14.1
	45–49	32.7	31.5	41.1	23.9	28.1	25.8
	50–54	61.0	58.2	75.2	53.5	34.8	50.6
	55–59	78.2	74.4	101.7	64.1	63.1	68.7
	60–64	105.1	99.0	143.5	101.9	96.3	107.6
	65–69	156.6	151.0	207.3	122.9	131.9	158.3
	70–74	203.5	199.1	247.0	155.6	177.8	210.0
	75–79	253.3	250.4	286.0	212.0	153.2	254.9
	80–84	296.5	294.3	312.0	263.6	167.4	270.4
	85+	332.1	330.4	345.4	282.0	226.5	296.6

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.[2]
* Not mutually exclusive from race categories

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

Table 3. FIT Characteristics, Including Those Unique to Qualitative and Quantitative Assays

FIT Characteristic	Qualitative FIT	Quantitative FIT
Cutoff value reported in ng Hb/mL buffer	Not comparable across studies/tests	Not comparable across studies/tests
Cutoff value reported in µg hemoglobin/g feces	Comparable across studies/tests	Comparable across studies/tests
Best interval for screening	Unknown	Unknown
Hb calibrator	May not be traceable to international reference preparation	May not be traceable to international reference preparation
Method	Immuno-chromatographic	Various; e.g. immuno-turbidometric
Cutoff value	Fixed	Adjustable by user
Results determination	Subjective	Objective; may be automated; results may be qualitatively reported*
Sample stabilization and transport	N/A	Various approaches to control sample size and stability
Suitable for large screening programs	No	Yes
Suitable for point of care testing	Yes	Dependent on volume

* Quantitative results may be transformed into qualitative results using the manufacturer's or a user-defined cutoff value. Performance characteristics of a quantitative assay used qualitatively may be adjusted by varying the cutoff value. In the US, the FDA has approved quantitative FITs only for dichotomous use.

Table 4. Included Studies for Key Question 1 (Mortality and/or Cancer Incidence)‡

Study Design	Colonoscopy	FS	CTC	gFOBT	FIT
Trials (screening versus no screening)	None	**Holme, 2014[143] (NORCCAP)** **Schoen, 2012[122] (PLCO)** Weissfeld, 2005[154] **Segnan, 2011[124] (SCORE)** Segnan, 2002[149] **Atkin, 2010[109] (UKFSST)** Atkin, 2002[133]	None	**Shaukat, 2013[127] (Minnesota Study)** Mandel, 2000[146] Mandel, 1993†[147] Thomas, 1995[150] **Scholefield, 2012[123] (Nottingham)** Hardcastle, 1996†[142] **Malila, 2011[119]** Malila, 2008[145] **Lindholm, 2008†[118]** **Faivre, 2004[113]** **Kronborg, 2004†[117] (Hemoccult II)**	None
Comparative effectiveness trials	**Quintero, 2012[120] (COLONPREV)** Parra-Blanco, 2006[148] **Stoop, 2012[128] (COCOS)** **Segnan, 2007[125] (SCORE III)**	**Hol, 2010*[116]** Hol, 2009[401] Hol, 2010[402] **Segnan, 2007[125] (SCORE III)** **Segnan, 2005[126] (SCORE II)** **Rasmussen, 1999[121]** **Verne, 1998[131]** **Berry, 1997[110]** **Brevinge, 1997[111]**	**Stoop, 2012[128] (COCOS)**	**Hol, 2010*[116]** Hol, 2009[401] Hol, 2010[402] **van Rossum, 2008[130]** **Rasmussen, 1999[121]** **Verne, 1998[131]** **Berry, 1997[110]** **Brevinge, 1997[111]**	**Zubero, 2014[132]** **van Roon, 2013*[129]** van Roon, 2011[152] **Quintero, 2012[120] (COLONPREV)** **Hol, 2010*[116]** Hol, 2009[401] Hol, 2010[402] **van Rossum, 2008[130]** Denters, 2012[137] Denters, 2009[138] **Segnan, 2007[125] (SCORE III)** **Segnan, 2005[126] (SCORE II)**
Observational	**Nishihara, 2013[41] (HPS, NHS)**	None	None	**Hamza, 2013[115]** **Faivre, 2012[112]** Faivre, 2012[139] **Guittet, 2009[114]** Guittet, 2012[140] Guittet, 2009[141]	**Hamza, 2013[115]** **Faivre, 2012[112]** Faivre, 2012[139] **Guittet, 2009[114]** Guittet, 2012[140] Guittet, 2009[141]

* Overlapping study populations
† Included in the 2008 USPSTF review[73]
‡ No included studies for mtsDNA or m*SEPT9*

Table 4. Included Studies for Key Question 1 (Mortality and/or Cancer Incidence)[‡]

Abbreviations: COCOS = COlonoscopy or COlonography for Screening; CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; HPS = Health Professionals Study; NHS = Nurses' Health Study; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial.

Table 5. Key Question 1: Overall Summary of Impact of Screening on Colorectal Cancer Incidence and Mortality

Screening test (total #studies, design) (Sample n)		# rounds	CRC incidence	f/u	CRC mortality	f/u
Screening versus no screening	Colonoscopy (k=1, cohort) (n=88,902)	1	*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)* *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)* *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)*	22y	*Total* HR, adj: 0.32 (95% CI, 0.24 to 0.45)* *Distal* HR, adj: 0.18 (95% CI, 0.10 to 0.31)* *Proximal* HR, adj: 0.47 (95% CI, 0.29 to 0.76)†	24 y
	FS (k=4, RCT) (n=458,002)	1-2 Q3-5y	*Total* IRR 0.79 (95% CI, 0.75 to 0.85) *Distal* IRR 0.71 (95% CI, 0.64 to 0.82) *Proximal* IRR 0.92 (95% CI, 0.84 to 1.02)	11-12y	*Total* IRR 0.73 (95% CI, 0.66 to 0.82) *Distal* IRR 0.63 (95% CI, 0.49 to 0.84) *Proximal* IRR 0.90 (95% CI, 0.77 to 1.04)	11-12y
	Hemoccult II (k=5, RCT) (n=404,396)	2-9 Q2y	*Total* RR range from 0.90 (95% CI, 0.77 to 1.04) from 1.02 (95% CI, 0.93 to 1.12) *Distal* NR *Proximal* NR	11-28y	*Total* RR range from 0.78 (95% CI, 0.65, 0.93) to 0.91 (95% CI, 0.84, 0.98)‡ *Distal* NR *Proximal* NR	11-30y

* 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

Abbreviations: adj = adjusted; CI = confidence interval; 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; RR = relative risk; w/ = with; y = years

Table 6. Key Question 1: FS Summary of Effectiveness on Colorectal Cancer Incidence and Mortality From Large Randomized, Controlled Trials

Trial, Year of publication	NORCCAP, 2014[143]	PLCO, 2012[122,154]	SCORE, 2011[124,149]	UKFSST, 2010[109,133]
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	11.2 (IG), 10.9 (CG)	11.9 (incidence), 12.1 (mortality)	10.5 (incidence), 11.4 (mortality)	11.2
Attendance to screening, %	63	1st Screen: 84 2nd Screen: 54	58	67
CRC, n/n (%)	1339/98,792 (1.4)	2299/154,900 (1.5)	557/34,272 (1.6)	2524/170,038 (1.5)
Criteria for colonoscopy	Polyp ≥10 mm; adenoma; CRC; positive 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	8.6	5.2
CRC Incidence rate, per 100,000 p-y RR (95% CI)	*Total* IG: 114.3‡ CG: 131.1‡ 0.87 (0.76, 1.00)*¥ *Distal* IG: 61.9‡ CG: 75.0‡ 0.83 (0.69, 0.99)* *Proximal* IG: 50.6‡ CG: 51.2‡ 0.99 (0.80, 1.22)* *Men* IG: 115.6 (age-adjusted) CG: 157.6 (age-adjusted) 0.73 (0.60, 0.89) (HR) *Women* IG: 109.6 (age-adjusted) CG: 125.5 (age-adjusted) 0.87 (0.72, 1.06) (HR)	*Total* IG: 119 CG: 152 0.79 (0.72, 0.85) *Distal* IG: 56 CG: 79 0.71 (0.64, 0.80) *Proximal* IG: 60 CG: 70 0.86 (0.76, 0.97) *Men* IG: 136 CG: 185 0.73 (0.66, 0.82) *Women* IG: 103 CG: 120 0.86 (0.76, 0.98)	*Total* IG: 144.1 CG: 176.4 0.82 (0.69, 0.97)* *Distal* IG: 87.3 CG: 114.2 0.76 (0.62, 0.94) *Proximal* IG: 56.8 CG: 62.3 0.91 (0.69, 1.20) *Men* IG: 190.9 CG: 216.8 0.88 (0.71, 1.09) *Women* IG: 98.5 CG: 136.1 0.72 (0.55, 0.96)	*Total* IG: 114 CG: 149 0.77 (0.70, 0.84) *Distal* IG: 62 CG: 98 0.64 (0.57, 0.72) *Proximal* IG: 50 CG: 51 0.98 (0.85, 1.12) Men IG: 142.4 CG: 191.1 0.75 (0.67, 0.83)* Women IG: 88.4 CG: 110.3 0.80 (0.70, 0.92)*

Table 6. Key Question 1: FS Summary of Effectiveness on Colorectal Cancer Incidence and Mortality From Large Randomized, Controlled Trials

Trial, Year of publication	NORCCAP, 2014[143]	PLCO, 2012[122,154]	SCORE, 2011[124,149]	UKFSST, 2010[109,133]
CRC Mortality rate, per 100,000 p-y RR (95% CI)	*Total* IG: 31.9‡ CG: 39.7‡ 0.80 (0.62, 1.04)* *Distal* IG: 17.5‡ CG: 20.2‡ 0.87 (0.61, 1.23)* *Proximal* IG: 13.5‡ CG: 16.7‡ 0.81 (0.54, 1.20)* *Men* IG: 28.6 (age-adjusted) CG: 49.1 (age-adjusted) 0.58 (0.40, 0.85) (HR) *Women* IG: 34.2 (age-adjusted) CG: 37.4 (age-adjusted) 0.91 (0.64, 1.30) (HR)	*Total* IG: 29 CG: 39 0.74 (0.63, 0.87) *Distal* IG: 10 CG: 20 0.50 (0.38, 0.64) *Proximal* IG: 16 CG: 17 0.97 (0.77, 1.22) *Men* IG: 32 CG: 49 0.66 (0.53, 0.81) *Women* IG: 26 CG: 29 0.87 (0.68, 1.12)	*Total* IG: 34.7 CG: 44.5 0.78 (0.56, 1.08) *Distal* IG: 18.7 CG: 25.7 0.73 (0.47, 1.12) *Proximal* IG: 16.0 CG: 18.7 0.85 (0.52, 1.39)	*Total* IG: 36 CG: 52 0.69 (0.59, 0.80)* *Distal†* IG: 14.8 CG: 25.4 0.58 (0.46, 0.74)* *Proximal†* IG: 14.8 CG: 16.9 0.87 (0.68, 1.12)* *Men†* IG: 38.1 CG: 57.4 0.66 (0.54, 0.82)* *Women†* IG: 23.4 CG: 31.4 0.74 (0.57, 0.97)*
All-cause Mortality rate, per 100,000 p-y RR (95% CI)	*Total* IG: 980.3‡ CG: 932.9‡ 1.05 (1.00, 1.10)‡	NR	*Total* IG: 644.2 CG: 666.1 0.97 (0.89, 1.05)*	*Total* IG: 1093 CG: 1124 0.97 (0.94, 1.00)

* Calculated RR, not study reported

† Data provided by author from personal communication

‡ Data presented here does not match study reported rates due to study adjustment for age

¥ Age-adjusted cancer incidence difference reported in the publication is statistically significant

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

Table 7. Key Question 1: Hemoccult II Summary of Effectiveness on Colorectal Cancer Incidence and Mortality From Large Controlled Trials

Trial, Year of publication	Burgundy, 2004[113]	Funen, 2004[117]	Göteborg, 2008[118]	Finland, 2011[119,145]	Nottingham, 2012[123,142]	Minnesota Colon Cancer Control Study, 2013[127,146,147,150]	
Country	France	Denmark	Sweden	Finland	England	US	
Screen Frequency	Biennial	Biennial	Varied (1 to 9 years)	Biennial	Biennial	Biennial	Annual
Targeted Age	45–74	45–75	60–64	60–69	45–74	50–80	50–80
Program n	SG: 45,642 CG: 45,557	SG: 30,967 CG: 30,966	SG: 34,144 CG: 34,164	SG: 52,998 CG: 53,002	SG: 76,056 CG: 75,919	SG: 15,587 CG: 15,394	SG: 15,570 CG: 15,394
Number of rounds	6	9	2-3	2	3-5	6	11
Length of followup, years	11	17	19	4	28	30 (18 for incidence)	30 (18 for incidence)
Attendance to round 1 (%)	53	67	62	70	53	NR	NR
Attendance to at least 1 round (%)	70	67	70	92	60	90	90
Round 1 test positivity, %	2.1	1.0	3.8‡	2.3	2.1	NR‡	NR‡
All rounds test positivity, %	1.5	1.5	4.1	2.5	NR	NR†	NR†
CRC in SG, n/n	699/45,642	889/30,967	721/34,144	126/52,998	2279/76,056	435/15,550	417/15,532
CRC in CG, n/n	696/45,557	874/30,966	754/34,164	98/53,002	2354/75,919	507/15,363	507/15,363
RR (95% CI)	1.01 (0.91, 1.12)	1.02 (0.93, 1.12)	0.96 (0.86, 1.06)	1.29 (0.98, 1.69)*	0.97 (0.91, 1.03)	0.85 (0.74, 0.96)*	0.81 (0.71, 0.93)*
CRC deaths in SG, n/n	254 /45,642	362/30,967	252/34,144	NR	1176/76,056	237/15,587	200/15,570
CRC deaths in CG, n/n	304/45,557	431/30,966	300/34,164	NR	1300/75,919	295/15,394	295/15,394
RR (95% CI)	0.84 (0.71, 0.99)	0.84 (0.73, 0.96)	0.84 (0.71, 0.99)	NR	0.91 (0.84, 0.98)	0.78 (0.65, 0.93)	0.68 (0.56, 0.82)
All-cause deaths in SG, n/n	NR	12,205/30,967	10,591/34,144	NR	40,681/76,056	11,004/15,587	11,072/15,570
All-cause deaths in CG, n/n	NR	12,248/30,966	10,432/34,164		40,550/75,919	10,944/15,394	10,944/15,394
RR (95% CI)	NR	0.99 (0.97, 1.02)	1.02 (0.99, 1.06)	NR	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	1.00 (0.99, 1.01)

* Calculated in Stata using iri; exact confidence interval

† 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; n = number; NR = not reported; RR = relative risk; SG = screened group; US = United States.

Table 8. Key Question 1: Included Comparative Effectiveness Studies (Reverse Chronological Order)

Study Design	Study	Country	gFOBT	FIT	FS	Colonoscopy	CTC
Trials	Zubero, 2014[132]	Spain		X			
	van Roon, 2013*[129]	The Netherlands		X†			
	Quintero, 2012[120,148] (COLONPREV)	Spain		X		X	
	Stoop, 2012[128] (COCOS)	The Netherlands				X	X
	van Roon, 2011*[152]	The Netherlands		X‡			
	Hol, 2010*[116]	The Netherlands	X	X	X		
	van Rossum, 2008[130,137,138]	The Netherlands	X	X			
	Segnan, 2007[125] (SCORE III)	Italy		X	X	X	
	Segnan, 2005[126] (SCORE II)	Italy		X	X**		
	Rasmussen, 1999[121]	Denmark	X		X**		
	Verne, 1998[131]	UK	X		X**		
	Berry, 1997[110]	UK	X		X**		
	Brevinge, 1997[111]	Sweden	X		X		
Observational	Hamza, 2013[115]	France	X	X			
	Faivre, 2012[112,139]	France	X	X‡			
	Guittet, 2009[114,140,141]	France	X	X			

* Overlapping study populations
‡ Compare different number of samples
† Compare intervals
** Study includes a FS+FOBT comparison

Abbreviations: COCOS = COlonoscopy or COlonography for Screening; CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; SCORE = Screening for COlon Rectum; UK = United Kingdom.

Table 9. Included Studies for Key Question 2

Reference Standard	Colonoscopy	FS	CTC	High sensitivity gFOBT	FIT	sDNA +/-FIT	m*SEPT9*
Colonoscopy or enhanced colonoscopy	CTC studies with relevant colonoscopy data: **Zalis, 2012[183]** **Johnson, 2008 (ACRIN)[50]** Johnson,2012[193] **Johnson, 2007*[169]** **Pickhardt, 2003*[52]**	None	**Lefere, 2013[51]** **Fletcher, 2013[165]** **Zalis, 2012[183]** **Graser, 2009[49]** **Johnson, 2008[50] (ACRIN)** Johnson, 2012[193] **Kim, 2008[170]** **Johnson, 2007*[169]** **Macari, 2004*[176]** **Pickhardt, 2003*[52]**	None	**Hernandez, 2014[166]** **Imperiale, 2014[167]** SSED[184] **Lee, 2014[172]** **Levy, 2014[174]** **Brenner, 2013[157] (BliTz)** Haug, 2011[189] Brenner, 2010[187] Brenner, 2010[186] Hundt, 2009[191] **Chiu, 2013[162]** **Ng, 2013[180]** **de Wijkerslooth, 2012[164] (COCOS)** **Park, 2010[181]** **Graser, 2009[49]** **Morikawa, 2005*[177]** Morikawa, 2007*[194] **Sohn, 2005[182]** **Cheng, 2002*[160]** **Nakama, 1999*[178]**	**Imperiale, 2014[167]** SSED[184] **Lin, 2012[175]** Haug, 2007[190] Imperiale, 2004[192] Ahlquist, 2008[185]	**Church, 2014[163]**

Table 9. Included Studies for Key Question 2

Reference Standard	Colonoscopy	FS	CTC	High sensitivity gFOBT	FIT	sDNA +/-FIT	m*SEPT9*
Differential followup (registry)	None	None	None	**Allison, 2007*[155]** **Allison, 1996*[156]** **Levi, 2011[173]**	**Chiang, 2014[161]** **Chen, 2011[159]** **Levi, 2011[173]** **Allison, 2007*[155]** **Castiglione, 2007[158]** Grazzini, 2004[188] **Launoy, 2005*[171]** **Allison, 1996*[156]** **Nakama, 1996*[179]** **Itoh, 1996*[168]**	None	None

* Included in 2008 USPSTF review

Abbreviations: ACRIN = American College of Radiology Imaging Network National CT Colonography Trial; BliTz = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung; COCOS = COlonoscopy or COlonography for Screening; CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid; sDNA = stool deoxyribonucleic acid.

Table 10. Key Question 2: Overall Summary of Diagnostic Accuracy per Person

Screening test (total # studies)		AA Sensitivity	AA Specificity	Adenoma ≥10 mm Sensitivity	Adenoma ≥10 mm Specificity	Adenoma ≥6 mm Sensitivity	Adenoma ≥6 mm Specificity
Direct Visualization†	Colonoscopy (k=4)	--	--	Low: 89.1 High: 94.7	88.7	Low: 74.6 High: 92.8	94.2
	CTC (k=9)	--	--	--	--	--	--
	With bowel prep (k=7)	Low: 87.5 High: 100	Low: 39.4 High: 87.1	Low: 66.7 High: 93.5	Low: 86.0 High: 97.9	Low: 72.7 High: 98.0	Low: 79.6 High: 93.1
	Without bowel prep (k=2)	64.0	--	Low: 66.7 High: 89.5	Low: 85.2 High: 97.3	Low: 57.7 High: 75.0	Low: 88.3 High: 92.2
Screening test (total # studies)		**CRC Sensitivity**	**CRC Specificity**	**AA Sensitivity**	**AA Specificity**	**AN Sensitivity**	**AN Specificity**
Stool tests	Differential followup – Hemoccult Sensa (k=2)	Low: 61.5 High: 79.4	Low: 86.7 High: 96.4	NA	NA	NA	NA
	All colonoscopy followup – Qualitative FIT (k=6)	Low: 54.5 High: 88.9	Low: 89.4 High: 93.1	Low: 25.4 High: 71.5	Low: 56.3 High: 96.4	Low: 5 High: 73.4	Low: 56.3 High: 99
	OC-Light (k=3)	Low: 78.6 High: 87.5	Low: 91 High: 92.8	Low: 28.0 High: 40.3	Low: 91.3 High: 93.5	Low: 5 High: 48.4	Low: 91.3 High: 99
	QuickVue (k=2)	--	--	56.2	67.9	Low: 50 High: 59.6	Low: 69.6 High: 88
	All colonoscopy followup – Quantitative FIT (k=9‡)	Low: 25 High: 92.3*	Low: 87.2* High: 95.5	Low: 6 High: 44.1*	Low: 85.8 High: 97.4	Low: 2.4 High: 76.2	Low: 85.8 High: 98.8
	OC FIT-CHEK (k=5‡)	Low: 73.3 High: 92.3*	Low: 87.2* High: 95.5	Low: 22.2 High: 44.1*	Low: 89.8* High: 97.4	Low: 25.7 High: 52.8*	Low: 89.8* High: 97.4
	Differential followup – Qualitative FIT (k=3)	Low: 68.8 High: 83.3	Low: 94.4 High: 96.2	--	--	--	--
	Differential followup – Quantitative FIT** (k=3)	Low: 77.1 High: 86.5	Low: 94.4 High: 96.4	--	--	--	--
	mtsDNA (k=1)	92.3	84.4	42.4	86.6	46.9	86.3
Blood test	m*SEPT9* (k=1)	48.2	91.5	--	--	--	--

* Results obtained using lower than manufacturer-recommended cutoff value and 3 stool samples

** Excluding Chen and colleagues[159] for study design differences that likely affected diagnostic accuracy calculations; excluding Levi and colleagues[173] for few CRC cases.

† Studies were not designed to determine sensitivity/specificity for CRC outcomes

‡Excluding Graser and colleagues[49] for CRC, CRC cases=1; excluding Hernandez and colleagues[166] for CRC, CRC cases=5.

Abbreviations: CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; k = number of studies; mm = millimeter; mtsDNA = multi-target stool deoxyribonucleic acid; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid; NA = not applicable.

