Evidence Synthesis

Number 135

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA-290-2012-00015-I-EPC4, Task Order No. 2

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

AHRQ Publication No. 14-05203-EF-1
October 2015

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-I-EPC4, Task Order No. 2). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors acknowledge the following individuals for their contributions to this project: Smyth Lai, MLS, for creating and conducting the literature searches; Kevin Lutz, MFA, for his editorial assistance; Jennifer Croswell, MD, MPH, at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; and James Allison, MD, Jason Dominitz, MD, Samir Gupta, MD, MSCS, Linda Kinsinger, MD, Carrie Klabunde, PhD, Barnett Kramer, MD, MPH, Theodore R. Levin, MD, David Lieberman, MD, Marion Nadel, PhD, Perry Pickhardt, MD, MPH, Paul Pinsky, PhD, MPH, David Ransohoff, MD, and Jean Shapiro, PhD, for their expert feedback on this report.

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 8492 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 26 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.

Flexible sigmoidoscopy (FS). Based on four RCTs (n=458,002), 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).

Guaiac fecal occult blood test (gFOBT). Based on five RCTs (n=442,088), biennial screening with Hemoccult II compared to no screening resulted in reduction of CRC-specific mortality, ranging from 9 to 22 percentage points after two to nine rounds of screening with 11 to 30 years of followup.

Colonoscopy. One prospective cohort (n=88,902) found CRC-specific mortality rate was lower at 24 years, in persons with self-reported screening colonoscopies, adjusted HR 0.32 (95% CI, 0.24 to 0.45), compared with 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.

Colonoscopy. Only four fair- to good-quality studies (n=4821) reported the diagnostic accuracy of colonoscopy generalizable to community practice. Based on three studies comparing colonoscopy to CTC or CTC-enhanced colonoscopy (n=2290), the per-person sensitivity for adenomas ≥10 mm ranged from 89.1 (95% CI, 77.8 to 95.7) to 94.7 (95% CI, 74.0 to 99.9) percent, and the per-person sensitivity for adenomas ≥6 mm ranged from 74.6 (95% CI, 62.9 to 84.2) to 92.8 (95% CI, 88.1 to 96.0) percent.

Computed tomographic colonography (CTC). Based on studies of CTC with bowel preparation (prep) (k=7), the per-person sensitivity and specificity to detect adenomas ≥10 mm 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 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.

Fecal immunochemical test (FIT)-based stool tests. The sensitivity varied considerably across different qualitative and quantitative FIT assays in the included diagnostic accuracy studies. Based on studies using colonoscopy as the reference standard (k=14), we focused on selected FDA-cleared qualitative and quantitative tests (i.e., OC-Light and OC FIT-CHEK respectively) 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=9989) 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=9989) evaluated an 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 FIT (92.3 percent [95% CI, 84.0 to 97.0]) but with a tradeoff of a lower specificity to detect CRC (84.4 percent [95% CI, 83.6 to 85.1]).

Blood test. 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 97 fair- to good-quality studies for the harms of CRC screening.

Endoscopy (colonoscopy and FS). Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons is relatively uncommon, with a pooled estimate of four perforations (k=26) per 10,000 procedures (95% CI, 2 to 5 per 10,000) and eight major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14 per 10,000). Serious adverse events from screening FS are even less common, with a pooled estimate of one perforation (k=16) per 10,000 procedures (95% CI, 0.4 to 1.4 per 10,000), and two major bleeds (k=10) per 10,000 procedures (95% CI, 1 to 4 per 10,000). 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.

CTC. The risk of perforation for screening CTC (k=14) was less than two events per 10,000 exams. CTC may also have harms resultant from exposure to low-dose ionizing radiation, range 1 to 7 mSv per exam. Approximately 5 to 37 percent of exams have extra-colonic 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 prep, CTC imaging itself, 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 non-endoscopy comparator arms. It is unclear if detecting extra-colonic 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 and the test performance of screening CTC and 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 US and FDA approved for screening. Currently used screening modalities including colonoscopy, FS, CTC, and various high sensitivity stool-based tests each has 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 on a hierarchy of preferred screening tests, will depend on the decisionmakers' criteria for sufficiency of evidence and weighing the net benefit.