Table 11. Key Question 2: Colonoscopy Summary of Diagnostic Accuracy

Author, Year Quality Country	N analyzed Age Female (%)	Prevalence (%)	Colonoscopy Protocol	Reference Standard	Most advanced finding (per person): CRC Adenoma ≥10 mm Adenoma ≥6 mm	Per Person Sensitivity (95% CI)	Specificity (95% CI)	Per Lesion Sensitivity (95% CI)
Zalis, 2012[183] Good US	605 60 47	CRC: 0.5 AA: NR	Number of Colonoscopists: NR Training: Fellowship-trained staff gastroenterologists Cecal Intubation Rate: NR	CTC informed colonoscopy (segmental unblinding)	3 19 71	CRC: 100 (29.2, 100) Adenoma ≥10 mm: 94.7 (74.0, 99.9) Adenoma ≥6 mm: 74.6 (62.9, 84.2)	CRC: NR Adenoma ≥10 mm: 88.7 (85.8, 91.1) Adenoma ≥6 mm: 94.2 (91.8, 96.0)	CRC: NR Adenoma ≥10 mm: 95.5 (77.2, 99.9) Adenoma ≥6 mm: 75.8 (65.9, 84.0)
Johnson, 2008[50] ACRIN National CT Colonography Trial Good US	2531 58 52	CRC: 0.28 AA: NR	Number of Colonoscopists: NR Training: Performed or directly supervised by an experienced gastroenterologist or surgeon Cecal Intubation Rate: NR	Repeat colonoscopy if indicated by CTC	7 102 203	NR	NR	CRC: 100 (59.0, 100) Adenoma ≥10 mm: 97.6 (93.1, 99.5) Adenoma ≥6 mm: NR
Johnson, 2007[169] Fair US	452 65 44	CRC: 1.1 AA: NR	Number of Colonoscopists: NR* Training: Performed or directly supervised by an experienced gastroenterologist or surgeon Cecal Intubation Rate: 99%	Repeat colonoscopy if indicated by CTC	5 21 NR	CRC: 17.9 (0.5, 71.6) Adenoma ≥10 mm: 90.5 (69.6, 98.8) Adenoma ≥6 mm: NR	NR	CRC: 17.9 (0.5, 71.6) Adenoma ≥10 mm: 90.5 (69.6, 98.8) Adenoma ≥6 mm: NR

Table 11. Key Question 2: Colonoscopy Summary of Diagnostic Accuracy

Author, Year Quality Country	N analyzed Age Female (%)	Prevalence (%)	Colonoscopy Protocol	Reference Standard	Most advanced finding (per person): CRC Adenoma ≥10 mm Adenoma ≥6 mm	Per Person Sensitivity (95% CI)	Specificity (95% CI)	Per Lesion Sensitivity (95% CI)
Pickhardt, 2003[52] Good US	1233 58 41	CRC: 0.16 AA: NR	Number of Colonoscopists: 17 Training: Experienced gastroenterologists or surgeons Cecal Intubation Rate: 99.4%	CTC informed colonoscopy (segmental unblinding)	2 46 166	CRC: 50.0 (1.3, 98.7) Adenoma ≥10 mm: 89.1 (77.8, 95.7) Adenoma ≥6 mm: 92.8 (88.1, 96.0)	NR	CRC: 50.0 (1.3, 98.7) Adenoma ≥10 mm: 89.8 (79.1, 96.0) Adenoma ≥6 mm: 90.4 (85.8, 93.8)

* Performed or supervised by 1 of 50 experienced endoscopists

Abbreviations: AA = advanced adenoma; CI = confidence interval; CRC = colorectal cancer; CTC = computed tomography colonography; mm = millimeters; N = no; n = number; NR = not reported; US = United States; Y = yes; 2D = two dimensional; 3D = three dimensional.

Table 12. Key Question 2: Computed Tomographic Colonography Summary of Diagnostic Accuracy

Author, Year Quality Country	N Age Female (%)	Prevalence (%)	CTC Protocol	Reference Standard	Persons with: CRC Advanced Adenoma Adenoma ≥10 mm Adenoma ≥6 mm	Adenoma ≥6 mm Sensitivity (95% CI) Specificity (95% CI)	Adenoma ≥10 mm Sensitivity (95% CI) Specificity (95% CI)	Advanced adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
Lefere, 2013[51] Fair Portugal	496 60 60 45	CRC: 0.8 AA: 5.6	Bowel Prep: Y Fecal Tagging: Y Number of Readers: 1 Training: >5000 exams Reading strategy: 3D (with 2D)	Repeat colonoscopy if indicated	4 32 NR 49	98.0 (90.9, 99.8) 91.0 (88.0, 93.4)	NR NR	100 (89.3, 100) 87.1 (83.8, 89.9)	100 (92.5, 100) 87.1 (83.8, 89.9)
Graser, 2009[49] Good Germany	307 60 45 45	CRC: 0.33 AA: 9.5	Bowel Prep: Y Fecal Tagging: N Number of Readers: 3 Training: >300 exams Reading strategy: 3D (with 2D)	Colonoscopy with segmental unblinding	1 29 24 45	91.1 (80.2, 96.9) 93.1 (89.5, 95.7)	91.7 (75.9, 98.2) 97.9 (95.7, 99.1)	96.6 (85.0, 99.6) 39.4 (33.7, 45.2)	96.7 (85.5, 99.6) 39.4 (33.7, 45.2)
Johnson, 2008[50] ACRIN‡ Good US	2531 58 52	CRC: 0.28 AA: NR	Bowel Prep: Y Fecal Tagging: Y Number of Readers: 15 Training: >500 examsβ Reading strategy: 3D (with 2D)	Repeat colonoscopy if indicated	7 NR* 102 203	77.8 (71.8, 83.1) 89.6 (88.4, 90.7)	90.2 (83.3, 94.8) 86.0 (84.6, 87.3)	NR NR	NR NR
Kim, 2008[170] Fair South Korea	241 58 49	CRC: 0.4 AA: 6.6	Bowel Prep: Y Fecal Tagging: N Number of Readers: 2 Training: >100 exams Reading strategy: 2D (with 3D)	Single colonoscopy	1 16 10 44	68.5 α** (55.4, 79.7) 88.8 α (83.7, 92.7)	86.7†** (63.7, 97.1) 97.3† (94.6, 98.9)	87.5 (65.6, 97.3) NR	88.2 (67.3, 97.5) NR
Johnson, 2007[169] Fair US	452 65 44	CRC: 1.1 AA: NR	Bowel Prep: Y Fecal Tagging: N Number of Readers: 3 Training: >1000 exams Reading strategy: 3D (with 2D)¥	Single colonoscopy	5 NR* 21 NR	NR NR	66.7 (45.4, 83.7) 97.6 (95.8, 98.8)	NR NR	NR NR

Table 12. Key Question 2: Computed Tomographic Colonography Summary of Diagnostic Accuracy

Author, Year Quality Country	N Age Female (%)	Prevalence (%)	CTC Protocol	Reference Standard	Persons with: CRC Advanced Adenoma Adenoma ≥10 mm Adenoma ≥6 mm	Adenoma ≥6 mm Sensitivity (95% CI) Specificity (95% CI)	Adenoma ≥10 mm Sensitivity (95% CI) Specificity (95% CI)	Advanced adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
Macari, 2004[176] Fair US	68 55 0	CRC: NR AA: NR	Bowel Prep: Y Fecal Tagging: N Number of Readers: 1 Training: 5 years experience Reading strategy: NR	Single colonoscopy	NR NR* NR 3† NR	NR NR	100† (46.4, 100) 98.5† (93.0, 99.8)	NR NR	NR NR
Pickhardt, 2003[52] Good US	1233 58 41	CRC: 0.16 AA: NR	Bowel Prep: Y Fecal Tagging: Y Number of Readers: 6 Training: >25 exams Reading strategy: 3D (with 2D)	Colonoscopy with segmental unblinding	2 NR* 46 166	88.6 (83.1, 92.7) 79.6 (77.1, 82.0)	93.5 (83.6, 98.1) 96.0 (94.8, 97.0)	NR NR	NR NR
Fletcher, 2013[165] Good US	564 NR 58	CRC: 0.18 AA: 4.4	Bowel Prep: N Fecal Tagging: Y Number of Readers: 2 Training: >150 exams Reading strategy: 2D and 3D	Single colonoscopy	1 25 15 36	75.0 (59.3, 86.8) 92.2 (89.7, 94.3)	66.7 (41.6, 86.0) 97.3 (95.6, 98.4)	64.0 (44.5, 80.5) NR	65.4 (46.3, 81.3) NR
Zalis, 2012[183] Good US	605 60 47	CRC: 0.5 AA: NR	Bowel Prep: N Fecal Tagging: Y Number of Readers: 3 Training: >200 exams Reading strategy: 2D and 3D	Colonoscopy with segmental unblinding	3 NR* 19 71	57.7 (46.1, 68.7) 88.3 (85.4, 90.8)	89.5 (70.3, 97.7) 85.2 (82.2, 88.0)	NR NR	NR NR

* Assumed zero CRC cases
α Any histology ≥6 mm;
† Any histology ≥10 mm
** Sensitivity for adenomas ≥6 mm 72.7 percent (95% CI, 58.4 to 84.1); Sensitivity for adenomas ≥10 mm 90.0 percent (95% CI, 61.9 to 99.0)
‡ National CT Colonography Trial
β Or 1.5 day training session
¥ Study evaluated different reading strategies, data shown reflect primary 3D strategy

Abbreviations: AA = advanced adenoma; CI = confidence interval; CRC = colorectal cancer; n = number; N = no; NR = not reported; mm = millimeters; US = United States; Y = yes; 2D = two dimensional; 3D = three dimensional.

Table 13. Key Question 2: Hemoccult SENSA Summary of Diagnostic Accuracy

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Followup	N Analyzed Female (%)	Prevalence (%)	Number of Samples	Cutoffs ng Hb/ml buffer µg Hb/g feces	CRC Cases	CRC Sensitivity (95% CI) Specificity (95% CI)
Levi, 2011[173] Fair Israel	9 primary care clinics	Asymptomatic people; 50–75 years; patients of selected 9 primary care clinics of Clalit Health Services	Colonoscopy for FOBT+; registry followup for 2 years after the last FOBT was performed.	2266 NR	CRC: 0.55 AA: NR	NR	Positive test = any of the 6 windows is positive NR	13	61.5 (35.0, 83.5) 96.4 (95.6, 97.2)
Allison, 1996[156] Fair US	Single Kaiser Permanente Medical Center	50 years of age or older; scheduled for a personal health appraisal	FS for all positive tests. If FS found a neoplasm, then referred to colonoscopy. If FS was negative, FOBT screen was repeated at 6 and 12 mo. Colonoscopy to anyone wishing to undergo one. Computerized databases were searched for two years after screening for interval CRC.	7904 59.3	CRC: 0.43 AA: 1.3	3	Blue color diffused into a 0.5-cm margin around the specimen within 1 min NR	34	79.4 (63.8, 90.3) 86.7 (85.9, 87.4)

Abbreviations: AA = advanced adenoma; CI = confidence interval; CRC = colorectal cancer; N = number; NR = not reported; US = United States.

Table 14. Description of Included Fecal Immunochemical Tests

Test Family	Test Name	Type of Test	Test Principle	Cutoff, ng Hb/mL buffer	Cutoff, µg Hb/g feces	Manufacturer (Current information, preferentially for US distribution, if applicable)	Test Name Aliases	FDA-cleared?
Hemosure	Hemosure	Qualitative	Immunochromatographic	50†	50*	W.H.P.M., Inc., Irwindale, CA	--	Yes
Hemoccult ICT	Hemoccult ICT	Qualitative	Immunochromatographic	--	300*	Beckman Coulter, Inc	FlexSure OBT	Yes
immoCARE-C	immoCARE-C	Qualitative	Immunochromatographic	50*	30*	CAREdiagnostica, Voerde, Germany	Hemocare	Yes
MonoHaem	MonoHaem	Qualitative	Immunochromatographic	--	1,050***	Silenus Laboratories Proprietary Ltd. , Wilmington, DE (distributor for Chemicon International, Inc)	--	Yes
QuickVue	QuickVue iFOB	Qualitative	Immunochromatographic	50*	50*	Quidel, San Diego, CA	--	Yes
OC Light	OC-L FIT-CHEK (manual)	Qualitative	Immunochromatographic	50*	10**	Eiken Chemical Co., Tokyo, Japan, distributed in the US by Polymedco, Inc., Cortlandt Manor, NY	OC-Light	Yes
OC (FIT-CHEK)	OC FIT-CHEK (using the OC-Auto Micro 80 Analyzer)	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-Auto, OC-Micro (using OC-Auto reagents)	Yes
	OC FIT-CHEK (using the OC-Sensor Diana automated analyzer)	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-Diana, OC-Sensor (using OC-Sensor Diana reagents)	Yes
OC (Hemodia)	OC-Hemodia (manual)	Qualitative	Visual particle agglutination		40**	Eiken Chemical Co., Tokyo, Japan		Discontinued[1]
	OC-Hemodia (automated, since 2000)	Quantitative‡	Latex agglutination, measured as optical change	100**	20**	Eiken Chemical Co., Tokyo, Japan	OC-Sensor micro (using OC-Hemodia reagents)	Discontinued[1]
Clearview (casette)	Clearview iFOB Complete (casette)	Qualitative	Immunochromatographic	50†	6 ug Hb†	Alere Inc., Waltham, MA	--	Yes
Clearview (test strip)	Clearview ULTRA iFOB (test strip)	Qualitative	Immunochromatographic	50[2]	50[2]	Inverness Medical Innovation, Inc., now Alere, Inc., Waltham, MA	--	Discontinued[2]
FOB advanced	FOB advanced	Qualitative	Immunochromatographic	50†	--	ulti med, Ahrensburg, Germany	--	No
PreventID CC	PreventID CC	Qualitative	Immunochromatographic	10**	--	Preventis, Bensheim, Germany	--	No

Table 14. Description of Included Fecal Immunochemical Tests

Test Family	Test Name	Type of Test	Test Principle	Cutoff, ng Hb/mL buffer	Cutoff, µg Hb/g feces	Manufacturer (Current information, preferentially for US distribution, if applicable)	Test Name Aliases	FDA-cleared?
Bionexia (Hb)	Bionexia FOBplus	Qualitative	Immunochromatographic	40†	--	Biomerieux, Marcy l'Etoile, France [originally supplied by Dima Diagnostika]	--	No
Bionexia (Hb-Hp)	Bionexia Hb-Hp Complex	Qualitative	Immunochromatographic	25†	--	Biomerieux, Marcy l'Etoile, France [originally supplied by Dima Diagnostika]	--	Discontinued? [not available on Biomerieux website]
Magstream/ Hemselect	HemeSelect	Qualitative	Reverse passive hemagglutination	Samples diluted 1:8 showing erythrocyte agglutinat-ion	100-200†	Fujirebio, Tokyo, Japan, distributed by Beckman-Coulter, Inc., Brea, CA	Immudia HemSp	Discontinued[1]
	Magstream 1000/Hem SP	Quantitative‡	Magnetic particle agglutination	20**	67**	Fujirebio, Tokyo, Japan	(Based on HemeSelect/ Immudia HemSp)	No
RIDASCREEN (Hb)	RIDASCREEN Hemoglobin	Quantitative‡	Enzyme immunoassay	--	2†	R-Biopharm AG, Darmstadt, Germany	--	No
RIDASCREEN (Hb-Hp)	RIDASCREEN Hemoglobin-Haptoglobin Complex	Quantitative‡	Enzyme immunoassay	--	2†	R-Biopharm AG, Darmstadt, Germany	--	No
FOB Gold	FOB Gold	Quantitative‡	Latex agglutination, measured as optical change	100 ** [CE marked for user-defined cutoff]	17**	Sentinel Diagnostics, Milan, Italy	--	No
Hemo Techt	Hemo Techt NS-Plus C system	Quantitative‡	Colloidal gold agglutination measured as optical change	--	19	Alfresa Pharma Co., Osaka, Japan	--	No
HM-JACK	HM-JACK	Quantitative‡	Latex agglutination, measured as optical change	8	20	Kyowa Medex Co., Ltd., Tokyo, Japan	--	No

[1] per Lee 2014[306]
[2] per Levy 2014[174]
* from FDA summary
† from manufacturer website or calculated from information provided
** from published literature

Table 14. Description of Included Fecal Immunochemical Tests

*** Calculated from information provided in device manual; also reported by Halloran and colleagues;[403] different cutoff of 0.2 mg/g feces (200 µg/g feces) reported by Nakama and colleagues[178]
‡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.

Abbreviations: CA = California; DE = Deleware; FDA = Food and Drug Administration; g = gram; Hb = hemoglobin; ng = nanogram; MA = Massachusetts; ml = milliliter; NY = New York; µg = microgram; US = United States.

Table 15. Fecal Immunochemical Test (With or Without Stool DNA) Study Characteristics, All Colonoscopy Followup (Ordered Reverse Chronologically)

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Mean or Median Age (years)	Female (%)	Prevalence (%)	N Analyzed	Test Name (Family Name)
Hernandez, 2014[166] Good Spain	Multicenter (3 tertiary hospitals)	Asymptomatic men and women; aged 50-69 years; included in the COLONPREV study in Galacia and Euskadi; offered colonoscopy during the inclusion period	Mean 57.6	50.4	CRC: 0.6 AA: 11.8	779	OC-Sensor (OC (FIT-CHEK))
Imperiale, 2014[167] Fair US; Canada	90 private-practice and academic sites	Asymptomatic; 50-84 years; average risk for CRC; scheduled to undergo screening colonoscopy	Mean 64.2	53.7	CRC: 0.65 AA: 6.9	9989	OC FIT-CHEK (assumed automated version, based on cutoff value) (OC (FIT-CHEK)) Cologuard (mtsDNA= FIT plus sDNA)
Lee, 2014[172] Good South Korea	Korean Association of Health Promotion	Received annual physical check-ups at the Gangnam branch of the Korean Association of Health Promotion (KAHP) during the period of July 2012 and March 2013. KAHP provides health checkups to >1 million annually in 16 branch clinics across Korea	Median 58	52	CRC: NR AA: NR	NR	Hemo Techt NS-Plus C system (Hemo Techt NS-Plus C system)
Levy, 2014[174] Fair US	University of Iowa Healthcare	40-75 years; scheduled for a screening colonoscopy (subgroup of total n)	Mean 56.9	59.2	CRC: NR AA: NR	44 308 217 52	clearview ULTRA iFOB (test strip) (Clearview (test strip)) Clearview iFOB complete (cassette) (Clearview (cassette)) OC-Light (OC Light) QuickVue (QuickVue)
Brenner, 2013[157] (BliTz) Good Germany	20 Gastroenterology practices	Participants of screening colonscopy; average risk; 55 years or older	Mean 62.7	50.8	CRC: 0.67 AA: 9.3	2235	RIDASCREEN Hemoglobin (RIDASCREEN (Hb)) RIDASCREEN Hemoglobin-Haptoglobin Complex (RIDASCREEN (Hb-Hp)) OC FIT-CHEK (using the OC-Sensor Diana automated analyzer) (OC (FIT-CHEK))

Table 15. Fecal Immunochemical Test (With or Without Stool DNA) Study Characteristics, All Colonoscopy Followup (Ordered Reverse Chronologically)

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Mean or Median Age (years)	Female (%)	Prevalence (%)	N Analyzed	Test Name (Family Name)
Brenner, 2010[186] (BliTz) Good Germany	20 Gastroenterology practices	Participants of the German colonscopy screening program	Median 63	49.4	CRC: 0.8 AA: 9.8	1330	immoCARE-C (immoCARE-C) FOB advanced (FOB advanced) PreventID CC (PreventID CC) Bionexia FOBplus (Bionexia (Hb)) QuickVue iFOB (QuickVue) Bionexia Hb/Hp Complex (Bionexia (Hb-Hp))
Chiu, 2013[162] Good Taiwan	Health check-ups at a university hospital	Adults who underwent screening colonoscopy as part of thorough health check-ups at the Health Management Center of National Taiwan University Hospital; aged 50 years or older	Mean 59.8	40.8	CRC: 0.15 AA: 3.5	18,296	OC-LIGHT
Ng, 2013[180] Fair Hong Kong	Bowel cancer screening community center	50-70 years; no symptoms in the past 6 months suggestive of CRC (hematochezia, melena, anorexia, change in bowel habit or weight loss greater than 5 kg; no screening test for CRC performed in the past 5 years	Mean 57.7	54.7	CRC: 0.48 AA: 4.3	4539	Hemosure (Hemosure)
de Wijkerslooth, 2012[164] Good The Netherlands	Population-based screening pilot	Asymptomatic individuals of the Amsterdam and Rotterdam regions	Median 60	49	CRC: 0.64 AA: 8.8	1256	OC-Sensor (automated, inferred from text) (OC (FIT-CHEK))
Park, 2010[181] Fair South Korea	4 tertiary medical centers	Asymptomatic, average-risk people; 50-75 years; undergoing screening colonoscopy	Mean 59.3	48.6	CRC: 1.7 AA: 7.7	770	OC-MICRO (OC (FIT-CHEK))
Graser, 2009[49] Good Germany	NR	>50 years old; free of colonic symptoms (e.g., melanic stools, hematocheiza, diarrhea, changes in stool frequency or abdominal pain)	Mean 60.5	45	CRC: 0.33 AA: 8.4	285	FOB Gold (FOB Gold)

Table 15. Fecal Immunochemical Test (With or Without Stool DNA) Study Characteristics, All Colonoscopy Followup (Ordered Reverse Chronologically)

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Mean or Median Age (years)	Female (%)	Prevalence (%)	N Analyzed	Test Name (Family Name)
Morikawa, 2005[177] Fair Japan	Single hospital or associated clinic	Asymptomatic volunteers who participated in a comprehensive health exam	Mean 48	28	CRC: 0.4 AA: 3.0	21805	Magstream 1000/Hem SP (Magstream/HemeSelect)
Sohn, 2005[182] Fair Korea	National Cancer Center, Korea	Subjects visiting the Center for Cancer Prevention and Detection for a medical check-up	Mean 48.9	43.3	CRC: 0.3 AA: 1.8	3794	OC-hemodia, using an OC-sensor analyzer (OC (Hemodia))
Cheng, 2002[404] Fair Taiwan	Health screening program at a single cancer center	NR	Mean 46.8	44.8	CRC: 0.22 AA: 1.0	7411	OC-Light (OC Light)
Nakama, 1999[178] Fair Japan	NR	Asymptomatic; participating in a medical check-up for colorectal cancer; 40 years and older	NR	NR	CRC: 0.39 AA: NR	4611	Monohaem (Monohaem)

Abbreviations: AA = advanced adenoma; BliTz = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung; CRC = colorectal cancer; FIT = fecal immunochemical test; N = number; NR = not reported; US = United States.

Table 16. Qualitative Fecal Immunochemical Test Summary of Diagnostic Accuracy (All Colonoscopy Followup)

Author, Year Quality Country	Test Name (Family*)	Number of Stools Sampled	Cutoff, ng Hb/mL buffer	Cutoff, ug Hb/g feces	N	Prevalence (n, %)	CRC Sensitivity (95% CI) Specificity (95% CI)	Advanced Adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
Levy, 2014[174] Fair US	Clearview iFOB complete (cassette) [Clearview (cassette)]	NR	50	6*	308	CRC: NR AA: NR	NR	NR	13 (2, 41) 86 (82, 90)
	clearview ULTRA iFOB (test strip) [Clearview (test strip)]	NR	50	50*	44	CRC: NR AA: NR	NR	NR	20 (1, 72) 92 (79, 98)
	OC-Light	NR	50	10*	217	CRC: NR AA: NR	NR	NR	5 (0, 26) 99 (96, 100)
	QuickVue	NR	50	50*	52	CRC: NR AA: NR	NR	NR	50 (1, 99) 88 (76, 95)
Chiu, 2013[162] Good Taiwan	OC-Light	1	50	10	18296	CRC: 28 (0.15) AA: 632 (3.5)	78.6 (61.0, 90.5) 92.8 (92.4, 93.2)	28.0 (24.6, 31.6) 93.5 (93.1, 93.9	30.2 (26.7, 33.7) 93.6 (93.2, 93.9)
Ng, 2013[162,180] Fair Hong Kong	Hemosure	NR	50*	50	4539	CRC: 22 (0.48) AA: 197 (4.3)	54.5 (32.3, 73.7) 89.4 (88.4, 90.2)	37.1 (30.5, 43.9) 90.6 (89.7, 91.4	38.8 (32.5, 45.4) 90.6 (89.7, 91.4)
Brenner, 2010[186] (BliTz) Good Germany	Bionexia FOBplus	NR	40*	NR	1319	CRC: 11 (0.8) AA: 130 (9.8)	NR	52.3 (43.8, 60.8) 79.6 (77.3, 81.9	56.0 (47.8, 64.0) 79.6 (77.3, 81.9)
	Bionexia Hb/Hp Complex	NR	25*	NR	1328	CRC: 11 (0.8) AA: 130 (9.8)	NR	71.5 (63.4, 78.8) 56.3 (53.5, 59.2	73.4 (65.2, 80.5) 56.3 (53.5, 59.2)
	FOB advanced	NR	50*	NR	1330	CRC: 11 (0.8) AA: 130 (9.8)	NR	26.9 (19.9, 35.0) 91.3 (89.6, 92.8	30.5 (23.4, 38.4) 91.3 (89.6, 92.8)
	immoCARE-C	NR	50*	30*	1319	CRC: 11 (0.8) AA: 130 (9.8)	NR	25.4 (18.5, 33.3) 96.4 (95.2, 97.3	29.8 (22.7, 37.7) 96.4 (95.2, 97.3)
	PreventID CC	NR	10*	NR	1330	CRC: 11 (0.8) AA: 130 (9.8)	NR	49.2 (40.7, 57.8) 81.3 (79.0, 83.5	53.2 (45.0, 61.3) 81.3 (79.0, 83.5)

Table 16. Qualitative Fecal Immunochemical Test Summary of Diagnostic Accuracy (All Colonoscopy Followup)

Author, Year Quality Country	Test Name (Family*)	Number of Stools Sampled	Cutoff, ng Hb/mL buffer	Cutoff, ug Hb/g feces	N	Prevalence (n, %)	CRC Sensitivity (95% CI) Specificity (95% CI)	Advanced Adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
Cheng, 2002[160] Fair Taiwan	QuickVue iFOB [QuickVue]	NR	50*	50*	1330	CRC: 11 (0.8) AA: 130 (9.8)	NR	56.2 (47.6, 64.5) 67.9 (65.2, 70.5	59.6 (51.3, 67.4) 69.6 (66.9, 72.1)
	OC-Light	NR	50*	10*	7411	CRC: 16 (0.22) AA: 77 (1.0)	87.5 (65.6, 97.3) 91.0 (90.3, 91.6)	40.3 (29.8, 51.4) 91.3 (90.6, 91.9	48.4 (38.4, 58.5) 91.3 (90.6, 91.9)
Nakama, 1999[178] Fair Japan	Monohaem	1	NR	~1000*	4611	CRC: 18 (0.39) AA: NR	55.6 (33.2, 76.2) 96.7 (96.1, 97.2)	NR	35.2 (25.9, 45.3) 97.1 (96.6, 97.6)
		2	NR	~1000*	4611	CRC: 18 (0.39) AA: NR	83.3 (61.9, 95.1) 95.3 (94.6, 95.9)	NR	57.1 (46.9, 67.0) 96.0 (95.4, 96.6)
		3	NR	~1000*	4611	CRC: 18 (0.39) AA: NR	88.9 (68.9, 97.6) 93.1 (92.4, 93.8)	NR	61.5 (51.3, 71.0) 93.9 (93.2, 94.6)

* Refer to Table 14 for source of cutoff
† If different than the test name

Abbreviations: AA = advanced adenoma; BliTz = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung; CI = confidence interval; CRC = colorectal cancer; Hb = hemoglobin; ml = milliliter; n = number; ng = nanogram; NR = not reported; µg = microgram.

Table 17. Quantitative Fecal Immunochemical Tests (With or Without Fecal DNA) Summary of Diagnostic Accuracy (All Colonoscopy Followup)

Author, Year Quality Country	Test Name [Family]†	Number of Stools Sampled	Cutoff, ng Hb/mL buffer	Cutoff, ug Hb/g feces	N	Prevalence (n, %)	CRC Sensitivity (95% CI) Specificity (95% CI)	Advanced Adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
Hernandez, 2014[166] Good Spain	OC-Sensor [OC (FIT-CHEK)]	1	50	10	779	CRC: 5 (0.6) AA: 92 (11.8)	100 (62.1, 100) 92.0 (89.9, 93.7)	NR	35.0 (26.1, 44.9) 95.2 (93.4, 96.6)
			100	20	779	CRC: 5 (0.6) AA: 92 (11.8)	100 (62.1, 100) 93.5 (91.6, 95.1)	NR	32.0 (23.3, 41.7) 96.5 (94.9, 97.7)
		2	50	10	779	CRC: 5 (0.6) AA: 92 (11.8)	100 (62.1, 100) 87.6 (85.1, 89.8)	NR	42.3 (32.8, 52.2) 91.2 (88.9, 93.2)
			100	20	779	CRC: 5 (0.6) AA: 92 (11.8)	100 (62.1, 100) 90.0 (87.8, 92.0)	NR	37.1 (28.0, 47.0) 93.3 (91.2, 95.0)
Imperiale, 2014[167] Fair US; Canada	OC FIT-CHEK (assumed automated version, based on cutoff value)	1	100	20*	9989	CRC: 65 (0.65) AA: 658 (6.9)	73.8 (62.3, 83.3) 93.4 (92.9, 93.9)	23.8 (20.8, 26.9) 94.8 (94.4, 95.3	27.7 (24.8, 30.9) 94.8 (94.4, 95.3)
	Cologuard (mtsDNA)	1	NR	NR	9989	CRC: 65 (0.65) AA: 658 (6.9)	92.3 (84.0, 97.0) 84.4 (83.6, 85.1)	42.4 (38.9, 45.9) 86.6 (85.9, 87.2	46.4 (43.0, 49.8) 86.6 (85.9, 87.2)
Lee, 2014[172] Good South Korea	Hemo Techt NS-Plus C system	NR	NR	6.3	NR	CRC: NR (NR) AA: NR (NR)	85.7 (57.2, 98.2) 94.0 (92.6, 95.2)	NR	76.2 (52.8, 91.8) 94.3 (92.9, 95.4)
Brenner, 2013[157] (BliTz) Good Germany	OC FIT-CHEK (using the OC-Sensor Diana automated analyzer)	1	100	20	2220	CRC: 15 (0.67) AA: 207 (9.3)	73.3 (48.3, 90.2) 95.5 (94.6, 96.3)	22.2 (17.0, 28.2) 97.4 (96.6, 98.0	25.7 (20.3, 31.7) 97.4 (96.6, 98.0)
	RIDASCREEN Hemoglobin	1	NR	2	2220	CRC: 15 (0.67) AA: 207 (9.3)	60.0 (35.3, 81.2) 95.4 (94.5, 96.2)	20.8 (15.7, 26.7) 97.1 (96.3, 97.7	23.4 (18.2, 29.3) 97.1 (96.3, 97.7)
	RIDASCREEN Hemoglobin-Haptoglobin Complex	1	NR	2	2235	CRC: 15 (0.67) AA: 207 (9.3)	53.3 (29.4, 76.1) 95.4 (94.5, 96.2)	17.9 (13.1, 23.5) 96.8 (95.9, 97.5	20.3 (15.4, 25.9) 96.8 (95.9, 97.5)

Table 17. Quantitative Fecal Immunochemical Tests (With or Without Fecal DNA) Summary of Diagnostic Accuracy (All Colonoscopy Followup)

Author, Year Quality Country	Test Name [Family]†	Number of Stools Sampled	Cutoff, ng Hb/mL buffer	Cutoff, ug Hb/g feces	N	Prevalence (n, %)	CRC Sensitivity (95% CI) Specificity (95% CI)	Advanced Adenoma Sensitivity (95% CI) Specificity (95% CI)	Advanced Neoplasia Sensitivity (95% CI) Specificity (95% CI)
de Wijkerslooth, 2012[164] Good The Netherlands	OC-Sensor (automated, inferred from text) [OC (FIT-CHEK)]	1	50	10	1256	CRC: 8 (0.64) AA: 111 (8.8)	87.5 (54.6, 98.6) 90.9 (89.2, 92.4)	34.2 (25.9, 43.4) 93.3 (91.8, 94.6	37.8 (29.5, 46.7) 93.3 (91.8, 94.6)
			100	20	1256	CRC: 8 (0.64) AA: 111 (8.8)	75.0 (40.8, 94.4) 94.8 (93.4, 95.9)	27.9 (20.2, 36.8) 97.0 (95.9, 97.9)	31.1 (23.3, 39.8) 97.0 (95.9, 97.9)
Park, 2010[181] Fair South Korea	OC-MICRO [OC (FIT-CHEK)]	3	50	10*	770	CRC: 13 (1.7) AA: 59 (7.7)	92.3 (69.3, 99.2) 87.2 (84.7, 89.4)	44.1 (31.9, 56.8) 89.8 (87.4, 91.9	52.8 (41.3, 64.0) 89.8 (87.4, 91.9)
			100 (other cutoffs available: 50, 75, 125, 150)	20*	757	CRC: 13 (1.7) AA: 59 (7.7)	92.3 (69.3, 99.2) 90.1 (87.8, 92.1)	33.9 (22.8, 46.5) 92.1 (89.9, 94.0	44.4 (33.4, 56.0) 92.1 (89.9, 94.0)
Graser, 2009[49] Good Germany	FOB Gold	2	14	NR	285	CRC: 1 (0.33) AA: 24 (8.4)	100.0 (14.7, 100.0) NR	29.2 (14.1, 48.9) 85.8 (81.1, 89.6	32.0 (16.4, 51.5) 85.8 (81.1, 89.6)
Morikawa, 2005[177] Fair Japan	Magstream 1000/Hem SP [Magstream/ HemeSelect]	1	20	100-200	21805	CRC: 79 (0.4) AA: 648 (3.0)	65.8 (54.9, 75.6) 94.6 (94.3, 94.9)	NR	27.1 (24.0, 30.4) 95.1 (94.8, 95.4)
Sohn, 2005[182] Fair Korea	OC-hemodia, using an OC-sensor analyzer [OC (Hemodia)]	1	100	20*	3794	CRC: 12 (0.3) AA: 67 (1.8)	25.0	6.0	2.4 (1.3, 3.9) 98.8 (98.4, 99.2)

* Refer to Table 14 for source of cutoff
† If different than the test name

Abbreviations: AA = advanced adenoma; AN = advanced neoplasia; BliTz = Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung; CI = confidence interval; CRC = colorectal cancer; g = gram; Hb = hemoglobin; ml = milliliter; ng = nanogram; NR = not reported; µg = microgram.

Table 18. Fecal Immunochemical Test Study Characteristics, Differential/Registry Followup (Ordered Reverse Chronologically)

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Differential Followup	Mean or Median Age (years)	% Female	Prevalence (%)	N Analyzed	Test Name [Family Name]†
Chiang, 2014[161] Fair Taiwan	Nationwide screening program	50-69 years; living in Taiwan	Colonoscopy or FS with barium enema for FIT+. All participants were linked to the Taiwan Cancer Registry	Mean 58	61.6	CRC: 2493 (0.3) AA: NR	3365	Monohaem
Chen, 2011[159] Fair Taiwan	Community-based colorectal cancer screening program	40-69 years	Colonoscopy for FOBT+; repeat screening and/or national cancer registry for FOBT-; staggered entry, minimum 1 year followup	52.10	63.1	CRC: 150 (0.32) AA: NR	46,355	OC-Sensor (assumed automated based on reported cutoff) [OC (FIT-CHEK)]
Levi, 2011[173] Fair Israel	9 primary care clinics	Asymptomatic people; 50-75 years; patients of selected 9 primary care clinics of Clalit Health Services	Colonoscopy for FOBT+; registry followup for 2 years after the last FOBT was performed.	NR	NR	CRC: 19 (0.55) AA: NR	1204	OC-Micro [OC (FIT-CHEK)]
Allison, 2007*[155] Fair US	3 Northern California Kaiser Permanente medical centers	Kaiser Foundation Health Plan members; ≥ 50 years	Colonoscopy (FOBT/FIT+); FS (FOBT/FIT-) with colonoscopy recommended for those with advanced colorectal neoplasms; at least 2 year followup using administrative databases for all patients	NR	52.5	CRC: 14 (0.3) AA: 128 (2.7)	5356	FlexSure OBT [Hemoccult ICT]
Castiglione, 2007[158] Fair Italy	Population-based screening program	Ages 50-70; living in 19 municipalities in the Province of Florence; attending FOBT screening during stated dates	FIT-positives were offered colonoscopy; FIT-negatives with interval cancers in following 2 years were identified in a regional cancer registry	NR	52.2	CRC: 83 (0.30) AA: 219 (0.80)	27,503	OC-Hemodia, developed with OC-Sensor instrument
Launoy, 2005[171] Fair France	General practitioner and occupational physician practices	Living in Cotentin; 50-74 years; seeing their physician for a regular consultation	All positive tests were invited to undergo colonoscopy; all negatives were followed up using a registry for 2 years (80% of cases were followed up for 2 years; 93% for 18 months; 100% with 12 months)	NR	56.9	CRC: 28 (0.38) AA: NR	7421	Magstream 1000 [Magstream/ HemeSelect]

Table 18. Fecal Immunochemical Test Study Characteristics, Differential/Registry Followup (Ordered Reverse Chronologically)

Author, Year Quality Country	Recruitment Setting	Inclusion Criteria	Differential Followup	Mean or Median Age (years)	% Female	Prevalence (%)	N Analyzed	Test Name [Family Name]†
Allison, 1996[156] Fair US	Single Kaiser Permanente medical center	50 years of age or older; scheduled for a personal health appraisal	FS for all positive tests. If FS found a neoplasm, then referred to colonoscopy. If FS was negative, FOBT screen was repeated at 6 and 12 mo. Colonoscopy to anyone wishing to undergo one. Computerized databases were searched for two years after screening for interval CRC.	NR	59.3	CRC: 35 (0.43) AA: 107 (1.3)	7493	HemeSelect [Magstream/ HemeSelect]
Itoh, 1996[168] Fair Japan	Worker colorectal cancer screening program	Aged 40 or above; workers at a Japanese corporation	Colonoscopy if test positive. If a target disease was detected or suspected a barium enema was given on the same day. 2-year followup using insurance claims for missed cancers.	NR	13.9	CRC: 89 (0.32) AA: NR	27,860	OC-Hemodia (automated)
Nakama, 1996[179] Fair Japan	Community screening in Nagano prefecture	Over 40 years of age	Colonoscopy (barium enema in 2% of cases) for FIT+; registry followup for 3 years	NR	NR	CRC: 14 (0.42) AA: NR	3365	Monohaem

* Note that Allison, 2007[155] only reports distal lesions and that data is not presented in the following tables.
† If different than the test name

Abbreviations: AA = advanced adenomas; CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; N = number; NR = not reported; US = United States.

Table 19. Qualitative Fecal Immunochemical Tests Summary of Diagnostic Accuracy, Differential/Registry Followup

Author, Year Quality Country	Test Name [Family]†	Number of Samples	Cutoff, ng Hb/mL buffer	Cutoff, µg Hb/g feces	N Analyzed	CRC Cases	Sensitivity (95% CI)	Specificity (95% CI)
Castiglione, 2007[158] Fair Italy	OC – Hemodia, developed with OC-Sensor instrument [OC (Hemodia)]	NR	100	20*	27,503	83	80.7 (70.6, 88.6)	96.2 (96.0, 96.5)
Allison, 1996[156] Fair US	HemeSelect [Magstream/ HemeSelect]	3	Erythrocyte agglutination at a sample dilution of 1:8	300*	7493	32	68.8 (50.0, 83.9)	94.4 (93.8, 94.9)
Nakama, 1996[179] Fair Japan	Monohaem (1 year followup)	1	NR	20*	3365	11	90.9 (58.7, 99.8)	95.6 (94.9, 96.3)
	Monohaem (2 year followup)	1	NR	20*	3365	12	83.3 (51.6, 97.9)	95.6 (94.9, 96.3)
	Monohaem (3 year followup)	1	NR	20*	3365	14	71.4 (41.9, 91.6)	95.6 (94.9, 96.3)

* Refer to Table 14 for source of cutoff
† If different than the test name

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; g = gram; Hb = hemoglobin; mL = milliliter; n = number; ng = nanogram; NR = not reported; µg = microgram; US = United States.

Table 20. Quantitative Fecal Immunochemical Tests Summary of Diagnostic Accuracy, Differential/Registry Followup

Author, Year Quality Country	Test Name [Family]†	Number of Stool Samples	Cutoff, ng Hb/mL buffer	Cutoff, ug Hb/g feces	N Analyzed	CRC Cases	Sensitivity (95% CI)	Specficity (95% CI)
Chiang, 2014 Fair Taiwan	OC-Sensor [OC (FIT-CHEK)]	1	100	20	747,076	1546	77.1 (75.2, 78.9)	96.4 (96.4, 96.5)
Chen, 2011[159] Fair Taiwan	OC-Sensor (assumed automated based on reported cutoff) [OC (FIT-CHEK)]	1	100	20*	46,355	202	45.0 (38.3, 51.9)	95.8 (95.6, 96.0)
Levi, 2011[173] Fair Israel	OC-Micro [OC (FIT-CHEK)]	3	70	NR	1204	6	100.0 (54.1, 100.0)	87.7 (85.7, 89.5)
Launoy, 2005[171] Fair France	Magstream 1000 [Magstream/ HemeSelect]	2	20	100-200*	7421	28	85.7 (67.3, 96.0)	94.4 (93.9, 95.0)
Itoh, 1996[168] Fair Japan	OC-Hemodia (automated)	1	50	10*	27,860	89	86.5 (77.6, 92.8)	94.9 (94.6, 95.2)

* Refer to Table 14 for source of cutoff
† If different than the test name

Abbreviations: CI = confidence interval; CRC = colorectal cancer; FIT = fecal immunochemical test; g = gram; Hb = hemoglobin; mL = milliliter; N = number; ng = nanogram; NR = not reported; ug = microgram.

Table 21. Stool-Based DNA Test Summary of Diagnostic Accuracy

Author, year Quality Country	CRC prevalence (%, n/n)	N analyzed Age Female (%)	Test	Test positivity	Completion rate	Sensitivity (95% CI)	Specificity (95% CI)	Limitations
Ahlquist, 2008[185] SDT-1: Fair SDT-2: Poor	0.5% (19/3764)	2497 60 54	SDT-1 (prototype sDNA version 1.0)	5.2% (129/2497)	98.2% (3766/3834)	CRC: 25 (5, 57) Advanced adenomas: 19 (5, 42) Advanced neoplasia: 20 (14, 26)	CRC: 95 (94, 96) Advanced adenomas: NA Advanced neoplasia: 96 (95, 97)	Small sample size for SDT-2 with limited sampling of controls, authors tried to weight sensitivity for proportion of screen relevant neoplasia in the entire population, but did not presented weighted adjustment for all outcomes
		217 66 50	SDT-2 (sDNA version 2.0)	35% (77/217)	98.2% (3766/3834)	CRC: 58 (36, 80)* Advanced adenomas: 39 (26, 52)* Advanced neoplasia: 40 (32, 49)	CRC: NR Advanced adenomas: NR Advanced neoplasia: NR	Poor precision around outcome measures Subset of patients did not get instructions on dietary restrictions required for FOBT, very low sensitivities reported for FOBT which are not consistent with best known estimates
Haug, 2007[190] Poor	1.6% (NR)	441 NR NR	*KRAS* testing	8% (70/875)	NR	CRC: 0 (NR) Advanced adenomas: 0 (NR)	CRC: NR Advanced adenomas: NR	Application of reference standard was opportunistic (patient who got colonoscopy were referred for colonoscopy) Average time between index and reference tests not presented, patients had to have colonoscopy within 2 years
Imperiale, 2004[192] Fair	0.7% (31/4404)	2507 70 55	SDT-1 (prototype sDNA version 1.0)	8.2% (205/2505)	88.3% (4845/5486)	CRC: 51.6 (34.8, 68.0) Advanced adenomas: 15.1 (12.0, 19.0) Advanced neoplasia: 17.7 (NR)	CRC: 92.8 (92.0, -93.5)* Advanced adenomas: Not calculated Advanced neoplasia: 93.6% (92.9, 94.3)*	Analysis focused on subset of patients, only basic demographic data presented detailing differences between full cohort and analyzed subset Poor precision around outcome measures Very low sensitivities reported for FOBT which are not consistent with best known estimates
			Hemoccult II	5.8% (146/2505)	92.2% (5060/5486)	CRC: 12.9 (5.1, 28.9) Advanced adenomas: 10.7% (8.0 to 14.1%) Advanced neoplasia: 10.8% (NR)	CRC: 94.6 (94.0, 95.3)* Advanced adenomas: Not calculated Advanced neoplasia: 95.2% (94.695.8%)*	

*Weighted sensitivities and CI calculated

Abbreviations: CRC = Colorectal cancer; NA = not applicable; NR = not reported; SDT-1 = sDNA version 1.0; SDT-2 = sDNA version 2.0.