Table of Contents

Figures

Tables

Appendixes

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 greater, 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 (US). 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 colorectal cancer to be 56.5 per 100,000. By 2011, the estimate had fallen to 39.9 per 100,000.[2] The National Cancer Institute (NCI) estimates that more than 50,000 people will die in the US 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 US is 43.7 cases per 100,000 persons, with approximately 95 percent of diagnoses occurring in individuals over the age of 45.[3] The lifetime risk of acquiring CRC in the US is about 5 percent, with an age-adjusted death rate of 15.9/100,000. 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, and nearly half of all new cases are diagnosed in individuals from ages 65 to 84.[3] Black men and women have the highest incidence of CRC compared with other racial/ethnic subgroups. This is troubling given that blacks 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 per 100,000 women, the rate for blacks is 27.7 per 100,000 men and 18.5 per 100,000 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 colorectal cancers 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 for 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 other 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 towards 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 clinic practice to distinguish neoplastic from non-neoplastic 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 <10mm were very common in this sample. The prevalence of diminutive polyps (≤5mm) was 27 percent, prevalence of small polyps (6–9mm) was 9 percent, and prevalence of large polyps (≥10mm) was 6 percent. Diminutive polyps (≤5mm) as the largest lesions accounted for 4.6 percent (95% CI, 3.4 to 5.8) of patients with advanced adenomas. Small polyps (6–9mm) accounted for 7.9 percent (95% CI, 6.3 to 9.4) of cases with advanced adenomas. In contrast, large lesions (≥10mm) 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 CORI database by Lieberman and colleagues.[32] In this study, polyps 6–9 mm were detected in 9.1 percent (1275/13,992) of patients. The proportion of advanced histology was 6.6 percent in those with polyps 6–9mm. Only two of these patients had CRC (0.2 percent).

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 suggested that many remain dormant or regress during a 2–3 year period.[23,33] More recently, however, a large cohort (n=22,006) of asymptomatic adults undergoing routine CRC screening with CTC at two US 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 (1982/22,006) 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 percent or more growth), 50 percent (153/306) were stable, and 28 percent (85/306) regressed (20 percent or more reduction). Histology was established in 43 percent of polyps (131/306) after final CTC. Ninety-one percent (21/23) proven advanced adenomas compared with 37 percent (31/84) proven non-advanced adenomas progressed.

Proximal vs. 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 versus 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 CRCs (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, as 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 prep) 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 both 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 (NAACCR) from 2006-2010, the age-adjusted incidence of cancer is 22.6 per 100,000 persons in the distal colon/rectum and 18.9 per 100,000 persons in the proximal colon. The proportion of proximal to total cancers is 42 percent.[46] CRC prognosis and mortality are also different by tumor location in the colon. Analyses of SEER data have shown a higher late- to early-stage incidence for proximal as compared to distal colon/rectum.[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 (NPS), 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 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 analyses suggests that proximal polyps with advanced neoplasia are smaller than distal polyps (7.6 versus 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 NAACCR from 2006-2010, proximal cancers are also more common in women than men, the proportion of proximal to total cancers is 46 percent 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 higher proportion of proximal cancers than other racial or 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 white, blacks, and Asians and Pacific Islanders.[47]

There is some evidence from separate analyses conducted from screening colonoscopy cohorts derived from the Clinical Outcomes Research Initiative (CORI) database on the difference of prevalence and distribution of polyps amongst different racial and ethnic subgroups. However, it

is still unclear the clinical importance of some of these differences. These studies found that blacks (both men and women) had higher prevalence of large adenomas and higher prevalence of proximal lesions (adenomas and advanced neoplasia).[56-59] Based on analogous data from CORI, there does not appear to be 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 (FAP) and Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer [HNPCC]).[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 when 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 of 1.25 percent) versus the highest quartile (average lifetime risk of 25 percent in persons with an inherited familial syndrome).[68]

Some lifestyle factors have also been linked to an individual's 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 colorectal cancer, risk prediction and use of risk prediction models for CRC is suboptimal.[69]

Colorectal Cancer 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 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 US 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 US 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 [gFOBT] or immunochemical-based fecal occult blood testing [FIT], fecal DNA testing), 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 US that have evidence to support their use include high sensitivity gFOBT (Hemoccult SENSA), 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 US, some have been reviewed by the 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 (CLIA) 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 in the US is produced by one primary manufacturer (Hemoccult SENSA by Beckman Coulter). Stool testing is generally performed on spontaneously voided stool samples, as opposed to in-office stool samples obtained by digital rectal exam, because of the less sensitive or unclear test performance of the latter.[75,76]

Since 2001, when the Centers for Medicare and Medicaid Services started covering screening colonoscopy, colonoscopy utilization for screening has increased and the use of FS has decreased.[77,78] Despite lack of randomized controlled-trial 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 CRC compared to distal CRC,[40,41,79-81] colonoscopy remains the most commonly used screening modality in the US.[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 CT colonography and stool DNA testing, have a growing evidence base, and may play an important role in CRC screening. In 2013, the US Food and Drug Administration (FDA) Medical Advisory panel agreed that the benefits of CT colonography to screen for colorectal cancer outweigh the risks (e.g., radiation exposure and identification of extracolonic findings).[84] Only one stool DNA test, a multi-target stool DNA (mtsDNA) test incorporating FIT testing, is currently available and FDA-approved for use for CRC screening. One new blood test for circulating methylated septin 9 gene DNA (m*SEPT9*) is currently available but has not been FDA-approved for use in CRC screening.