Table 22. Included Studies for Key Question 3*

Colonoscopy			FS		CTC		FOBT Program	FS Program
Adeyemo, 2014[209]	**Sagawa, 2012**[268]	**Warren, 2009**[280]	**Kim, 2013**[243]	**Wallace, 1999**[279]	**Zafar, 2014**[282]	**Flicker, 2008**[229]	**Parente, 2013**[258]	**Schoen, 2012**[122] **(PLCO)**
Bielawska, 2014[215]	**Stoop, 2012**[128] **(COCOS)**	**Kang, 2008**[240]	**Tam, 2013**[276]	**Atkin, 1998**[290]	**Fletcher, 2013**[165]	**Johnson, 2008**[50] **(ACRIN)** Johnson,2012[193]	**Quintero, 2012**[120] **(COLONPREV)**	**Segnan, 2005**[126] **(SCORE III)**
Blotiere, 2014[216]	**Suissa, 2012**[275]	**Johnson, 2008**[50] **(ACRIN)** Johnson,2012[193]	**Schoen, 2012**[122] **(PLCO)**	**Verne, 1998**[131]	**Iafrate, 2013**[237]	**Kim, 2008**[244]	**Dancourt, 2008**[225]	**Gondal, 2003**[283] **(NORCCAP)** Hoff, 2009[284]
Layton, 2014[248]	**Zalis, 2012**[183]	**Mansmann, 2008**[254]	**Senore, 2011**[269] **(SCORE III)**	**Brevinge, 1997**[111]	**Lefere, 2013**[51]	**Kim, 2008**[170]	**MACS group, 2006**[255]	**Atkin, 2002**[133] **(UKFSST)**
Zafar, 2014[282]	**Ferlitsch, 2011**[48]	**Rabeneck, 2008**[265]	**Viiala, 2007**[278]		**Cash, 2012**[218]	**Pickhardt, 2008**[288]	**Faivre, 2004**[113]	**Segnan, 2002**[149] **(SCORE)**
Adler, 2013[210]	**Loffeld, 2011**[251]	**Kim 2007**[242]	**MACS group, 2006**[255]		**Durbin, 2012**[227]	**Kim, 2007**[242]	**Kewenter, 1996**[405] **(Göteborg)** Lindholm, 2008[118]	**Rasmussen, 1999**[121]
Castro, 2013[219]	**Lorenzo-Zungia, 2010**[252]	**Ko, 2007**[291]	**Segnan, 2005**[126] **(SCORE II)**		**Stoop, 2012**[128] **(COCOS)**	**Pickhardt, 2007**[261]	**Mandel, 1993**[147] **(Minnesota)** Shaukat, 2013[127]	
Chiu, 2013[162]	**Xirasagar, 2010**[281]	**Levin, 2006**[249]	**Gondal, 2003**[283] Hoff, 2009[284]		**Zalis, 2012**[183]	**MACS group, 2006**[255]		
Chukmaitov, 2013[221]	**Arora, 2009**[212]	**MACS group, 2006**[255]	**Atkin, 2002**[133] **(UKFSST)**		**Macari, 2011**[253]	**Pickhardt, 2006**[262]		
Cooper, 2013[222]	**Bair, 2009**[213]	**Rathgaber, 2006**[266]	**Jain, 2002**[238]		**O'Connor, 2011**[257]	**Sosna, 2006**[272]		
Dominitz, 2013[226]	**Berhane, 2009**[214]	**Strul, 2006**[274]	**Levin, 2002**[250]		**Pickhardt, 2011**[259]	**Chin, 2005**[220]		
Hamdani, 2013[232]	**Bokemeyer, 2009**[217]	**Cotterhill, 2005**[223]	**Segnan, 2002**[149] **(SCORE)**		**Kim, 2010**[285]	**Edwards, 2004**[228]		
Kim, 2013[243]	**Crispin, 2009**[224]	**Korman, 2003**[247]	**Hoff, 2001**[235] **(Telemark Polyp Study I)** Thiis-Evensen, 1999[17] Hoff, 1996[33]		**Pickhardt, 2010**[260]	**Ginnerup, 2003**[230]		
Ng, 2013[180]	**Hsieh, 2009**[236]	**Cheng, 2002**[160]			**Veerappan, 2010**[277]	**Gluecker, 2003**[231]		
Stock, 2013[273]	**Kamath, 2009**[239]	**Nelson, 2002**[256]			**Graser, 2009**[49]	**Hara, 2000**[233]		
Tam, 2013[276]	**Quallick, 2009**[264]	**Sieg, 2001**[270]			**An, 2008**[211]			
Ho, 2012[234]	**Singh, 2009**[271]							
Pox, 2012[263]								
Quintero, 2012[120] **(COLONPREV)**								
Rutter, 2012[267]								

* No articles included for harms of m*SEPT9* or mtsDNA

Abbreviations: ACRIN = American College of Radiology Imaging Network National CT Colonography Trial; COCOS = COlonoscopy or COlonography for Screening; MACS = Multicentre Austrailian Colorectal-neoplasia Screening; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial.

Table 23. Key Question 3: Summary Table of Serious Adverse Events From Colonoscopy in Screening Programs

Screening Strategy	Study Quality	Recruited Population Country	Study Design Followup	Test Positivity, % Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
gFOBT/FIT	Parente, 2013[258] Fair	FIT positives Italy	Prospective NR	6.2 (round 1); 5.8 (round 2) 4373	2 (0.05)	5 (0.1)	NR	Hospitalization††: 5 (0.1)
	Quintero, 2012[120] Fair	FIT positives Spain	Prospective NR	7.2 587	0 (0)	8 (1.4)	NR	Hypotension or bradycardia: 2 (0.3)
	Dancourt, 2008[225] Fair	FOBT or FIT positives France	Prospective NR	9.0 1205	0 (0)	0 (0)	NR	NR
	MACS group, 2006[255] Fair	FIT positives Australia	Prospective 4 weeks	3.2 4	0 (0)	0 (0)	0 (0)	0 (0)
	Faivre, 2004[113] Fair	FOBT positives France	Prospective NR	1.5 1298	0 (0)	0 (0)	NR	NR
	Kewenter, 1996[118,405] Fair	FOBT positives (FS) or those with an adenoma above the sigmoid (colo) Sweden	Prospective NR	4.1 FS: 2108 Colo: 190	FS: 3 (0.1) Colo: 2 (1.1)	FS: 0 (0) Colo: 1 (0.5)	NR	NR
	Mandel, 1993[127,147] Good	FOBT positives US	Prospective NR	2.4 (unhydrated slides) 9.8 (hydrated slides) 12246	4 (0.03)	11 (0.09)	NR	NR
FS†	Schoen, 2012[122] PLCO Fair	FS positives€ US	Prospective NR	28 17,672¥	19 (0.1)	NR	NR	NR
	Segnan, 2005[126]† SCORE II Fair	FS positives[θ] Italy	Prospective NR	7.6 332	NR	1 (0.3)	NR	Hospitalization††: 1

Table 23. Key Question 3: Summary Table of Serious Adverse Events From Colonoscopy in Screening Programs

Screening Strategy	Study Quality	Recruited Population Country	Study Design Followup	Test Positivity, % Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Gondal, 2003[283,284] NORCCAP Fair	FS or FS/FIT positives[α] Norway	Prospective NR	20.4 (FS or FS/FIT) 2524	6 (0.2)	4 (0.2)	NR	Hospitalization††: 4 (0.2) Syncope: 24 (1.0)
	Atkin, 2002[133] Fair	Patients with polyps meeting high-risk criteria‡ UK	Prospective 30 days	5.3 2051	4 (0.2)	9 (0.4)	1 (0.05)	Hospitalization††: 9
	Segnan, 2002[149] SCORE Fair	FS positivesδ Italy	Prospective 30 days	8.4 775	1 (0.1)	1 (0.1)	NR	0 (0)
	Rasmussen, 1999[121] Fair	FS or gFOBT positives£ Denmark	Prospective NR	18-25 (FS); 1.4-4.9 (gFOBT) 502	0 (0)	0 (0)	0 (0)	0 (0)

* Study has a comparison group
† Harms from the screening FS reported in Table 24
‡ High risk polyps included any of: diameter 1 cm or larger; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignancy; and 20 or more hyperplastic polyps above the distal rectum.
α FS positive includes any polyp ≥10 mm or a finding of any bioptically verified neoplasia, irrespective of its size
¥ exams, not patients
€ FS positive includes detection of a polyp or mass
δ FS positives includes those who had one distal polyp larger than 5 mm, or inadequate bowel preparation and at least one polyp, or invasive colorectal cancer. In a few cases the referral to colonoscopy was made by the endoscopist, based on his or her clinical judgment.
£ Persons with possible neoplasia detected at FS (all polyps >3 mm in diameter, and/or mucosal ulcerations, and/or stricturing carcinoma; persons with a positive Hemoccult II test
θ Subjects with polyps that were 10 mm or larger, as well as those who had " high-risk " polyps smaller than 10 mm (i.e., patients whose polyps had any of the following features at histologic examination: more than two adenomas, a villous component of more than 20%, or high-grade dysplasia) were referred for colonoscopy. Subjects who had inadequate bowel preparation were also referred for colonoscopy if at least one polyp was identified during sigmoidoscopy.
†† Hospitalizations are not mutually exclusive from the perforation and serious bleeding patients

Abbreviations: FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; FOBT = fecal occult blood test; gFOBT = guaiac fecal occult blood test; MACS = Multicentre Austrailian Colorectal-neoplasia Screening; n = number; NORCCAP = Norwegian Colorectal Cancer Prevention; NR = not reported; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UK = United Kingdom; US = United States; UKFSST = UK Flexible Sigmoidoscopy Screening Trial.

Table 24. Key Question 3: Summary Table of Serious Adverse Events From Screening Flexible Sigmoidoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Sigmoidosco-pies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
Prospective	Schoen, 2012[122]	Screening	NR	NR	NR	67,071	3 (0.004)	NR	NR	NR
		US	NR	50						
	Fair									
	Senore, 2011[269]	Screening	NR	NR	30 days	1502	0 (0)	12 (0.8)ð	NR	Hospitalization: 16 ED: 2
		Italy	NR	49						Other: 18 (CVD, hernia, severe pain, hypotension)
	Fair									
	MACS group, 2006[255]	Screening	NR	NR	4 weeks	52	0 (0)	0 (0)	NR	0 (0)
		Australia	NR	49						
	Fair									
	Segnan, 2005[126]	Screening	NR	NR	NR	4466	NR	0 (0)	NR	Syncope: 1
		Italy	87 (to distal)	52‡						
	Fair									
	Gondal, 2003[283,284]	Screening	NR	NR	NR	12,960	0 (0)	0 (0)	NR	Syncope: 26 Other: 1 (PE)
		Norway	NR	66						
	Fair									
	Atkin, 2002[133]	Screening	NR	NR	30 days	40,332	1 (0.002)	12 (0.03)	6 (0.01)	Hospitalization: 12 MI: 2
		UK	NR	50						Syncope: 95 Other: 1 (PE)
	Fair									
	Segnan, 2002[149]	Screening	NR	NR	30 days	9911	1 (0.01)	0 (0)	NR	Other: 4 (colitis, seizure)
		Italy	84 (to distal)	50						
	Fair									
	Hoff, 2001[17,33,235]	Screening	NR	NR	NR	355	0 (0)	0 (0)	0 (0)	Hospitalization: 1** Other: 0
		Norway	NR	NR						
	Fair									
	Rasmussen, 1999[121]	Screening	15	NR	NR	2235	0 (0)	0 (0)	0 (0)	Other: 0 (0)
		Denmark	85 (60 cm)	NR						
	Fair									
	Wallace, 1999[279]	US	18	59	NR	3701	0 (0)	0 (0)	0 (0)	NR
		Screening	77 (50 cm)	50						
	Fair									

Table 24. Key Question 3: Summary Table of Serious Adverse Events From Screening Flexible Sigmoidoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Sigmoidoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Atkin, 1998[290]	Screening	NR	NR	NR	1285	NR	40 (3.1)δ	1 (0.08)	Hospitalization: 1 MI: 1
	Fair	UK	NR	NR						Syncope: 1 Other†: 1 (severe diarrhea)
	Verne, 1998[131]	Screening	1	NR	NR	1116	0 (0)	0 (0)	NR	Other: 0 (0)
	Fair	UK	NR	49						
	Brevinge, 1997[111]	Screening	NR	NR	NR	1431	NR	1 (0.07)	NR	Other: 1 (diverticulitis)
	Fair	Sweden	NR	49						
Retrospective	Kim, 2013[243]	Mixed (including symptomatic)	NR	NR	NR	20,653	1 (0.005)	NR	NR	NR
	Fair	South Korea	NR	63						
	Tam, 2013[276]	Screening	NR	NR	NR	46,158	1 (0.002)	NR	5 (0.004)β	Other: 4 (0.003) ("long-term complications")β
	Fair	US	NR	NR						
	Viiala, 2007[278]	Screening	NR	60	NR	3402	0 (0)	0 (0)	NR	NR
	Fair	Australia	73 (50 cm)	41						
	Jain, 2002[238]	Screening	NR	NR	NR	5017	0 (0)	0 (0)	0 (0)	NR
	Fair	US	NR	NR						
	Levin, 2002[250]	Screening	NR	61	4 weeks	109,534	2 (0.002)	2 (0.002)	10 (0.009)	MI: 33 Other†: 3 (GI serious adverse events)
	Fair	US	NR	49						

* Study has a comparison group
** Unclear if this hospitalization is from the bowel prep for FS or colonoscopy
† Other serious adverse events are mutually exclusive from perforation, bleeding, MI, syncope
‡ All groups screened
δ Unspecified bleeding
β For those with perforations only (n=26), includes patients with perforations from mixed population colonoscopy as well as screening FS (n=132,259).
Abbreviations: cm = centimeters; CVD = cardiovascular disease; ED = emergency department; FS = flexible sigmoidoscopy; GI = gastrointestinal; MACS = Multicentre Austrailian Colorectal-neoplasia Screening; MI = myocardial infarction; n = number; PE = pulmonary embolism; UK = United Kingdom; US = United States.

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
Prospective	Adler, 2013[210] Fair	Screening Germany	21 98	64 53	NR	12,134	NR	NR	NR	NR***
	Castro, 2013[219] Fair	Mixed (including symptomatic) US	NR NR	56 74	30 days	3355	3 (0.09)	1 (0.03)	NR	Other: 4 (severe pain, cardiopulmonary event)
	Chiu, 2013[162] Fair	Screening Taiwan	7 NR	60 41	NR	18296	0 (0)	NR	NR	NR
	Ng, 2013[180] Fair	Screening Hong Kong	NR NR	58 55	NR	4539	0 (0)	0 (0)	NR	NR
	Pox, 2012[263] Fair	Screening Germany	>2100 NR	65 56	NR	2,821,392	439 (0.02)	573 (0.02)	2 (0.00007)	Other: 128 (cardiopulmonary and "other major")
	Quintero, 2012[120] COLONPREV Fair	Screening Spain	NR NR	NR NR	NR	4953	1 (0.02)	12 (0.2)	NR	Other: 11 (cardiopulmonary event)
	Stoop, 2012[128] COCOS Fair	Screening The Netherlands	5 98	61 49	4 weeks	1276	0 (0)	2 (0.2)	1 (0.08)**	Other: 3 (infection)
	Suissa, 2012[275] Fair	Screening Israel	NR NR	58 NR	NR	839	0 (0)	0 (0)	NR	NR
	Zalis, 2012[183] Fair	Screening US	NR NR	60 47	NR	618	0 (0)	0 (0)	NR	NR
	Ferlitsch, 2011[48] Fair	Screening Austria	NR 96	NR 51	NR	44,350	3 (0.007)	54 (0.1)€	0 (0)	Other: 111 ("clinically relevant complication")

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Loffeld, 2011[251] Fair	Mixed (including symptomatic) The Netherlands	NR NR	NR NR	NR	19,135	26 (0.1)	NR	NR	NR
	Senore, 2011[269] SCORE III Fair	Screening Italy	NR NR	NR 49	30 days	1198	0 (0)	15 (1.2) €	NR	Hospitalization: 11 ED: 2 Other: 7 (CVD, hernia, severe pain, GI symptom)
	Ko, 2010[245] Fair	Mixed (excluding symptomatic) US	NR NR	NR 45	30 days	21,375	4 (0.02)	34 (0.2)	3 (0.01)	MI: 12 (includes angina) Other: 27 (infection, CVA, severe pain)
	Bair, 2009[213] Fair	Screening Canada	9 99	57 52	NR	3741	1 (0.03)	2 (0.05)	NR	NR
	Bokemeyer, 2009[217] Fair	Screening Germany	280 NR	NR 56	NR	269,144	55 (0.02)	442 (0.16)	NR	Other: 222 (cardiopulmonary event)
	Quallick, 2009[264] Fair	Mixed (including symptomatic) US	NR NR	NR NR	NR	39,054	4 (0.01)	NR	NR	NR
	Johnson, 2008[50] ACRIN Fair	Screening US	NR NR	58 52	NR	2531	0 (0)	1 (0.04)	NR	Hospitalization: 2 Other: 1 (infection)
	Kim, 2007*[242] Fair	Screening US	10 NR	58 56	NR	3163	7 (0.2)	NR	NR	NR

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Ko, 2007[291]	Mixed (including	8	NR	30 days	502	0 (0)	3 (0.6)	NR	Hospitalization: 2
	Fair	symptomatic)	99	51						ED: 2
		US								Other: NR
	MACS group, 2006[255]	Screening	NR	NR	4 weeks	63	0 (0)	0 (0)	NR	0 (0)
	Fair	Australia	NR	49						
	Cotterhill, 2005[223]	Screening	NR	NR	NR	324	0 (0)	0 (0)	NR	NR
	Fair	Canada	94	44						
	Cheng, 2002[160]	Screening	NR	47	NR	7411	2 (0.03)	5 (0.07)	0 (0)	Hospitalization: 0 (0)
	Fair	Taiwan	99	45						
	Nelson, 2002[256]	Screening	NR	63	30 days	3196	0 (0)	7 (0.2)§	3 (0.09)	MI: 4 (includes CVA)
	Fair	US	97	3						Other: 19 (infection, CV event, syncope)
	Sieg, 2001[270]	Mixed (including	94	NR	NR	96,665	13 (0.01)	17 (0.02)	2 (0.002)	Other: 12 (cardiopulmonary events)
	Fair	symptomatic)	95	NR						
		Germany								
Retrospective	Adeyemo, 2014[209]	Mixed (including	NR	61	NR	118,004	48 (0.04)	NR	NR	NR
	Fair	symptomatic)	NR	54						
		US								
	Bielawska, 2014[215]	Mixed (including	NR	NR	NR	1,144,900	192 (0.02)	NR	NR	NR
	Fair	symptomatic)	NR	48						
		US								

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Blotiere, 2014[216]	Mixed (including symptomatic)	NR	NR	3 days	947,061	424 (0.04)	182 (0.02)	NR	NR
	Fair	France	NR	56						
	Layton, 2014[406]	Screening	NR	59	6 months	550,696	NR	NR	NR	AKI††: 1595
	Fair	US	NR	40						
	Zafar, 2014[282]	Screening	NR	74	30 days	54,039	46 (0.08)	371 (0.7)	NR	Other: 921 (CVD or other GI events)
	Fair	US	NR	55						
	Chukmaitov, 2013[221]	Mixed (including symptomatic)	NR	NR	30 days	2,315,126	773 (0.03)	3822 (0.2)	NR	NR
	Fair	US	NR	54						
	Cooper, 2013[222]	Mixed (including symptomatic)	NR	76	30 days	100,359	101 (0.1)	NR	291 (0.2)	Other: 185 (splenic injury, aspiration)
	Fair	US	NR	55						
	Dominitz, 2013[226]	Mixed (including symptomatic)	18,578	NR	30 days	328,167	374 (0.1)	2299 (0.7)€	NR	Hospitalization: 10,478 ED: 14,278
	Fair	US	NR	58						
	Hamdani, 2013[232]	Mixed (including symptomatic)	NR	NR	7 days	80,118	50 (0.06)	NR	NR	NR
	Fair	US	NR	51						
	Kim, 2013[243]	Mixed (including symptomatic)	NR	NR	NR	94,632	26 (0.03)	NR	NR	NR
	Fair	South Korea	NR	NR						
	Stock, 2013*[273]	Screening	NR	66	30 days	8658	7 (0.08)	4 (0.05)	5 (0.06)	MI: 2 Other: 8 (CV, splenic injury, syncope)
	Good	Germany	100	55						

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Tam, 2013[276]	Mixed (including	NR	NR	NR	86,101	25 (0.03)	NR	NR	Other: 4 ("long-term
	Fair	symptomatic)	NR	NR						complications") £
		US								
	Ho, 2012[234]	Mixed (including	NR	NR	7 days	50,660	NR	NR	≤13	Hospitalization: 534
	Fair	symptomatic)	NR	52						ED: 682
		Canada								Other: 1218 (not specified)
	Rutter, 2012[267]	Mixed (excluding	NR	NR	30 days	43,456	21 (0.05)	122 (0.3)	15 (0.03)	Hospitalization: 508
	Fair	symptomatic)	NR	51						ED: 1019
		US								
	Sagawa, 2012[268]	Mixed (including	NR	67	NR	10,826	8 (0.07)	NR	NR	NR
		symptomatic)	NR	38						
	Fair	Japan								
	Lorenzo-Zuniga, 2010[252]	Mixed (including	NR	57	NR	25,214	13 (0.05)	59 (0.2)	NR	NR
		symptomatic)	NR	NR						
	Fair	Spain								
	Xirasagar, 2010[281]	Mixed (including	51	58	NR	10,958	2 (0.02)	1 (0.009)	NR	Other: 3 (severe pain, aspiration,
		symptomatic)	98	52						AKI)
	Fair	US								
	Arora, 2009[212]	Screening	NR	NR	7 days	58,457	39 (0.07)	NR	NR	NR
	Fair	US	NR	NR						
	Berhane, 2009[214]	Screening	NR	NR	NR	11,808	2 (0.02)	5 (0.04)	0 (0)	MI: 1
		US	98	NR						Other: 8 (CV event other than MI)
	Fair									
	Crispin, 2009[224]	Screening	NR	NR	NR	55,993	22 (0.04)	10 (0.02)	NR	Other: 39 (cardiopulmonary
		Germany	98	56						events)
	Fair									

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Hsieh, 2009[236] Fair	Mixed (including symptomatic) Taiwan	NR NR	51 42	NR	9501	3 (0.03)	NR	NR	NR
	Kamath, 2009[239] Fair	Mixed (including symptomatic) US	NR NR	NR NR	22 months (median)	296,248	NR	NR	NR	Splenic injury‡: 7
	Singh, 2009[271] Fair	Mixed (including symptomatic) Canada	NR 65	59 56	30 days	24,509£	29 (0.1)	22 (0.09)€	NR	MI: 3 Other: 17 (GI symptoms, infection, AKI)
	Warren, 2009*[280] Good	Screening US	NR NR	NR NR	30 days	5349	3 (0.06)	11 (0.2)	NR	MI: 13 Otherð: 119 (GI symptoms or events, CV events)
	Kang, 2008[240] Fair	Mixed (including symptomatic) South Korea	NR NR	60 36	NR	44,534£	53 (0.1)	NR	NR	NR
	Mansmann, 2008[254] Fair	Mixed (including symptomatic) Germany	NR 97	59 57	NR	236,087	69 (0.03)	10 (0.004)	NR	Other: 152 (cardiopulmonary events)
	Rabeneck, 2008[265] Fair	Mixed (including symptomatic) Canada	NR NR	61 54	30 days	97,091	54 (0.06)	137 (0.1)	51 (0.05) (5 colo related or possibly colo related)	NR

Table 25. Key Question 3: Summary Table of Serious Adverse Events From Screening Colonoscopy

Study Design	Study Quality	Recruited Population Country	Number of Endoscopists Completion Rate, %	Mean Age, years Female, %	Followup	Colonoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
	Levin, 2006[249]	Mixed (excluding	NR	62	30 days	16,318	15 (0.09)	15 (0.09)	10 (0.06)θ	MI: 9
	Fair	symptomatic)	70	40						Other: 82 (not specified, unclear if bleeding and perf are included)‡‡
		US								
	Rathgaber, 2006[266]	Mixed (including	8	60	30 days	12,407	2 (0.02)	11 (0.09)	0 (0)	Other: 1 (CV)
	Fair	symptomatic)	98	52						
		US								
	Strul, 2006†[274]	Screening	NR	60	NR	1177	0 (0)	0 (0)	0 (0)	Other: 1 (severe pain)
	Fair	Israel	NR	53						
	Korman, 2003[247]	Mixed (including	265	NR	NR	116,000	37 (0.03)	NR	NR	NR
	Fair	symptomatic)	NR	NR						
		US								

*** Study reports "complications," so they could not be categorized as serious
** Likely not attributable to colonoscopy
€ Unspecified bleeds
* Study has a comparison group
§ Only bleeds requiring hospitalization
†† Study focuses on harms of AKI
£ For colonoscopy and FS combined
‡ Study focuses on harms of splenic injury only
δ Harms from bleeding and perforation are mutually exclusive from other serious events.
θ 1 death directly related to colonoscopy
‡‡ No harms from screening colonoscopies (n=117)
† Prospective from 2002-2003, retrospective from 1996-2001

Abbreviations: ACRIN = American College of Radiology Imaging Network National CT Colonography Trial; AKI = acute kidney injury; COCOS = COlonoscopy or COlonography for Screening; CV = cardiovascular; ED = emergency department; GI = gastrointestinal; MACS = Multicentre Austrailian Colorectal-neoplasia Screening; MI = myocardial infarction; n = number; NR = not reported; SCORE = Screening for COlon Rectum; US = United States.

Table 26. Key Question 3: Summary Table of Serious Adverse Events From Screening CTC

Study Design	Study Quality	Recruited population Country	Followup	Readers	Mean Age Female, %	CTC exams	Perforations, n (%)	Other Serious Adverse Events
Prospective	Fletcher, 2013[165] Fair	Screening US	NR	2	56 (median) 58	568	0 (0)	No serious adverse events
	Lefere, 2013[51] Fair	Screening Portugal	NR	1	60 60	510	0 (0)	No serious adverse events
	Stoop, 2012[128] Fair	Screening The Netherlands	4 weeks	3	61 48	982	0 (0)	Collapse: 1/982 (0.1) Myocardial infarction: 1/982 (0.1) Cerebrovascular accident: 1/982 (0.1)
	Zalis, 2012[183] Fair	Screening US	NR	3	60 47	618	0 (0)	No serious adverse events
	Graser, 2009[49] Fair	Screening Germany	NR	3	60 45	309	0 (0)	No serious adverse events
	An, 2008[211] Fair	Screening South Korea	NR	2	51 40	1015	0 (0)	No serious adverse events
	Johnson, 2008[50,193] (ACRIN) Fair	Screening US	NR	15	58 52	2531	0 (0)	Hospitalizations (total): 2/2531 (0.08)* Severe nausea and vomiting: 1/2531 (0.04)
	Kim, 2008[170] Fair	Screening South Korea	NR	2	58 49	241	0 (0)	No serious adverse events
	Kim, 2007[242] Fair	Screening US	NR	5	57 56	3120	0 (0)	NR
	MACS group, 2006[255] Fair	Screening Australia	4 weeks	NR	NR 49	38	0 (0)	No serious adverse events
	Edwards, 2004[228] Fair	Screening Australia	NR	2	NR 46	340	0 (0)	No serious adverse events
Retrospective	Zafar, 2014[282] Fair	Screening US	30 days	NR	77 64	1384	1 (0.07)	Major bleeding events: 4 (0.3%) Other GI events: 5 (0.4) CVD events: 26 (1.9)
	Iafrate, 2013[237] Fair	Mixed (including symptomatic) Italy	NR	NR	NR NR	40,121	7 (0.02)	Mortality: 0 Self-limiting vasovagal episodes: 63 (0.16; 95% CI, 0.09-0.3)

Table 26. Key Question 3: Summary Table of Serious Adverse Events From Screening CTC

Study Design	Study Quality	Recruited population Country	Followup	Readers	Mean Age Female, %	CTC exams	Perforations, n (%)	Other Serious Adverse Events
	Sosna, 2006[272]	Mixed (including symptomatic)	NR	16	60	11,870	7 (0.06) (only 1 was in a screening patient)	Mortality: 0 (0)
	Fair	Israel			42			
	Pickhardt, 2006[262]	Screening	NR	NR	NR	11,707	0 (0)	NR
	Fair	US, Belgium, Ireland, Italy, The Netherlands			NR			

* after CTC and colonoscopy

Abbreviations: ACRIN = American College of Radiology Imaging Network National CT Colonography Trial; CI = confidence interval; CTC = computed tomographic colonography; MACS = Multicentre Austrailian Colorectal-neoplasia Screening; n = number; NR = not reported; US = United States.

Table 27. Key Question 3: Radiation Exposure From Screening CTC

Author, Year	Total radiation exposure	Supine radiation exposure	Prone radiation exposure
Fletcher, 2013[165]	6–7 mGy	NR	NR
Lefere, 2013[51]	NR	50 mAs*	30 mAs*
Zalis, 2012[183]	5.3mSv	NR	NR
Graser, 2009[49]	4.5 mSv	3.2 mSv	1.3 mSv
An, 2008[211]	0.8–1.0 mSv	NR	NR
Johnson, 2008[50]	50 mAs*	NR	NR
Kim, 2008[170]	NR	120 mAs*	50 mAs*
Johnson, 2007[169]	70 mAs*	NR	NR
MACS group, 2006[255]	<5 mSv	NR	NR
Edwards, 2004[228]	5 mSv	NR	NR
Macari, 2004[176]	50 mAs*	NR	NR
Pickahrdt, 2003[52]	100 mAs*	NR	NR

* mSv NR

Abbreviations: MACS = Multicentre Austrailian Colorectal-neoplasia Screening; mAs = milliamperage second; mGy = milligray; mSv = millisievert; NR = not reported.

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
Screening	Durbin, 2012[227] Prospective Fair	N= 490 Asymptomatic, mean 60 years Followup: NR	Major: high clinical importance, required definitive management Moderate: Potential moderate clinical significance Minor: no or little clinical importance Only evaluated genitourinary findings	10 (2%) persons with major genitourinary findings 86 (17.6%) persons with moderate genitourinary findings 100 (20.4%) with minor genitourinary findings	25 (5.1%) had additional diagnostic evaluation 2 (0.4%) required surgical resection (clear cell renal carcinoma)
	Stoop, 2012[128] Prospective Fair	N= 982 Asymptomatic, mean 61 years Followup: NR	C-RADS	E3/E4: 107 (11%)	94 (10%) had additional diagnostic evaluation <u>Findings of diagnostic evaluations:</u> 5 (0.5%) extracolonic cancer (4 renal-cell carcinoma, 1 duodenal carcinoma). 7 (0.7%) abdominal aortic aneurysms (3 underwent surgical treatment) 3 (0.3%) aneurysms of smaller vessel 1 (0.1%) low-risk myelofibrosis 1 (0.1%) Paget's disease 1 (0.1%) glandular papilloma 76 (7.7%) benign lesions (19 kidney, 12 gynecological, 7 liver, 7 lung, 5 adrenal, 26 in other organs)
	Zalis, 2012[183] Prospective Fair	N= 605 Asymptomatic, mean 60 years Followup: chart review, timing NR	C-RADS	E3: 97 (16%) E4: 16 (3%)	33 (5.5%) had additional diagnostic evaluation Diagnostic outcome NR
	Pickhardt, 2010*[260] Prospective Fair	N= 10286 Asymptomatic, mean 60 years Followup: Chart review, 13-56 months	C-RADS	NR	36 (0.35%) extracolonic malignancy after diagnostic workup (3 adrenal, 1 appendix, 1 stomach, 1 hepatocellular, 8 lung, 1 breast, 1 endometrial, 1 skin, 6 non-Hodgkin lymphoma, 2 prostate, 11 renal cell) 32 (0.31%) received treatment for malignancy 3 (0.03%) deceased upon followup

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
	O'Connor, 2011*[257] Retrospective Fair	N= 3001 Asymptomatic, mean 57 years Followup: chart review, 3 years	Benign renal mass (masses containing fat or with attenuation <20 HU or >70 HU without thickened walls or septations, ≥3 septations, mural nodules, or thick clacifications. Indeterminate renal mass (attenuation 20 to 70 HU or any without thickened walls or septations, ≥3 septations, mural nodules, or thick calcifications) Evaluated renal masses only	376 (12.5%) benign renal masses 57 (1.9%) indeterminate renal masses	41 (1.4%) underwent additional diagnostic evaluation <u>Findings from diagnostic evaluation:</u> 4 (0.13%) identified with renal cell carcinoma 2 additional patients who had benign index masses were found to have renal cell carcinoma 3 years later, but did not originate from the index mass or any other identifiable mass on CTC.
	Pickhardt, 2011*[259] Retrospective Fair	N= 3126 Asymptomatic, mean 57 years Followup: NR	Small hiatal hernia Moderate hiatal hernia Large hiatal hernia Evaluated hiatal hernias only	1281 (41%) small hiatal hernia 194 (6.2%) moderate hiatal hernia 20 (0.64%) large hiatal hernia	Subsequent evaluation NR
	Kim, 2007*[242] Prospective Fair	N=3120 98% asymptomatic, mean 57 years Followup: NR	C-RADS	E2: 1490 (47.8%) E3: 265 (8.5%) E4: 70 (2.2%)	241 (7.7%) recommended to have additional diagnostic evaluation 8 (0.3%) patients with extracolonic cancer (treatment NR) (3 renal, 2 bronchogenic, 1 non-Hodgkin's lymphoma, 1 endometrial, 1 GI stromal tumor)
	Kim, 2010*[285] Retrospective Fair	N= 577 Assumed asymptomatic, mean 69 years Followup: Chart review, 17–62 months	C-RADS	E3/E4: 89 (15.4%)	45 (7.8%) had subsequent evaluation. 21 (3.6%) had substantial but unsuspected diagnoses 18 (3.1%) vascular aneurysms 1 (0.2%) lung cancer 1 (0.2%) malrotation 1 (0.2%) femoral hernia

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
	Pickhardt, 2008*[288] Prospective Fair	N=2195 Asymptomatic, mean 58 years Followup: chart review, up to 18 months	C-RADS	E4: 204 (9.3%)	157 (7.2%) recommended to have additional diagnostic evaluation 133 (6.1%) had additional diagnostic evaluation (includes 18 patients with findings of less than moderate importance (not recommended)) 55 (2.5%) with confirmed diagnosis of an unsuspected condition of at least 'moderate' importance 9 (0.4%) had a malignant tumor (3 non-Hodgkin lymphoma, 3 renal cell carcinoma, 2 abdominal metastatic disease, 1 bronchogenic carcinoma) 22 (1.0%) required surgical procedures as followup <u>Findings of diagnostic evaluations:</u> 13 (0.6%) benign ovarian tumor 9 (0.4%) malignant tumor 12 (0.5%) aortoilaic aneurysm 4 (0.2%) congenital renal anomaly 3 (0.1%) obstructing urolithiasis 2 (0.1%) mucinous adenoma of appendix 2 (0.1%) endometriosis 2 (0.1%) porcelain gallbladder 1 (0.04%) polycystic disease 1 (0.04%) polysplenia 1 (0.04%) malrotation 1 (0.04%) hydrosalpinx
	Pickhardt, 2007*[261] Prospective Fair	N=2014 Presumed asymptomatic, mean 57 years Followup: chart review, unclear duration	NR Only evaluated extracolonic GI tumors	10 (0.5%) focal extracolonic GI tumors	0.5% (10/2014) had further diagnostic evaluation (cancer locations: 3 stomach, 2 jejunum, 3 ileum, 2 appendix) 0.3% (7/2014) required surgical resection; 0.05% (1/2014) required endoscopic resection *All GI tumors found to be benign*

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
	Veerappan, 2010[277] Retrospective Fair	N= 2277 Assumed asymptomatic, mean 59 years Followup: Database, 6 months–4 years	C-RADS	E2-E4: 1037 (45.5%) E2: 787 (34.6) E3: 211 (9.3%) E4: 39 (1.7%)	8.7% (199/2277) received additional diagnostic evaluation 0.83% (19/2277) required surgical treatment 0.26% (6/2277) found to have cancer (1 lung adenocarcinoma, 2 renal cell carcinomas, 1 bronchoalveolar carcinoma of the lung, 1 nodular lymphoma) 0.04% (1/2277) large abdominal aortic aneurysm (8 cm)
	Johnson, 2008[50,193] (ACRIN) Prospective Fair	N=2531 Asymptomatic, mean 58 years 50-64 years: N=2054 ≥65 years: N=477 Followup: NR	NR†	E2-E4: 1665 (66%) 50-64 years: 1278 (62%) ≥65 years: 387 (81%) (E3)/E4‡ (requiring additional evaluation): 428 (17%) 50-64 years: 104 (5.1%) ≥65 years: 324 (68%) E4 (requiring urgent care): 50-64 years: 26 (1.3%) ≥65 years: 4 (0.8%)	Subsequent evaluation NR
	Flicker, 2008[229] Retrospective Fair	N= 210 Asymptomatic, mean 61 years Followup: Medical records, 1–76 months	C-RADS	E3: 30 (14.3%) E4: 6 (2.9%)	6 (2.8%) received additional diagnostic imaging <u>Findings of diagnostic imaging:</u> 2 (1.0%) abdominal aortic aneurysms ≥3 cm 2 (1.0%) renal solid masses 1 (0.5%) liver solid mass 1 (0.5%) pneumoperitoneum
	Kim, 2008[244] Prospective Fair	N= 2230 Asymptomatic, mean 58 years Followup: Medical records, 1-3 years	C-RADS	E2-E4: 1484 (66.5%) E2: 1707 (76.5%) E3: 358 (16.1%) E4: 115 (5.2%)	100 (4.5%) received additional diagnostic evaluation (15 patients did not need further imaging for treatment decisions) 45 (2.0%) required surgical or medical treatment <u>Findings of diagnostic evaluations:</u> 0.5% (12/2230) extracolonic cancer (5 renal cell, 3 hepatocellular, 1 pancreatic, 1 lung, 1 cervical, 1 stomach)

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
	Chin, 2005[220] Prospective Fair	N=432 Asymptomatic, mean 59 years Followup: through GP, 2 years	Clinically relevant: required medical or surgical attention, or further hematological, biochemical, and/or radiological investigation after reviewing patient's medical history†	E2-E4: 118 (27.3%) (E3)/E4‡: 32 (7.4%)	32 (7.4%) required further diagnostic evaluation: <u>Findings of diagnostic evaluations:</u> 1 (0.2%) renal cell carcinoma 6 (1.4%) abdominal aortic aneurisms 1 (0.2%) splenic artery aneurysm 24 (5.5%) benign lesions
	Pickhardt, 2003** [52] Prospective Fair	N= 1233 Asymptomatic, mean 58 years Followup: NR	High, moderate, low importance§	E4: 56 (4.5%)	Persons requiring diagnostic imaging: NR <u>Findings of diagnostic evaluations</u>: 5 (0.4%) extracolonic malignancy (1 lymphoma, 2 bronchogenic carcinoma, 1 ovarian cancer, 1 renal cancer) 2 (0.2%) underwent successful repair of unsuspected abdominal aortic aneurysms
Mixed (includes surveillance, individuals with family history, iron deficiency anemia)	Cash, 2012[218] Prospective Fair	N= 1410 Asymptomatic, mean 75 years Followup: None	C-RADS	E3: 196 (13.9%) E4: 41 (2.9%)	Subsequent evaluation NR
	Macari, 2011[253] Retrospective Fair	N= 454 Assumed asymptomatic (16.5% positive guaiac test) (57.3% referred from incomplete colonoscopy), mean 62 years N=204 <65 N=250 ≥65 Followup: NR	C-RADS	E2-E4: 298 (66%) <65 years: 113 (55.4%) ≥65 years: 185 (74.0%) E3/E4: 24 (5.3%) <65 years: 9 (4.4%) ≥65 years: 15 (6.0%)	10 (2.2%) additional diagnostic evaluation <65 years: 4 (2.0%) ≥65 years: 6 (2.4%)

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

Population	Author, Year Study design Quality	Population Followup	Categorization of extracolonic findings	Prevalence of extracolonic findings	Workup of extracolonic findings
	Ginnerup, 2003[230] Prospective Fair	N=75 Asymptomatic undergoing surveillance, median 61 years Followup: chart review, 6 months	NR†	E2-E4: 49 (65%) (E3)/E4‡: 9 (12%)	8 (11%) had further diagnostic evaluation 2 (3%) had surgery due to findings or adverse events of workup <u>Findings of diagnostic evaluations:</u> 1 (1.3%) Lung cancer (lung resection, died 1 year later) 1 (1.3%) Fatty sparing hepatic mass 1 (1.3%) Renal cyst 2 (2.7%) Adrenal incidentaloma 1 (1.3%) Endometrioma (surgical draining of infection after exam) 1 (1.3%) Ovarian cyst >4 cm 1 (1.3%) Fibromatous uterus
	Gluecker, 2003[231] Prospective Fair	N=681 Asymptomatic, median 64 years Followup: chart review, at least 12 months	High, moderate, low importance§	E2-E4: 469 (69%) E2: 341 (50%) E3: 183 (27%) E4: 71 (10%)	94 followup diagnostic procedures in patients with 'high' clinical importance findings 15 followup diagnostic procedures in 183 persons with 'moderate' clinical importance findings 9 (1%) needed treatment (1 AAA, 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)
	Hara, 2000 [233] Prospective Fair	N=264 Asymptomatic (high risk), 162 undergoing surveillance, age NR Followup: chart review, 7-22 months	High, moderate, low importance§	E2-E4: 109 (41%) E2: 55 (21%) E3: 46 (17%) E4: 30 (11%)	18 (6.8%) had further diagnostic evaluation 6 (2.3%) had surgery due to malignant or nonmalignant findings 4 (1.5%) required ongoing followup <u>Finding of diagnostic evaluations:</u> 2 (0.8%) Renal cancer (required surgery) 2 (0.8%) Abdominal aortic aneurysm 1 (0.4%) Pneumothorax (required surgery) 4 (1.6%) Indeterminate lesions (2 pulmonary nodules, 2 probable adrenal adenomas) 9 (3.4%) Benign lesions (Renal cysts 4, pulmonary granuloma 1, liver with focal fat 1, 4.2 cm AAA 1, hepatic cyst 1, splenic cyst 1)

* Overlapping populations from the University of Wisconsin screening program.
** From the University of Wisconsin screening program but in a non-overlapping time frame.

Table 28. Extracolonic Findings in Asymptomatic Persons Undergoing CT Colonography

† 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
§ 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]

Abbreviations: AAA = abdominal aortic aneurysm; cm = centimeter; C-RADS = Computed Tomographic Colonography Reporting and Data System; CTC = computed tomographic colonography; E1 = normal examination or anatomic variant; E2 = clinically unimportant finding; E3 = findings unlikely to be clinically significant; E4 = potentially clinically important findings; GI = gastrointestinal; GP = general practitioner; N = number; NR = not reported.

Table 29. Summary of Evidence by Key Question and Screening Test

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ1: Effectiveness of screening on CRC mortality	Colonoscopy	k=1 n=88,902 Prospective cohort	After 24 years, CRC specific mortality was lower in persons with self-reported screening colonoscopy (multivariate adjusted HR, 0.32 [95% CI, 0.24-0.45]) compared to those who had never had screening endoscopy. Mortality benefit observed for both proximal and distal CRC.	Single study. No reporting bias.	Fair	Fair- cohort limited to health professionals
	FS	k=4 n=458,002 RCT	FS consistently decreased CRC-specific mortality compared to no screening at 11 to 12 years of followup (IRR, 0.73 [95% CI, 0.66-0.82]). Only 1 trial, PLCO, evaluated more than 1 round of screening. Mortality benefit is limited to distal CRC.	Variation in referral criteria led to differing rates of followup colonoscopy. No reporting bias.	Fair to good	Fair to poor- no longer widely used in US
	gFOBT	k=5 n=419,966 RCT‡	Biennial screening with Hemoccult II compared to no screening (n=404,396) consistently resulted in reduction of CRC-specific mortality, ranging from 9 to 22 percentage points after 2 to 9 rounds of screening with 11 to 30 years of followup (RR, 0.91 [95% CI, 0.84-0.98] at 19.5 years to RR, 0.78 [95% CI, 0.65-0.93] at 30 years).	Variation in number of screening rounds, use of rehydrated samples, definition of "test positive," and recommended diagnostic followup. No reporting bias.	Fair to good	Poor- Hemoccult II no longer widely used
	Comparative effectiveness	k=12 n=94,526 RCT k=3 n=346,494 Prospective cohort	Trials comparing different screening tests do not provide evidence of comparative benefit in CRC incidence or mortality outcomes.	Studies are not designed to assess screening impact on mortality; limited to a single round of screening, low number of cancers detected, and few interval cancers reported.	Poor to fair	Not applicable

Table 29. Summary of Evidence by Key Question and Screening Test

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ2: Diagnostic accuracy of screening	Colonoscopy	k=4 n=4821 Prospective diagnostic accuracy	In 2 studies (n=1685), colonoscopy missed cancers. In 3 studies (n=2290) comparing colonoscopy to CTC or CTC-enhanced colonoscopy, the per-person sensitivity for adenomas ≥10 mm ranged from 89.1% to 94.7%, and the per-person sensitivity for adenomas ≥6 mm ranged from 74.6% to 92.8%.	Studies are not designed to assess diagnostic accuracy to detect cancer. Limited number of studies with large number of endoscopists, thus applicable to community practice. No reporting bias.	Fair to good	Fair- colonoscopies were conducted or supervised by "experienced" specialists
	FS	None**	Not applicable	Not applicable	Not applicable	Not applicable
	CTC	k=9 n=6497 Prospective diagnostic accuracy	In 1 study (n=2531), CTC missed 1 of 7 cancers. In 7 studies of CTC with bowel prep (n=5328), the per-person sensitivity and specificity to detect adenomas ≥10 mm ranged from 66.7% to 93.5% and 86.0% to 97.9%, respectively; the per-person sensitivity and specificity to detect adenomas ≥6 mm ranged from 72.7% to 98.0% and 79.6% to 93.1%, respectively. Only 3 studies (n=1044) reported sensitivity to detect advanced adenomas, ranging from 87.5% to 100%. In 2 studies (n=1169) of CTC without bowel prep, it appears that sensitivity without bowel prep to detect advanced adenomas, adenomas ≥10 mm, or adenomas ≥6 mm is lower than CTC protocols including bowel prep.	Studies are not designed to assess diagnostic accuracy to detect cancer. Unclear if the variation of test performance is due to differences in study design, populations, bowel prep, CTC imaging itself, or differences in reader experience or reading protocols. No reporting bias.	Fair to good	Fair- mostly single-center studies, the majority of studies (k=7) used 3 or fewer highly trained radiologists, current practice may use lower doses of radiation (therefore different technology and protocols)
	gFOBT	k=3 n=15,969 Prospective diagnostic accuracy	The sensitivity and specificity of Hemoccult SENSA to detect CRC ranged from 61.5% to 79.4% and from 86.7% to 96.4%, respectively.	Verification bias (i.e., screen-negative persons did not receive colonoscopy). No reporting bias.	Fair	Fair to poor- Hemoccult SENSA no longer widely used in US

Table 29. Summary of Evidence by Key Question and Screening Test

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
	FIT	**Qualitative** k=6 n=36,808 Prospective diagnostic accuracy **Quantitative** k=7 n=40,134 Prospective diagnostic accuracy	In studies with colonoscopy followup for all, qualitative and quantitative FIT sensitivity varied considerably across different assays for each outcome. Good results were seen from specific FITs with supporting data from more than 1 study, and best results from small studies using more than 1 stool sample or lower than manufacturer-recommended cutoffs. In 4 studies (n=34,857) evaluating 3 FDA-cleared qualitative FITs, OC-Light had the best sensitivity and specificity for CRC (87.5% and 91.0%, respectively, in 1 study, and 78.6% and 92.8% in another). For advanced adenoma, sensitivity and specificity were lower (40.3% and 92.3%, respectively, in 1 study and 28.0% and 93.5% in another). In 9 studies (n=42,310) evaluating 7 quantitative FITs, best results were seen with OC FIT-CHEK, the only FDA-cleared test. Sensitivity and specificity for CRC varied from 73.3% and 95.5%, respectively, to 92.3% and 87.2%. For advanced adenoma, sensitivity and specificity varied from 22.2% and 97.4%, respectively, to 44.1% and 89.8%.	Variation in test performance resulted from the use of 18 different FITs (FIT families), different numbers of stool samples, and to a limited extent, different assay cutoff value. Sparse data on most individual tests limited comparisons. Quantitative FITs included some that are older and now discontinued. In a separate group of studies (k=7), verification bias (i.e., screen-negative persons did not receive colonoscopy) did not change results or conclusions. No reporting bias.	Fair to good	Fair to good- for specific qualitative (OC-Light) and quantitative (OC-FIT CHEK) tests
	mtsDNA	k=1 n=9989 Prospective diagnostic accuracy	mtsDNA assay had better sensitivity but lower specificity compared to a commercial FIT (OC-FIT CHEK) for the detection of CRC and advanced adenoma. The sensitivity and specificity for CRC was 92.3% (95% CI, 84.0 to 97.0) and 84.4% (95% CI, 83.6 to 85.1), respectively; and for advanced adenoma was 42.4% (95% CI, 38.7 to 46.2) and 86.3% (95% CI, 85.5, 87.0), respectively.	Single study. 6% inadequate stool sample. No reporting bias.	Fair	Fair- only 1 mtsDNA test available, incorporates FIT in stool test, Cologuard (Exact Sciences)
	m*SEPT9*	k=1 n=1516 Prospective diagnostic accuracy	Weighted sensitivity and specificity of the m*SEPT9* assay to detect CRC was 48.2% (95% CI, 32.4 to 63.6) and 91.5% (95% CI, 89.7 to 93.1), respectively.	Single study. Large attrition due to incomplete data or inadequate sample. Analyses conducted in random subsample stratified by colonoscopy findings. No reporting bias.	Fair	Poor- only 1 blood test available and not FDA-approved for screening, Epi proColon Assay (Epigenomics AG)

Table 29. Summary of Evidence by Key Question and Screening Test

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ3: Serious adverse events of screening	Screening program	k=13 n=45,867 RCT	We found no evidence for any serious harms resultant from stool testing other than false-negative results and risk of serious adverse events associated with diagnostic colonoscopy. The rate of perforation in colonoscopies for positive FOBT may be higher, the pooled estimate was 8 perforations (k=6) per 10,000 (95% CI, 2 to 32). Likewise, rates of serious adverse events from followup diagnostic/therapeutic colonoscopy post FS (k=6) is estimated at 14 perforations per 10,000 (95% CI, 9 to 26), and 34 major bleeds per 10,000 (95% CI, 5 to 63).	Serious adverse events not reported in comparator arms (persons without endoscopy). Likely reporting bias of serious harms other than perforation and bleeding. No studies report differential harms by age groups.	Fair	Fair to good- reflects community practice, limited studies in US
	Colonoscopy	k=55 n=10,398,876 24 prospective cohorts or trials, 31 retrospective studies	Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons is estimated at 4 perforations (k=26) per 10,000 procedures (95% CI, 2 to 5) and 8 major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14). Other serious harms were not consistently reported. Risk of perforations, bleeding and other serious harms increase with age.	Only 2 studies reported serious adverse events in persons without colonoscopy (no difference in serious harms other than perforation and bleeding. Likely reporting bias of serious harms other than perforation and bleeding.	Fair	Good- reflects community practice
	FS	k=18 n=331,181 13 prospective cohorts or trials, 5 retrospective studies	Serious adverse events from screening FS are estimated at 1 perforation (k=16) per 10,000 procedures (95% CI, 0.4 to 1.4) and 2 major bleeds (k=10) per 10,000 procedures (95% CI, 1 to 4).	No studies reported serious adverse events in persons without FS. Likely reporting bias of serious harms other than perforation and bleeding. Only 1 study reported differential harms by age groups (no difference with increasing age).	Fair	Good- reflects community practice
	CTC harms	k=15 n=75,354 11 prospective cohorts or trials, 4 retrospective studies	Serious harms from CTC in asymptomatic persons are uncommon. Risk of perforation for screening CTC was less than 2 per 10,000 exams. The range of low-dose ionizing radiation per exam is 1 to 7 mSv.	No studies reported serious adverse events in persons without CTC. More limited evidence in true average-risk screening populations. Likely reporting bias of serious harms other than perforation. No studies report differential harms by age groups.	Fair	Fair to good- radiation exposure per exam may be decreasing over time

Table 29. Summary of Evidence by Key Question and Screening Test

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
	CTC ECF	k=21 n=38,193 retrospective studies	Extracolonic findings, which could be a benefit or harm, are estimated to occur in 41% to 69% of examinations. Similarly, the estimated proportion of these findings that necessitate actual diagnostic followup varies widely from 5% to 37%, with a very small proportion that require any type of definitive treatment (up to 3%). Higher prevalence of ECF with increasing age.	No studies able to quantify net benefit/harms of ECF findings. Varying levels of followup, few studies with final disposition of ECF. Some variation in definition of clinical importance of ECF. Very limited studies comparing ECF by age groups.	Fair	Fair to good-categorization of ECF using C-RADS

* Includes consistency and precision
† Includes reporting bias
‡ Total 6 RCTs identified, but 1 trial (from Finland) has not yet reported mortality outcomes
** No studies meeting inclusion criteria requiring comparison against criterion standard of colonoscopy

Abbreviations: CI = confidence interval; C-RADS = Computed Tomographic Colonography Reporting and Data System; CRC = colorectal cancer; CTC = computer tomographic colonography; ECF = extracolonic findings; k = number of studies; FDA = Food and Drug Administration; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; FOBT = fecal occult blood test; HR = hazard ratio; IRR = incidence rate ratio; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid; mSv = millisievert; mtsDNA = multi-target stool deoxyribonucleic acid; n = number; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RCT = randomized controlled trial; RR = relative risk

Appendix A Table 1. Recommended Screening Tests for Colorectal Cancer by Selected Society or Professional Organization Since 2008

Society or Professional Organization, Year	Colonoscopy	FS*	gFOBT†	FIT	CTC	Stool DNA	DCBE	MRC
USPSTF, 2008[87]	Y	Y	Y	Y	I	I	--	--
ACS/USMSTF***/ACR, 2008[88]	Y**	Y**	Y	Y	Y**	Y	Y**	--
KPCMI, 2008[407]	Y	Y	Y	Y	N	N	N	--
ACG, 2008[392]	Y	M	Y	Y	Y	M	--	--
ACR, 2010[408]	--	--	--	--	Y	--	Y	M
SIGN, 2011[409]	--	--	Y	--	--	--	--	--
ICSI, 2012[410]	Y	Y	Y	Y	Y	--	--	--
ACP, 2012[411]	Y	Y	Y	Y	I	Y	Y	--
NCCN, 2013[412]	Y‡	Y‡	Y	Y	Y‡	Y	--	--

* with or without stool testing

† high sensitivity

** The ACS/USMSTF/ACR guideline strongly recommends screening tests that are designed to detect both early cancer and adenomatous polyps if resources are available and patients are willing to receive an invasive test.

‡ 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

Abbreviations: ACG = American College of Gastroenterology; ACP = American College of Physicians; ACR = American College of Radiology; ACS = American Cancer Society; CTC = computed tomography colonography; DCBE = double-conrast 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; KPCMI = Kaiser Permanente Care Management Institute; M = maybe, weak recommendation or may be appropriate; MRC = magnetic resonance colonography; N = no, not recommended; NCCN = National Comprehensive Cancer Network; SIGN = Scottish Intercollegiate Guidelines Network; USMSTF = U.S. Multi-Society Task Force; USPSTF = U.S. Preventive Services Task Force; Y = yes, recommended as an acceptable option; -- = not addressed in the guideline

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
kw=keyword
mo=mortality
nm = name of substance
pt = publication type
ti = word in title

Cochrane Central Register of Controlled Trials (via Wiley)

#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 (fecal or faecal or stool):ti,ab,kw near/5 molecular*:ti,ab,kw
#8 (fecal or faecal or stool):ti,ab,kw near/5 (DNA or "deoxyribonucleic acid"):ti,ab,kw
#9 (f-dna or fdna):ti,ab,kw
#10 (s-dna or sdna):ti,ab,kw
#11 (fecal or faecal or stool):ti,ab,kw near/5 test*:ti,ab,kw
#12 (fecal or faecal or stool):ti,ab,kw near/5 (immunochemical or immunoassay):ti,ab,kw
#13 (fecal or faecal or stool):ti,ab,kw next occult:ti,ab,kw
#14 "occult blood":ti,ab,kw
#15 guaiac:ti,ab,kw
#16 (FOBT or IFOBT):ti,ab,kw
#17 ("SEPTIN 9" or SEPT9 or mSEPT9):ti,ab,kw
#18 #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 from 2008 to 2014, in Trials

Ovid MEDLINE search strategy

KQ1
1 Colonoscopy/
2 colonoscop$.ti,ab.
3 Sigmoidoscopy/
4 sigmoidoscop$.ti,ab.
5 Colonography, Computed Tomographic/

6 colonograph$.ti,ab.
7 Occult Blood/
8 occult blood.ti,ab.
9 ((fecal or faecal or stool) adj occult).ti,ab.
10 (fobt or ifobt or gfobt).ti,ab.
11 guaiac.ti,ab.
12 ((fecal or faecal or stool) adj5 test$).ti,ab.
13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab.
14 DNA/
15 DNA Methylation/
16 DNA Mutational Analysis/
17 DNA, neoplasm/
18 14 or 15 or 16 or 17
19 Feces/
20 18 and 19
21 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab.
22 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab.
23 ((fecal or faecal or stool) adj5 molecular).ti,ab.
24 (f-dna or fdna or s-dna or sdna).ti,ab.
25 "SEPT9 protein, human".nm.
26 Septins/
27 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab.
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 Mass screening/ or "Early Detection of Cancer"/
30 (screen$ or detect$).ti,ab.
31 29 or 30
32 28 and 31
33 Colorectal Neoplasms/
34 Adenomatous Polyposis Coli/
35 Colonic Neoplasms/
36 Sigmoid Neoplasms/
37 Colorectal Neoplasms, Hereditary Nonpolyposis/
38 Rectal Neoplasms/
39 Anus Neoplasms/
40 Anal Gland Neoplasms/
41 Colonic Polyps/
42 Adenomatous Polyps/
43 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab.
45 limit 44 to ("in data review" or in process or "pubmed not medline")
46 43 or 45
47 (screen$ or detect$).ti.
48 46 and (29 or 47)

49 32 or 48
50 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (165918)
51 meta-analysis as topic/
52 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
53 control groups/ or double-blind method/ or single-blind method/
54 Random$.ti,ab.
55 clinical trial$.ti,ab.
56 controlled trial$.ti,ab.
57 meta analy$.ti,ab.
58 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59 49 and 58
60 Mortality/
61 mortality.fs.
62 Survival rate/
63 Survival analysis/
64 Life Expectancy/
65 "Cause of Death"/
66 mortality.ti,ab.
67 (death or deaths).ti,ab.
68 survival.ti,ab.
69 (registry or registries).ti,ab.
70 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71 49 and 70
72 59 or 71
73 limit 72 to humans
74 limit 72 to animals
75 74 not 73
76 72 not 75
77 limit 76 to english language
78 limit 77 to yr="2008 -Current"
79 remove duplicates from 78

KQ2

1 Colonoscopy/
2 colonoscop$.ti,ab.
3 Sigmoidoscopy/
4 sigmoidoscop$.ti,ab.
5 Colonography, Computed Tomographic/
6 colonograph$.ti,ab.
7 Occult Blood/
8 occult blood.ti,ab.
9 ((fecal or faecal or stool) adj occult).ti,ab.
10 (fobt or ifobt or gfobt).ti,ab.
11 guaiac.ti,ab.
12 ((fecal or faecal or stool) adj5 test$).ti,ab.

13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab.
14 DNA/
15 DNA Methylation/
16 DNA Mutational Analysis/
17 DNA, neoplasm/
18 14 or 15 or 16 or 17
19 Feces/
20 18 and 19
21 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab.
22 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab.
23 ((fecal or faecal or stool) adj5 molecular).ti,ab.
24 (f-dna or fdna or s-dna or sdna).ti,ab.
25 "SEPT9 protein, human".nm.
26 Septins/
27 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab.
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 "Sensitivity and Specificity"/
30 "Predictive Value of Tests"/
31 ROC Curve/
32 False Negative Reactions/
33 False Positive Reactions/
34 Diagnostic Errors/
35 "Reproducibility of Results"/
36 Reference Values/
37 Reference Standards/
38 Observer Variation/
39 Receiver operat$.ti,ab.
40 ROC curve$.ti,ab.
41 sensitivit$.ti,ab.
42 specificit$.ti,ab.
43 predictive value.ti,ab.
44 accuracy.ti,ab.
45 false positive$.ti,ab.
46 false negative$.ti,ab.
47 miss rate$.ti,ab.
48 error rate$.ti,ab.
49 detection rate$.ti,ab.
50 diagnostic yield$.ti,ab.
51 likelihood ratio$.ti,ab.
52 diagnostic odds ratio$.ti,ab.
53 29 or 30 or 31 or 32 or 33 or 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
54 28 and 53
55 Colonoscopy/st
56 Sigmoidoscopy/st

57 Colonography, Computed Tomographic/st
58 55 or 56 or 57
59 54 or 58
60 Mass screening/ or "Early Detection of Cancer"/
61 (screen$ or detect$).ti,ab.
62 60 or 61
63 59 and 62
64 limit 63 to english language
65 limit 64 to yr="2008 -Current"
66 remove duplicates from 65

KQ3

1 Colonoscopy/ae, mo [Adverse Effects, Mortality]
2 Sigmoidoscopy/ae, mo
3 Colonography, Computed Tomographic/ae, mo
4 1 or 2 or 3
5 Colonoscopy/
6 Sigmoidoscopy/
7 Colonography, Computed Tomographic/
8 Occult Blood/
9 DNA/
10 DNA Methylation/
11 DNA Mutational Analysis/
12 DNA, neoplasm/
13 9 or 10 or 11 or 12
14 Feces/
15 13 and 14
16 "SEPT9 protein, human".nm.
17 Septins/
18 5 or 6 or 7 or 8 or 15 or 16 or 17
19 Colorectal Neoplasms/
20 Adenomatous Polyposis Coli/
21 Colonic Neoplasms/
22 Sigmoid Neoplasms/
23 Colorectal Neoplasms, Hereditary Nonpolyposis/
24 Rectal Neoplasms/
25 Anus Neoplasms/
26 Anal Gland Neoplasms/
27 Colonic Polyps/
28 Adenomatous Polyps/
29 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 Mass screening/ or "Early Detection of Cancer"/
31 (screen$ or detect$).ti.
32 29 and (30 or 31)
33 Mortality/
34 Morbidity/
35 Death/

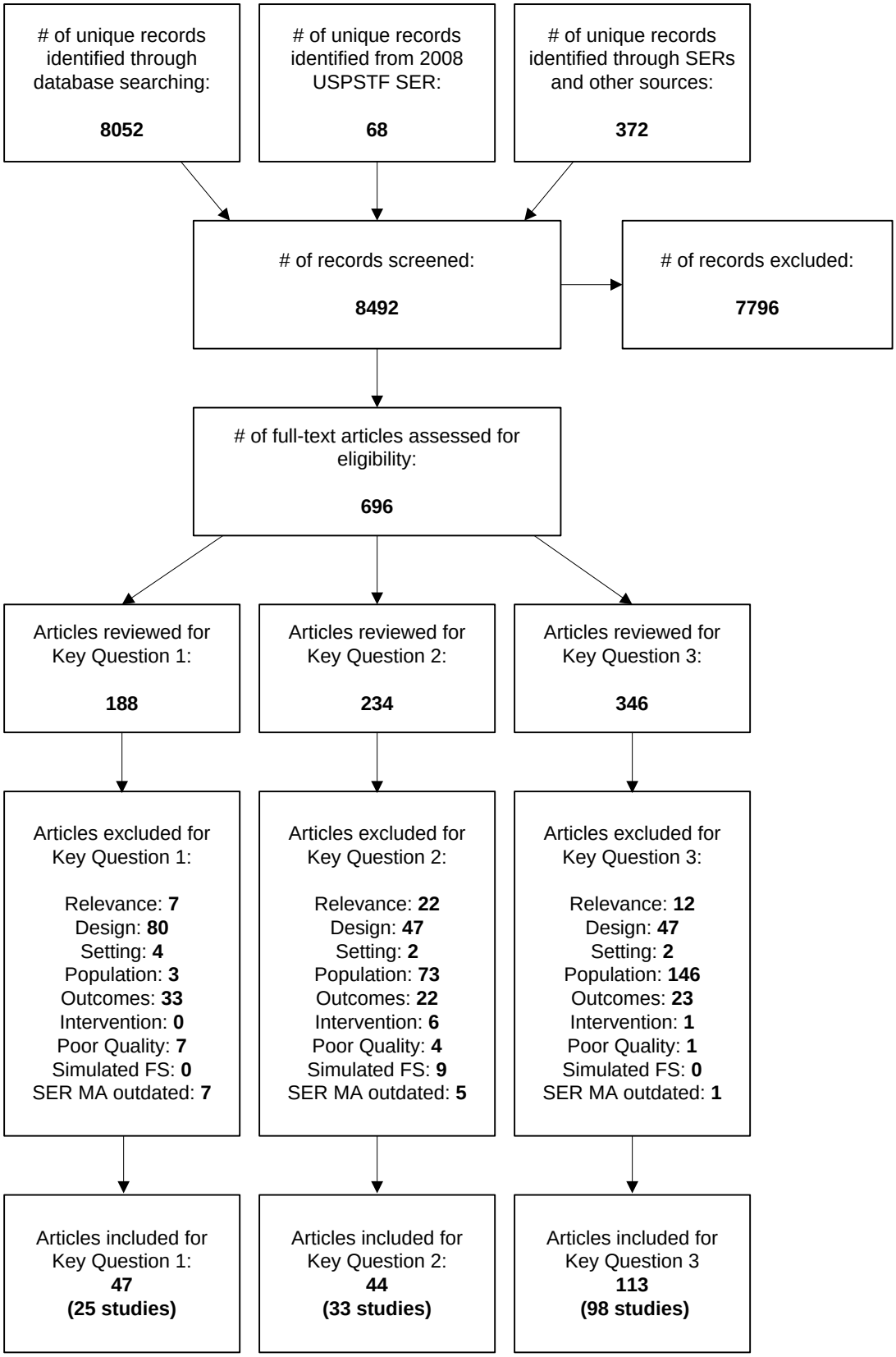
36 Hemorrhage/
37 Gastrointestinal hemorrhage/
38 Postoperative hemorrhage/
39 Intraoperative complications/
40 Postoperative complications/
41 incidental findings/
42 (harm or harms or harmful or harmed).ti.
43 (adverse adj (effect$ or event$ or outcome$)).ti.
44 safety.ti.
45 complication$.ti.
46 (death or deaths).ti.
47 (hemorrhag$ or haemorrhag$).ti.
48 bleed$.ti.
49 (death or deaths).ti.
50 ((incidental or extracolonic) adj finding$).ti.
51 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52 (18 or 32) and 51
53 4 or 52
54 limit 53 to humans
55 limit 53 to animals
56 55 not 54
57 53 not 56
58 limit 57 to (english language and yr="2008 -Current")
59 colonoscop$.ti,ab.
60 sigmoidoscop$.ti,ab.
61 colonograph$.ti,ab.
62 occult blood.ti,ab.
63 ((fecal or faecal) adj occult).ti,ab.
64 (fobt or ifobt or gfobt).ti,ab.
65 guaiac.ti,ab.
66 ((fecal or faecal or stool) adj5 test$).ti,ab.
67 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab.
68 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab.
69 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab.
70 ((fecal or faecal or stool) adj5 molecular).ti,ab.
71 (f-dna or fdna or s-dna or sdna).ti,ab.
72 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab.
73 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab.
75 (screen$ or detect$).ti.
76 74 and 75
77 73 or 76
78 (harm or harms or harmful or harmed).ti,ab.

79 (adverse adj (effect$ or event$ or outcome$)).ti,ab.
80 safety.ti,ab.
81 complication$.ti,ab.
82 (death or deaths).ti,ab.
83 (hemorrhag$ or haemorrhag$).ti,ab.
84 bleed$.ti,ab.
85 perforat$.ti,ab.
86 ((incidental or extracolonic) adj finding$).ti,ab.
87 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86
88 77 and 87
89 limit 88 to ("in data review" or in process or "pubmed not medline")
90 limit 89 to (english language and yr="2008 -Current")
91 58 or 90
92 remove duplicates from 91

PubMed search strategy (publisher-supplied)

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])
2 Search (screen*[ti] OR detect*[ti] OR surveillance[ti])
3 Search #1 AND #2
4 Search (colonoscop*[ti] OR colonograph*[ti] OR sigmoidoscop*[ti])
5 Search (fecal[ti] OR faecal[ti] OR stool[ti]) AND (DNA[ti] OR "deoxyribonucleic acid"[ti])
6 Search (fecal[ti] OR faecal[ti] OR stool[ti]) AND (molecular[ti] OR genetic[ti] OR genetics[ti])
7 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 (immunochemical[ti] OR immunoassay[ti])
9 Search ("fecal occult"[ti] OR "faecal occult"[ti] OR “stool occult”[ti] OR "occult blood"[ti] OR FOBT[ti] OR IFOBT[ti])
10 Search ("septin 9"[ti] OR septin9[ti] OR sept9[ti])
11 Search #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12 Search #11 AND publisher[sb] Filters: English
13 Search #11 AND publisher[sb] Filters: Publication date from 2008/01/01 to 2014/12/31; English

Appendix B Figure 1. Literature Flow Diagram



Abbreviations: FS = flexible sigmoidoscopy; MA = meta-analysis; SER = systematic evidence review; USPSTF = U.S. Preventive Services Task Force

Appendix B Table 1. Inclusion and Exclusion Criteria

	KQ	Inclusion	Exclusion
Populations	1-3	Age ≥40 years, average risk or unselected populations; Screening populations (i.e., asymptomatic)	Populations selected for personal or family history of CRC, known genetic susceptibility syndromes (e.g., Lynch Syndrome, FAP), personal history of inflammatory bowel disease; Non-screening populations (e.g., symptomatic, screening test positive, iron deficiency anemia, surveillance for previous colorectal lesion)
Settings	1-3	Settings representative of community practice for FS and colonoscopy studies; Developed countries (as defined by "very high" development using the Human Development Index [top quartile of 2012 rankings])*	Primarily research based settings (or select academic settings that would not be applicable to most practice settings) for endoscopy studies (e.g., small studies aimed at evaluating new endoscopy technologies, studies with operator or resource characteristics not applicable to community practice); Developing countries
Screening tests	1	Any program of CRC screening, including endoscopy, imaging, stool or blood testing	
	2-3	Colonoscopy; Flexible sigmoidoscopy (FS); Computed tomography colonography (CTC); Stool screening tests: i. High sensitivity guaiac fecal occult blood test (gFOBT) (i.e., Hemoccult SENSA) ii. Fecal immunochemical test (FIT) (quantitative and qualitative testing) iii. Stool DNA test; Blood screening test: m*SEPT9*	Hemoccult II (note: review of test performance and harms limited to high-sensitivity gFOBT); Stool testing using in-office digital rectal exam (DRE); Double contrast barium enema (DCBE); Capsule endoscopy [Pill Cam]; Magnetic resonance colonography (MRC)
Comparisons	1	No screening or alternate screening strategy	
	2	Diagnostic accuracy studies must use colonoscopy as a reference standard	
	3	No comparator necessary	
Outcomes	1	CRC incidence (by stage), interval CRC; CRC-specific or all-cause mortality	Incidence of adenomas or advanced neoplasia (composite outcome of advanced adenomas and CRC)
	2	Test performance including: Sensitivity and specificity (per person); Positive (PPV) and negative (NPV) predictive value (per person); Yield and miss rates (per lesion) for structural exams (i.e., colonoscopy, FS, CTC); For CRC, advanced adenoma (high grade dysplasia, villous histology, and/or ≥10 mm), and/or adenomatous polyps by size (i.e., ≤5 mm, 6-9 mm, ≥10 mm) By location in colon (e.g., proximal versus distal)	

Appendix B Table 1. Inclusion and Exclusion Criteria

	KQ	Inclusion	Exclusion
	3	Serious adverse events requiring unexpected or unwanted medical attention and/or resulting in death (e.g., requiring hospitalization), including but not limited to perforation, major bleeding, severe abdominal symptoms, cardiovascular events; Extra-colonic findings and subsequent diagnostic work-up and adverse events from diagnostic testing for incidental findings on CTC Radiation exposure per CTC exam	Minor adverse events defined as those not necessarily needing or resulting in medical attention (e.g., patient dissatisfaction, anxiety/worry, minor GI complaints)
Study design	1-3	Fair to good quality studies	Poor quality studies with a fatal flaw
	1	Systematic reviews (of included study designs), RCT, selected well-designed CCT, cohort studies, or case-control studies	Decision analyses
	2	Systematic reviews (of included study designs), trials, cohort or well-conducted nested case-control diagnostic accuracy studies, screening registry studies	Diagnostic accuracy studies without colonoscopy as a reference standard, diagnostic accuracy studies without representation of a full spectrum of disease (e.g., case-control studies, excluded indeterminate results)
	3	Systematic reviews (of included study designs), RCT/CCT, large screening registry or database observational studies, cohort studies, systematically selected case series	

* Taiwan is not incorporated into HDI calculations for the People's Republic of China. Therefore it is considered very high HDI based on calculations from Taiwan's government.

Abbreviations: CCT = controlled clinical trial; CRC = colorectal cancer; CTC = computed tomographic colonography; DCBE = Double contrast barium enema; DRE = digital rectal exam; e.g. = exempli gratia; FAP = familial adenomatous polyposis; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; GI = gastrointestinal; HDI = human development index; i.e. = id est; mm = millimeter; MRC = Magnetic resonance colonography; NPV = negative predictive value; PPV = positive predictive value; RCT = randomized controlled trial.

Appendix B Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[97]	• Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Was there a difference in attrition between groups? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there intervention fidelity? • Was there risk of contamination? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable followup? • Was there evidence of selective reporting of outcomes?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS)[100]	• Was there representativeness of the exposed cohort? • Was the non-exposed systematically selected? • Was the ascertainment of exposure reported? • Was the outcome of interest not present at baseline? • Were measurements equal, valid and reliable? • Were outcome assessors blinded? • Was followup long enough for the outcome to occur? • Was there acceptable followup?

Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) I[102] and II[101] instrument	• Could the selection of patients have introduced bias?
	  o Was the spectrum of patients representative of the patients who will receive the test in PC?
	  o Was the selection process clearly defined?
	  o Are there concerns that the included patients and setting do not match review question?
	• Could the conduct or interpretation of the index test have introduced bias?
	  o Was the index test interpreted without knowledge of the reference standard results?
	  o If a threshold was use, was it pre-specified?
	  o Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
	• Could the conduct or interpretation of the reference standard have introduced bias?
	  o Is the reference standard likely to correctly classify the target condition?
	  o Was the reference standard interpreted without knowledge of the index test results?
	  o Are there concerns that the target condition as defined by the reference standard does not match the review question?
	  o Did the whole or partial selection of patients receive the reference standard?
	• Could the patient flow have introduced bias?
	  o Was there an appropriate interval between the index test and reference standard?
	  o Did all patients receive the same reference standard?
	  o Were all patients included in the analysis?

Assessment of Multiple Systematic Reviews (AMSTAR)[99]	• Was an 'a priori' design provided? • Was there dual study selection? • Was there dual data extraction? • Was a comprehensive literature search performed? • Was the status of publication used as an inclusion criterion? • Was a list of studies included provided? • Was a list of excluded studies provided? • Were the characteristics of the included studies provided? • Was the scientific quality of the included studies assessed and documented? • Was the scientific quality of the included studies used appropriately in formulating conclusions? • Were the methods used to combine the findings of studies appropriate? • Was the likelihood of publication bias assessed? • Were potential conflicts of interest/source(s) of support of the systematic review stated? • Were potential conflicts of interest/source(s) of support of the included studies stated?

Appendix C. Excluded Studies

Reason for Exclusion	
E1.	Study relevance
E1a.	Primary aim technology improvements
E2.	Study design
E2a.	Case-control study design
E2b.	No use of reference standard (reference standard not applied to all/subset of screen negative)
E2c.	Case report
E3.	Setting
E3a.	Not a very high Human Development Index country
E4.	Population
E4a.	High-risk or symptomatic
E5.	No relevant outcomes or incomplete outcomes
E5a.	No additional relevant data (primary article included)
E6.	Intervention (including outdated technology)
E7.	Poor Study Quality
E8.	Simulated flexible sigmoidoscopy
E9.	Key existing SER with out of date meta-analysis

1. Senore C, Armaroli P, Silvani M, et al. Comparing different strategies for colorectal cancer screening in Italy: predictors of patients' participation. Am J Gastroenterol 2010 Jan;105(1):188-98. PMID: 19826409. **KQ1E1.**
2. Stegeman I, de Wijkerslooth TR, Stoop EM, et al. Combining risk factors with faecal immunochemical test outcome for selecting CRC screenees for colonoscopy. Gut 2014 Mar;63(3):466-71. PMID: 23964098. **KQ1E1.**
3. Alford SH, Rattan R, Buekers TE, et al. Protective effect of bisphosphonates on endometrial cancer incidence in data from the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Cancer 2014 Dec 22 PMID: 25533883. **KQ1E1.**
4. Benson M, Lucey M, Pfau P. Caecal intubation rates and colonoscopy competency. Gut 2014 Apr 9 PMID: 24717933. **KQ1E1.**
5. Jones RM, Mongin SJ, Lazovich D, et al. Validity of four self-reported colorectal cancer screening modalities in a general population: differences over time and by intervention assignment. Cancer Epidemiology, Biomarkers & Prevention 2008 Apr;17(4):777-84. PMID: 18381476. **KQ1E1, KQ2E1, KQ3E1.**
6. Mittal S, Lin YL, Tan A, et al. Limited Life Expectancy Among a Subgroup of Medicare Beneficiaries Receiving Screening Colonoscopies. Clin Gastroenterol Hepatol 2013 Aug 22 PMID: 23973925. **KQ1E1, KQ2E1, KQ3E1.**
7. John A, Al KS, Dweik N, et al. Emerging role for colorectal cancer screening in Asian countries. Tropical Gastroenterology 2014 Jan;35(1):21-4. PMID: 25276902. **KQ1E1, KQ2E5.**
8. Newcomb PA, Norfleet RG, Storer BE, et al. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 1992 Oct 21;84(20):1572-5. PMID: 1404450. **KQ1E2.**
9. Scheitel SM, Ahlquist DA, Wollan PC, et al. Colorectal cancer screening: a community case-control study of proctosigmoidoscopy, barium enema radiography, and fecal occult blood test efficacy. Mayo Clin Proc 1999 Dec;74(12):1207-13. PMID: 10593348. **KQ1E2.**
10. Faivre J, Tazi MA, El MT, et al. Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. Br J Cancer 1999 Feb;79(3-4):680-3. PMID: 10027349. **KQ1E2.**
11. Slattery ML, Edwards SL, Ma KN, et al. Colon cancer screening, lifestyle, and risk of colon cancer. Cancer Causes Control 2000 Jul;11(6):555-63. PMID: 10880038. **KQ1E2.**
12. Brenner H, Arndt V, Sturmer T, et al. Long-lasting reduction of risk of colorectal cancer following screening endoscopy. Br J Cancer 2001 Sep 28;85(7):972-6. PMID: 11592768. **KQ1E2.**
13. Newcomb PA, Storer BE, Morimoto LM, et al. Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst 2003 Apr 16;95(8):622-5. PMID: 12697855. **KQ1E2.**

14. Costantini AS, Martini A, Puliti D, et al. Colorectal cancer mortality in two areas of Tuscany with different screening exposures. J Natl Cancer Inst 2008 Dec 17;100(24):1818-21. PMID: 19066268. **KQ1E2.**
15. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiology, Biomarkers & Prevention 2008 May;17(5):1163-8. PMID: 18483338. **KQ1E2.**
16. Goulard H, Boussac-Zarebska M, Ancelle-Park R, et al. French colorectal cancer screening pilot programme: results of the first round.[Erratum appears in J Med Screen. 2008;15(4):214]. Journal of Medical Screening 2008;15(3):143-8. PMID: 18927097. **KQ1E2.**
17. Manfredi S, Piette C, Durand G, et al. Colonoscopy results of a French regional FOBT-based colorectal cancer screening program with high compliance. Eur J Radiol 2008 May;40(5):422-7. PMID: 18231963. **KQ1E2.**
18. Jones AM, Morris E, Thomas J, et al. Evaluation of bowel cancer registration data in England, 1996-2004. British Journal of Cancer 2009 Oct 20;101(8):1269-73. PMID: 19773758. **KQ1E2.**
19. Ananda SS, McLaughlin SJ, Chen F, et al. Initial impact of Australia's National Bowel Cancer Screening Program. Med J Aust 2009 Oct 5;191(7):378-81. PMID: 19807627. **KQ1E2.**
20. Kahi CJ, Imperiale TF, Juliar BE, et al. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clinical Gastroenterology & Hepatology 2009;7(7):770-5. PMID: 19268269. **KQ1E2.**
21. Steele RJ, McClements PL, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. Gut 2009 Apr;58(4):530-5. PMID: 19036949. **KQ1E2.**
22. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009 Jan 6;150(1):1-8. PMID: 19075198. **KQ1E2.**
23. Denis B, Gendre I, Aman F, et al. Colorectal cancer screening with the addition of flexible sigmoidoscopy to guaiac-based faecal occult blood testing: a French population-based controlled study (Wintzenheim trial). European Journal of Cancer 2009 Dec;45(18):3282-90. PMID: 19665368. **KQ1E2.**
24. Singh H, Nugent Z, Demers AA, et al. The Reduction in Colorectal Cancer Mortality After Colonoscopy Varies by Site of the Cancer. Gastroenterology 2010 Oct;139(4):1128-37. PMID: 20600026. **KQ1E2.**
25. Brenner H, Altenhofen L, Hoffmeister M. Eight years of colonoscopic bowel cancer screening in Germany: initial findings and projections. Deutsches Arzteblatt International 2010 Oct;107(43):753-9. PMID: 21085544. **KQ1E2.**
26. Majek O, Danes J, Zavoral M, et al. Czech National Cancer Screening Programmes in 2010. Klinicka Onkologie 2010;23(5):343-53. PMID: 21058528. **KQ1E2.**
27. Ellul P, Fogden E, Simpson CL, et al. Downstaging of colorectal cancer by the National Bowel Cancer Screening programme in England: first round data from the first centre. Colorectal Disease 2010 May;12(5):420-2. PMID: 19843116. **KQ1E2.**
28. Brenner H, Hoffmeister M, Arndt V, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010 Jan 20;102(2):89-95. PMID: 20042716. **KQ1E2.**
29. Steele RJ, Kostourou I, McClements P, et al. Effect of repeated invitations on uptake of colorectal cancer screening using faecal occult blood testing: analysis of prevalence and incidence screening. BMJ 2010;341:c5531. PMID: 20980376. **KQ1E2.**
30. Brenner H, Chang-Claude J, Seiler CM, et al. Protection From Colorectal Cancer After ColonoscopyA Population-Based, Case □ÇôControl Study. A 2011 Jan 4;154(1):22-30. PMID: 21200035. **KQ1E2.**
31. Gross CP, Soulos PR, Ross JS, et al. Assessing the impact of screening colonoscopy on mortality in the medicare population. Journal of General Internal Medicine 2011 Dec;26(12):1441-9. PMID: 21842323. **KQ1E2.**

32. Strock P, Mossong J, Scheiden R, et al. Colorectal cancer incidence is low in patients following a colonoscopy. Digestive & Liver Disease 2011 Nov;43(11):899-904. PMID: 21831735. **KQ1E2.**
33. Kistler CE, Kirby KA, Lee D, et al. Long-term outcomes following positive fecal occult blood test results in older adults: benefits and burdens. Archives of Internal Medicine 2011 Aug 8;171(15):1344-51. PMID: 21555655. **KQ1E2.**
34. Stock C, Knudsen AB, Lansdorp-Vogelaar I, et al. Colorectal cancer mortality prevented by use and attributable to nonuse of colonoscopy. Gastrointest Endosc 2011 Mar;73(3):435-43. PMID: 21353840. **KQ1E2.**
35. Manfredi S, Philip J, Campillo B, et al. The positive predictive value of guaiac faecal occult blood test in relation to the number of positive squares in two consecutive rounds of colorectal cancer screening. Eur J Cancer Prev 2011 Jul;20(4):277-82. PMID: 21633201. **KQ1E2.**
36. Katicic M, Antoljak N, Kujundzic M, et al. Results of National Colorectal Cancer Screening Program in Croatia (2007-2011). World Journal of Gastroenterology 2012 Aug 28;18(32):4300-7. PMID: 22969192. **KQ1E2.**
37. Logan RF, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut 2012 Oct;61(10):1439-46. PMID: 22156981. **KQ1E2.**
38. Van RS, Hoeck S, Van HG. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiology 2012 Oct;36(5):e317-e324. PMID: 22560885. **KQ1E2.**
39. Morris EJ, Whitehouse LE, Farrell T, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. British Journal of Cancer 2012 Aug 21;107(5):757-64. PMID: 22850549. **KQ1E2.**
40. Gill MD, Bramble MG, Rees CJ, et al. Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. British Journal of Cancer 2012 Jul 24;107(3):417-21. PMID: 22782347. **KQ1E2.**
41. Jacob BJ, Moineddin R, Sutradhar R, et al. Effect of colonoscopy on colorectal cancer incidence and mortality: an instrumental variable analysis. Gastrointest Endosc 2012 Aug;76(2):355-64. PMID: 22658386. **KQ1E2.**
42. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. Journal of Clinical Oncology 2012 Jul 20;30(21):2664-9. PMID: 22689809. **KQ1E2.**
43. Ferrari BM, De C, V, Devoto GL, et al. Colorectal cancer screening in LHU4 Chiavarese, Italy: ethical, methodological and outcome evaluations at the end of the first round. Journal of Preventive Medicine & Hygiene 2012 Mar;53(1):37-43. PMID: 22803318. **KQ1E2.**
44. Libby G, Brewster DH, McClements PL, et al. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study. British Journal of Cancer 2012 Jul 10;107(2):255-9. PMID: 22735907. **KQ1E2.**
45. McClements PL, Madurasinghe V, Thomson CS, et al. Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiology 2012 Aug;36(4):e232-e242. PMID: 22425027. **KQ1E2.**
46. Manser CN, Bachmann LM, Brunner J, et al. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. Gastrointest Endosc 2012 Jul;76(1):110-7. PMID: 22498179. **KQ1E2.**
47. Steele RJ, McClements P, Watling C, et al. Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. Gut 2012 Apr;61(4):576-81. PMID: 21930729. **KQ1E2.**
48. Gupta S, Saunders BP, Fraser C, et al. The first 3 years of national bowel cancer screening at a single UK tertiary centre. Colorectal Disease 2012 Feb;14(2):166-73. PMID: 21689280. **KQ1E2.**
49. Brenner H, Chang-Claude J, Seiler CM, et al. Interval cancers after negative colonoscopy: population-based case-control study. Gut 2012 Nov;61(11):1576-82. PMID: 22200840. **KQ1E2.**

50. Fraser CG, Digby J, McDonald PJ, et al. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. Journal of Medical Screening 2012 Mar;19(1):8-13. PMID: 22156144. **KQ1E2.**
51. Park MJ, Choi KS, Lee YK, et al. A comparison of qualitative and quantitative fecal immunochemical tests in the Korean national colorectal cancer screening program. Scand J Gastroenterol 2012 Apr;47(4):461-6. PMID: 22428929. **KQ1E2.**
52. Moss SM, Campbell C, Melia J, et al. Performance measures in three rounds of the English bowel cancer screening pilot. Gut 2012 Jan;61(1):101-7. PMID: 21561880. **KQ1E2.**
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We found 12 fair-quality trials [110,111,116,120,121,125,126,128-132] in 16 articles[110,111,116,120,121,125,126,128-132,137,138,148,152] examining the comparative effectiveness of different screening tests in average-risk screening populations. We also found three fair-quality large prospective cohort studies[112,114,115] (in six articles[112,114,115,139-141]) examining the comparative effectiveness of gFOBT versus FIT in average risk screening populations (**Table 9**).

Trials and cohort studies included asymptomatic adults between ages 50–74 years. Mean age, when reported, was approximately 59 to 62 years, with approximately equal numbers of men and women (when reported). Studies generally excluded persons at high risk for CRC due to symptoms, personal history of CRC, and/or strong family history. All studies were conducted in Western European countries.

Trials were primarily designed to assess the differential uptake (adherence) of testing and relative detection of colorectal lesions and were limited to a single round of screening. Although these trials did include CRC outcomes, the trials were not powered to detect differences in yield of CRC. For example, approximately 6000 participants *per arm* would be needed to detect a 0.3% difference in CRC incidence with 80% power, assuming 100% adherence.The trials that have been conducted generally had less than 6000 participants per arm with less than 60% adherence to testing.

Comparative uptake and cancer yield of stool tests (versus stool tests).

gFOBT versus FIT. Two trials included the comparative uptake and detection of CRC of Hemoccult II versus FIT (OC-Sensor);[116,130] in addition, three cohort studies[112,114,115] included the comparative detection of CRC as part national screening programs of Hemoccult II versus FITs (Immudia (discontinued), FOB Gold, Magstream, OC-Sensor) (**Appendix D Table 1**). From the two trials reporting comparative uptake, it appears that there was greater adherence to OC-Sensor (~59%) than to Hemoccult II (~47%). Across all the studies reporting test positivity, it appears that there was a greater proportion of FIT test positive as compared to Hemoccult II. Although the test positivity was higher for OC-Sensor, and a greater number of cancers was detected in the FIT versus gFOBT arm, the difference in number of cancers detected in the two comparative trials after one round of testing was not statistically significant.[116,130] The national screening program cohort studies had much larger numbers of cancers being detected. Again, all of these cohort studies showed a higher test positivity for FIT than Hemoccult II and two showed statistically significant higher detection of CRC for FIT (FOB Gold, Magstream, OC-Sensor) than Hemoccult II.[112,115] One cohort study did not show statistically significant difference in cancer detection between Immudia and Hemoccult II despite the higher test positivity of Immudia.[114] None of these studies, however, have reported number of interval cancers or mortality outcomes.

FIT versus FIT. Two trials included the comparative uptake and yield of detection of CRC of different FIT tests or test intervals (**Appendix D Table 1**).[129,132] The first trial was conducted by van Roon and colleagues in the Netherlands and it evaluated comparative uptake and yield of OC-Sensor at 1-year (n=1541 analyzed per arm), 2-year (n=1474 analyzed per arm), and 3-year (n=1492 analyzed per arm) intervals of testing over two rounds.[129] The adherence to testing was similar (61-65%) over rounds one and two regardless of interval length. The test positivity was

expectedly slightly lower the second round of testing, 6.0% compared with 8.4% in the first round. Overall, the number of cancers detected was low and there were no statistically significant differences in the number of cancers or interval cancers between the different intervals of testing. The second trial, conducted by Zubero and colleagues in Spain, evaluated the comparative uptake and yield of OC-Sensor (n=11,153 analyzed per arm) versus FOB Gold (n=11,725 analyzed per arm) over one round.[132] The adherence to testing was similar between the two FITs. FOB-Gold had a higher test positivity rated (8.5%) compared to OC-Sensor (6.6%), both of which used similar cut-off values. Although test positivity and the number of cancers detected were higher in the FOB Gold arm compared to the OC-Sensor arm, the difference in cancers was not statistically significant. This trial has not yet reported on interval cancers or mortality.

Comparative uptake and cancer yield stool tests versus direct visualization.

gFOBT versus FS. Five comparative trials[110,111,116,121,131] published from 1997 to 2010 included the comparative uptake and yield of CRC cases detected after one round of Hemoccult II versus FS with (three trials[110,121,131]) or without Hemoccult II (**Appendix D Table 2**). These trials were relatively small, again with very low number of cancers in each trial, such that differences in cancer detection were not statistically significant except for in one trial by Rasmussen and colleagues.[121] In this trial (n=3055 analyzed per gFOBT arm, n=2222 analyzed per FS plus gFOBT arm), although the adherence was lower in the FS plus Hemoccult II arm compared to the Hemoccult II only arm, the test positivity and CRC yield was statistically significantly higher in the combined arm. In addition, the interval number of cancers (up to about 5 years of followup) amongst the screen negative persons was 8/3051 in the combined arm versus 18/2210 in the Hemoccult II only arm. The CRC mortality, however, was not statistically significantly different, 2.00/1000 persons in the combined arm versus 2.55/1000 persons in the Hemoccult II only arm.

FIT versus FS. Three trials[116,125,126] included comparative uptake and yield of detection of CRC with one round of FIT (Immudia, OC-Sensor) versus FS (**Appendix D Table 2**). In these trials, both conducted by Segnan and colleagues in Italy, the adherence to both FIT and FS was similarly low, around 30%;[125] as compared to the other trial by Hol and colleagues in the Netherlands, the adherence to FIT (59%) was higher than to FS (28%).[116] In all three trials the test positivity was higher for FS (with or without FIT) than FIT alone. Only one trial, conducted by Segnan and colleagues, found a statistically significant higher yield of CRC in the FS screened group versus Immudia alone screened group.[125] These trials, however, were not necessarily powered to detect a difference in CRC detection. Interval cancers and mortality was not reported in either trial.

FIT versus colonoscopy or CTC. Two trials[120,125] included the comparative uptake and yield of detection of CRC with one round of FIT (Immudia, OC-Sensor) and colonoscopy (**Appendix D Table 3**). No trials compared FIT to CTC. In both these two trials, the adherence to FIT was higher than to colonoscopy. One trial by Segnan and colleagues (n=1596 analyzed per colonoscopy arm, n=1965 analyzed per FIT arm) conducted in Italy found statistically significant higher number of cancers in the colonoscopy screened group compared to the Immudia screened group. In the other trial by Quintero and colleagues, powered to detect a difference in cancers (n=5059 analyzed per colonscopy arm, n=10,507 analyzed per FIT arm) conducted in Spain

found statistically significantly more cancers in the colonoscopy arm versus the FIT arm. Neither of these trials reported interval cancers or mortality.

Comparative uptake and cancer yield of direct visualization tests (endoscopy, CT).

FS versus colonoscopy. Only one trial[125] included the comparative uptake and yield of detection of CRC with FS versus colonoscopy (**Appendix D Table 4**). In this trial, conducted by Segnan and colleagues, (n=1596 per colonoscopy arm, n=1922 per FS arm) in Italy, adherence to FS was higher than to colonoscopy (32.3% versus 26.5% respectively). However, there was no statistically significant difference in the number of cancers detected in each arm. This trial was not powered to detect a difference in CRC yield, furthermore, interval cancers and mortality were not reported.

Colonoscopy versus CTC. Only one trial[128] included the comparative uptake and yield of detection of CRC with colonoscopy versus CTC (**Appendix D Table 4**). This trial by Stoop and colleagues, (n=5924 per colonoscopy arm, n=2920 per CTC arm) conducted in the Netherlands found adherence to CTC was higher than to colonoscopy (33.6% versus 21.5%, respectively); however there was no statistically significant difference in the number of cancers detected in each arm. This trial was not powered to detect a difference in cancers; furthermore, interval cancers and mortality were not reported.

Appendix D Table 1. Key Question 1: gFOBT vs. FIT or FIT vs. FIT Comparative Effectiveness Studies

Design	Author, Year	Round	Test	Adherence, %	Test Positivity	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Trials	Zubero, 2014[132]	1	FIT (OC-Sensor)	61.8	6.6	35/11,153	(0.3)	NR	
			FIT (FOB Gold)	59.1	8.5	44/11,725	(0.4)	NR	
	van Roon, 2013*[129] (intervals)	1	FIT (OC-Sensor Micro), 1 year interval	64.7		4/1541	(0.3)	NR	
			FIT (OC-Sensor Micro), 2 year interval	61.0	8.4	10/1474	(0.7)	NR	
			FIT (OC-Sensor Micro), 3 year interval	62.0		8/1492	(0.5)	NR	
		2	FIT (OC-Sensor Micro), 1 year interval	63.2		1/1286	(0.08)	0/1285†	(0)
			FIT (OC-Sensor Micro), 2 year interval	62.5	6.0	4/1280	(0.3)	1/1276††	(0.08)
			FIT (OC-Sensor Micro), 3 year interval	64.0		2/1298	(0.2)	2/1296**	(0.2)
	van Roon, 2011*[152] (1, 2 sample FIT)	1	FIT (OC-Sensor Micro), 1 sample	61.5	8.1	16/2975	(0.5)	NR	
			FIT (OC-Sensor Micro), 2 samples	61.3	12.8	12/1874	(0.6)	NR	
	Hol, 2010*[116]	1	gFOBT (Hemoccult II)	47.0	2.8	6/2351	(0.3)	NR	
			FIT (OC-Sensor Micro)	59.4	4.8	14/2975	(0.5)	NR	
	van Rossum, 2008**[116,137,138]	1	gFOBT (Hemoccult II)	46.9	2.4	11/4836	(0.2)	NR	
			FIT (OC-Sensor)	59.6	5.5	24/6157	(0.4)	NR	
Cohort studies	Hamza, 2013[115]	2-4	gFOBT (Hemoccult II)	NR	2.1	29/23,231	(0.1)	NR	
			FIT (FOB Gold)	NR	4.6	63/23,231	(0.3)‡	NR	
	Faivre, 2012[112,139]	1	gFOBT (Hemoccult II)	NR	2.0	117/85,026	(0.1)	NR	
			FIT (FOB Gold), 1 sample	NR	3.3	74/32,077	(0.2)‡	NR	
			FIT (FOB Gold), 2 samples	NR	5.2	91/32,077	(0.3)‡	NR	
			FIT (Magstream)	NR	4.6	65/19,180	(0.3)‡	NR	
			FIT (OC-Sensor), 1 sample	NR	2.5	76/33,611	(0.2)‡	NR	
			FIT (OC-Sensor), 2 samples	NR	3.7	92/33,611	(0.3)‡	NR	
	Guittet, 2012[140]	1	gFOBT (Hemoccult II)	NR	2.5	46/32225	(0.1)	NR	
			FIT (Immudia)	NR	6.4	60/32225	(0.2)	NR	

* Overlapping study populations
† Followup 1 year
†† Followup 2 years
** Followup 3 years
‡ p<0.01 versus gFOBT

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

Appendix D Table 2. Key Question 1: Stool Test vs. FS (With or Without Stool Test) Comparative Effectiveness Studies

Design	Author, Year	Round	Test	Adherence, %	Test Positivity	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Trials	Hol, 2010*[116]	1	gFOBT (Hemoccult II)	47.0	2.8	6/2351	(0.3)	NR	
			FIT (OC-Sensor Micro)	59.4	4.8	14/2975	(0.5)	NR	
			FS	27.7	10.2	8/1386	(0.6)	NR	
	Segnan, 2007[125] SCORE III	1	FIT (Immudia-HemSp)	32.3	4.7	2/1965	(0.1)	NR	
			FS	32.3	7.2	12/1922	(0.6)‡	NR	
	Segnan, 2005[126] SCORE II	1	FIT (Immudia-HemSp)	28.1	4.6	8/2336	(0.3)	NR	
			FS +/- FIT (Immudia-HemSp)	28.1	7.6*	14/4075	(0.3)	NR	
	Rasmussen, 1999[121]	1	gFOBT (Hemoccult II)	55.7	2.4	4/3055	(0.1)	18/2210†	(0.8)
			gFOBT (Hemoccult II) + FS	38.9	19.4	12/2222	(0.5)‡	8/3051†‡	(0.3)
	Verne, 1998[131]	1	gFOBT (Hemoccult II)	31.6	8.2	1/854	(0.1)	NR	
			FS	46.6	9.9	4/1116	(0.4)	NR	
			gFOBT (Hemoccult II) + FS	30.1	NR	1/401	(0.2)	NR	
	Berry, 1997[110]	1	gFOBT (Hemoccult II)	50	NR	2/1564	(0.1)	NR	
			gFOBT (Hemoccult II) + FS	20.2	NR	3/656	(0.5)	NR	
	Brevinge, 1997[111]	1	gFOBT (Hemoccult II)	59	4.4	2/1893	(0.1)	NR	
			FS	42.5	NR	5/1371	(0.4)	NR	

* 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; SCORE = Screening for COlon Rectum.

Appendix D Table 3. Key Question 1: FIT vs. CTC or Colonoscopy Comparative Effectiveness Studies

Design	Author, Year	Round	Test	Adherence, %	Test Positivity	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Trials	Quintero, 2012[120,148]	1	Colonoscopy	17.3	10.3	30/5059	(0.6)*	NR	
	COLONPREV		FIT (OC-Sensor)	31.3	7.2	33/10507	(0.3)	NR	
	Segnan, 2007[125]	1	Colonoscopy	26.5	5.1	13/1596	(0.8)‡	NR	
	SCORE III		FIT (Immudia-HemSp)	32.3	4.7	2/1965	(0.1)	NR	

* $p<0.05$
‡ $p<0.01$

Abbreviations: CRC = colorectal cancer; FIT = fecal immunochemical test; n = number; NR = not reported; SCORE = Screening for COlon Rectum.

Appendix D Table 4. Key Question 1: Direct Visualization Comparative Effectiveness Studies

Design	Author, Year	Round	Test	Adherence, %	Test Positivity	n CRC/ n Analyzed	(%)	Interval CRC	(%)
Trials	Stoop, 2012[128]	1	Colonoscopy	21.5	8.7	7/5924	(0.1)	NR	
	COCOS		CTC	33.6	8.6	5/2920	(0.2)	NR	
	Segnan, 2007[125]	1	Colonoscopy	26.5	5.1	13/1596	(0.8)	NR	
	SCORE III		FS	32.3	7.2	12/1922	(0.6)	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 E Table 1. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Adeyemo, 2014[209] Fair	118,004	Mixed (including symptomatic)	Perforation	OR per decade (95% CI), unadjusted* Propofol sedation: 1.41 (1.05, 1.89) p=0.02 No propofol: 1.30 (0.93, 1.81) p=0.12 Diagnostic colonoscopy: 1.46 (1.01, 2.13) p=0.04 Therapeutic colonoscopy: 1.32 (1.01, 1.74) p=0.04
Bielawska, 2014[215] Fair	1,144,900	Mixed (including symptomatic)	Perforation	OR (95% CI), unadjusted Age <60: 1.0 60-74: 2.83 (1.94, 4.14) p<0.0001 ≥75: 6.73 (4.55, 9.96) p<0.0001
Blotiere, 2014[216] Fair	947,061	Mixed (including symptomatic)	Perforation	OR (95% CI), unadjusted* Age 0-39: 1.0 (reference) 40-49: 0.78 (0.38, 1.58) 50-59: 1.56 (0.87, 2.79) 60-69: 2.89 (1.66, 5.05) 70-79: 5.75 (3.32, 9.97) ≥80: 10.83 (6.16, 19.05)
			Hemorrhage	OR (95% CI), unadjusted* Age 0-39: 1.0 (reference) 40-49: 1.06 (0.70, 1.62) 50-59: 1.75 (1.22, 2.52) 60-69: 2.51 (1.76, 3.58) 70-79: 4.54 (3.19, 6.45) ≥80: 8.23 (5.71, 11.85)
Zafar, 2014 (1384 CTC) Fair	54,039	Screening	Serious bleeding	OR (95% CI), adjusted[α] Age 66-74: 1.0 (reference) 75-84: 1.14 (0.87, 1.48) ≥85: 1.49 (0.81, 2.75)
			Perforation	OR (95% CI), adjusted[α] Age 66-74: 1.0 (reference) 75-84: 1.02 (0.49, 2.14) ≥85: 1.99 (0.45, 8.69)
			Other GI events	OR (95% CI), adjusted[α] Age 66-74: 1.0 (reference) 75-84: 0.92 (0.70, 1.22) ≥85: 1.22 (0.68, 2.20)
			Cardiovascular events	OR (95% CI), adjusted[α] Age 66-74: 1.0 (reference) 75-84: 1.35 (1.10, 1.64) ≥85: 1.56 (1.05, 2.32)

Appendix E Table 1. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Chukmaitov, 2013[221] Fair	2,315,126	Mixed (including symptomatic)	Serious bleeding	OR (95% CI), multivariate Age 50-65: 1.08 (0.94, 1.25) 65-74: 1.22 (1.03, 1.45) 75-84: 1.71 (1.43, 2.05) ≥85: 2.34 (1.90, 2.88)
			Perforation	OR (95% CI), multivariate Age 50-65: 1.38 (1.01, 1.87) 65-74: 1.80 (1.24, 2.62) 75-84: 2.36 (1.61, 3.48) ≥85: 2.88 (1.75, 4.72)
Cooper, 2013[222] Fair	100,359	Mixed (including symptomatic)	Perforation, splenic injury/rupture, or aspiration pneumonia	OR (95% CI), multivariate Age 66-69: 1 (reference) 70-74: 3.36 (2.03, 5.56) 75-79: 3.63 (2.18, 6.05) 80-84: 5.97 (3.58, 9.97) ≥85: 10.41 (6.18, 17.54) p<0.001
Hamdani, 2013[232] Fair	80,118	Mixed (including symptomatic)	Perforation	For every year increase in age, the risk of a perforation increased by 7% (95% CI, 5 to 9%) Incidence per 10,000: Age 18-49: 3.6† 50-64: 2.6† 65-79: 8.7† ≥80: 31.7 p<0.0001
Pox, 2012[263] Fair	2,821,392	Screening	Major and minor complications	OR (95% CI) Males 55-59: 1.0 (reference) 60-64: 1.2 (1.0, 1.3) 65-69: 1.3 (1.2, 1.5) 70-74: 1.5 (1.3, 1.7) 75-79: 1.7 (1.5, 2.0) 79+: 1.6 (1.3, 2.0) Females 55-59: 1.0 (reference) 60-64: 1.5 (1.3, 1.7) 65-69: 1.8 (1.6, 2.0) 70-74: 2.1 (1.8, 2.4) 75-79: 2.8 (2.4, 3.2) 79+: 3.4 (2.8, 4.1)

Appendix E Table 1. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Rutter, 2012‡[267] Fair	43,456	Mixed (excluding symptomatic)	Perforation	Age 40-49: 0.00% 50-64: 0.03 65-74: 0.10 75-85: 0.17
			Hemorrhage	Age 40-49: 0.23% 50-64: 0.21 65-74: 0.43 75-85: 0.81
			Hospitalization	Age 40-49: 1.1% 50-64: 0.89 65-74: 2.0 75-85: 2.7
			ED/urgent care visit	Age 40-49: 2.9% 50-64: 2.2 65-74: 2.5 75-85: 3.5
Ferlitsch, 2011[48] Fair	44,350	Screening	Cardiopulmonary adverse events	Cardiopulmonary adverse events increased with age- from 0.05% in 50- to 60-year-old patients to 0.25% in 70- to 80-year-old patients (p<0.001)
			Bleeding	Bleeding events were unchanged by age (p=0.23)
Ko, 2010[245] Fair	21,375	Mixed (excluding symptomatic)	Serious bleeding, diverticulitis, perforation, post-polypectomy syndrome	Incidence per 1000 exams (95% CI): Age 40-59: 1.19 (0.59, 2.13) 60-69: 1.80 (0.93, 3.14) 70-79: 3.48 (1.94, 5.72) ≥80: 4.36 (1.41, 10.14)
			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	Incidence per 1000 exams: Age 40-59: 1.95 (1.16, 3.08) 60-69: 3.14 (1.95, 4.80) 70-79: 5.32 (3.38, 7.98) ≥80: 5.23 (1.92, 11.35)
Lorenzo-Zuniga, 2010[252] Fair	25,214	Mixed (including symptomatic)	Perforation	Mean age of patients with perforation: 71.15 (range 36-89) Mean age of patients without perforation: 57.42 (range 5-97) p<0.001

Appendix E Table 1. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Arora, 2009[212] Fair	277,434	Mixed (including symptomatic)	Perforation	Incidence per 100,000 Age 18-50: 66 50-65: 71 65-80: 85 ≥80: 119
Crispin, 2009[224] Fair	236,087	Mixed (including symptomatic)	Bleeding Perforation Cardiorespiratory complication	OR (95% CI) for age squared, per year: 1.0001 (1.0001, 1.0002) p<0.0001 OR (95% CI) for age squared, per year: 1.0003 (1.0002, 1.0005) p<0.0001 OR (95% CI) for age squared, per year: 1.0003 (1.0002, 1.0004) p<0.0001
Warren, 2009**[280] Good	53,220	Mixed (including symptomatic)	Serious GI events (perforation, GI bleeding, transfusion) Cardiovascular events	Adjusted risk per 1000 (95% CI) Age 66-69: 5.0 (3.8, 6.2) 70-74: 5.8 (4.6, 6.9) 75-79: 7.2 (5.9, 8.6) 80-84: 8.8 (6.9, 10.7) ≥85:12.1 (8.7, 15.5) Adjusted risk per 1000 (95% CI) Age 66-69: 12.6 (11.0, 14.3) 70-74: 16.0 (14.4, 17.6) 75-79: 20.6 (18.6, 22.5) 80-84: 25.7 (23.0, 28.4) ≥85: 31.8 (27.4, 36.1)
Mansmann, 2008[254] Fair	236,087	Mixed (including symptomatic)	Serious adverse events (including bleeding, perforation, and cardiorespiratory events)	All serious adverse events were more frequent in older age groups
Rabeneck, 2008[265] Fair	97,091	Mixed (including symptomatic)	Bleeding Perforation	OR (95% CI), multivariate Age 50-59: 1.00 60-75: 1.61 (1.20, 2.16) p= 0.001 Age 50-59: 1.00 60-75: 2.06 (1.79, 2.37) p<0.0001

Appendix E Table 1. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Levin, 2006[249] Fair	16,318	Mixed (excluding symptomatic)	Perforation	RR (95% CI) Age 40-59: 1.0 60+: 5.2 (1.4, 19.2)
			Serious bleeding or diverticulitis requiring surgery	RR (95% CI) Age 40-59: 1.0 60+: 1.8 (0.81, 3.9)
			Any serious complication	RR (95% CI) Age 40-59: 1.0 60+: 1.2 (0.9, 1.7)
Korman, 2003[247] Fair	116,000	Mixed (including symptomatic)	Perforation	Most perforations occurred in patients over 60 years of age.

* Similar findings for adjusted odds ratios
† Calculated
‡ Also reports deaths, diverticulitis, abdominal pain, and any serious adverse event
** Also reports paralytic ileus, nausea, vomiting and dehydration, abdominal pain
α Adjusted for sex, age, race, comorbidities associated with adverse events, and adverse events in preceding 90 day

Abbreviations: CI = confidence interval; ED = emergency department; GI = gastrointestinal; n = number; OR = odds ratio; p = p-value; RR = rate ratio.

Appendix F Table 1. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	Relevant Outcomes	2015 Status
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	20,000	Randomized trial comparing CTC with FS	Advanced neoplasia incidence; adverse events	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	140,000	Randomized trial comparing FOBT and FS	CRC mortality and incidence; adverse events	Recruiting
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	200,000	Randomized trial comparing FIT and colonoscopy	CRC mortality and incidence	Recruiting
Maximizing yield of the fecal immunochemical test for colorectal cancer screening (MY-FIT). https://clinicaltrials.gov/ct2/show/NCT01634126. Accessed February 9, 2015. NCT01634126	NR	US	3000	Single-sample versus two-sample FIT, using various cut-points	Sensitivity and specificity for CRC and AA	Ongoing
Colonoscopy or fecal occult blood test in screening healthy participants for colorectal cancer. https://clinicaltrials.gov/ct2/show/NCT00102011. Accessed February 9, 2015. NCT00102011	NR	US	4952*	Randomized trial comparing colonoscopy to FOBT	CRC incidence; adverse events	Final data collection completed
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	66,000	Randomized trial comparing colonoscopy to usual care	CRC mortality and incidence; all-cause mortality	Recruiting
Comparative effectiveness of FIT, colonoscopy, and usual care screening strategies. https://clinicaltrials.gov/ct2/show/NCT01710215. Accessed February 9, 2015. NCT01710215	NR	US	6000	Randomized trial comparing FIT, colonoscopy, and usual care	CRC and AA incidence	Recruiting

Appendix F Table 1. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	Relevant Outcomes	2015 Status
Sali L, Grazzini G, Carozzi F, et al. Screening for colorectal cancer with FOBT, virtual colonoscopy and optical colonoscopy: study protocol for a randomized controlled trial in the Florence district (SAVE study). Trials [Electronic Resource] 2013;14:74. NCT01651624	SAVE	Italy	14,000	Randomized trial comparing CTC, FOBT, and colonoscopy	CRC and AA incidence; adverse events	Recruiting
Study of in-home tests for colorectal cancer (SIT). https://clinicaltrials.gov/ct2/show/NCT01998009. Accessed February 9, 2015. NCT01998009	SIT	US	2000	Two FIT and one gFOBT screening with a colonoscopy reference standard	Sensitivity and specificity for advanced neoplasia	Recruiting
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	50,000	Randomized trial comparing FIT with colonoscopy	CRC mortality	Recruiting
Implementation of colorectal cancer screening with FOBT in the Netherlands. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1006. Accessed February 9, 2015. NTR1006	FOCUS	The Netherlands	20,000	Randomized trial comparing gFOBT with FIT	CRC incidence	Recruiting
Screening for colorectal cancer in the Netherlands: A study comparing attendance and feasibility of two different forms of faecal occult blood testing and sigmoidoscopy. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1096. Accessed February 9, 2015. NTR1096	CORERO	The Netherlands	15,000	Randomized trial comparing gFOBT, FIT, and FS	CRC incidence	Recruiting
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	10,000	Randomized trial comparing FOBT with FOBT and colonoscopy	CRC incidence	Recruiting
Implementation of population screening for colorectal cancer by repeated Fecal Immunochemical Test (FIT): 3 round. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2755. Accessed February 9, 2015. NTR2755	FITTeR	The Netherlands	10,000	FIT screening	Sensitivity and specificity for CRC	

* Actual enrollment

Abbreviations: AA = advanced adenoma; CONFIRM = Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer; CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; FOBT = fecal occult blood test; n = number; NordICC = The Northern European Initiative on Colorectal Cancer; SCREESCO = Screening of Swedish Colons; SIT = Study of In-home Tests for Colorectal Cancer; US = United States.