While other tests are available for CRC testing, these are no longer widely used as screening tests. 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). Double contrast barium enema (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™), 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. 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 age 76 to 85 years should be individualized based on the patient's comorbidities and prior screening results.

Currently, most US 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 US and internationally (**Appendix A Table 1**).

The largest difference in recommendations exist between the 2008 USPSTF and the 2008 American Cancer Society (ACS), the U.S. Multi-Society Task Force (MSTF), and the American College of Radiology (ACR) on Colorectal Cancer 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 recommendation 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.

In addition to the USPSTF, the Canadian Task Force on Preventive Health Care is also planning an update of its screening for CRC recommendation in 2015.[89]

Previous USPSTF Recommendation

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

- The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, 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 colorectal cancer in adults age 76 to 85 years (C recommendation). There may be considerations that support colorectal cancer screening in an individual patient.
- The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years (D recommendation).
- The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic (CT) colonography and stool DNA testing as screening modalities for colorectal cancer (I statement).

The USPSTF determined that for all screening modalities, starting screening at age 50 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 ages 75 to 85 was small in comparison to the risks of screening people in this decade. 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 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 cannot be determined for this test. The USPSTF concluded that the evidence for CTC to assess the harms related to extracolonic findings is insufficient, and, as a result, could not determine the balance of benefits and harms. They did state, however, that the option of CTC could help reduce colorectal cancer mortality in the population if patients who would otherwise refuse screening found it 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 colorectal cancer in conjunction with microsimulation decision models from CISNET. This review addresses the benefit and harms associated with colorectal cancer screening and the diagnostic accuracy of the individual screening tests currently available, and most commonly used, in US 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 colorectal cancer?
    i. Colonoscopy
    ii. Flexible sigmoidoscopy (FS)
    iii. Computed tomography (CT) colonography
    iv. Stool screening tests:
        a. Any guaiac fecal occult blood test (gFOBT)
        b. Fecal immunochemical test (FIT)
        c. Stool DNA or multi-target stool test
    v. Blood screening test: circulating methylated septin 9 DNA (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) colorectal cancer, b) advanced adenomas, and/or c) adenomatous polyps based on size?
    i. Colonoscopy
    ii. FS
    iii. CT colonography
    iv. Stool screening tests:

   a. high sensitivity gFOBT
   b. FIT
   c. Stool DNA or multi-target stool test
v. Blood screening test: m*SEPT9*

3. a) What are the adverse effects (i.e., serious harms) of the different screening tests (either as single application or in a screening program)? b) 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 WHO International Clinical Trials Registry Platform (ICTRP), for ongoing trials.

Study Selection

Two investigators independently reviewed 8492 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 ages 40 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 colorectal cancer, known genetic susceptibility syndromes (e.g., Lynch syndrome, FAP), personal history of inflammatory bowel disease, previous screening test positive (e.g., gFOBT or FIT positive), iron deficiency anemia, or surveillance for previous colorectal lesion. In studies with mixed populations, we limited our inclusion of studies 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 sample was larger than 10,000 participants. This allowed us to include studies that may detect rare or uncommon harms. We arrived at this number 10,000 based on estimates derived from our previous systematic review.[90] Because many studies reporting extra-colonic 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 colorectal cancer, e.g., anemia, FOBT positive, personal history or colorectal cancer or colorectal lesions.

For the greatest applicability to US practice, we focused on studies conducted in developed countries, as defined by "very high" development according to the UN 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 (KQ1), we did not update the evidence of its test accuracy (KQ2) as it has been replaced with high-sensitivity gFOBT and FIT testing in US practice. We excluded stool testing based on in-office digital rectal exam, double contrast barium enema (DCBE), capsule endoscopy (i.e., PillCam™), and MRC. We also excluded studies that primarily focused on evaluating technological improvements to colonoscopy or CT colonography. We excluded endoscopy studies conducted in primarily single-center research settings or those with a limited number of endoscopists (e.g., less than 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 colorectal cancer 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 colorectal cancer 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 got 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 colorectal cancer, advanced adenoma, and/or adenomatous polyp by size ($\leq$5 mm, 6-9 mm, $\geq$10 mm). We also captured test performance by location in the colon (i.e., proximal versus 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 result 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 extra-colonic findings (incidental findings on CT colonography) and resultant diagnostic work-up and harms of work-up. We extracted extra-colonic findings and radiation exposure per CT colonography exam from relevant diagnostic accuracy (KQ2) 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 Clinical 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 is 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 the synthesis 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 with 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 on CRC incidence and mortality of screening tests without trial evidence (i.e., colonoscopy) compared with no screening; 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 versus 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 (events per person-year) in R version 3.0.2 (The R Project for Statistical Computing, http://www.r-project.org/).[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, <6 mm, ≥6 mm, ≥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 (people who had CRC were removed from the 2x2 table). We calculated sensitivity and specificity in Stata using Jeffrey's confidence intervals. We used 2x2 tables

constructed from data reported in the primary studies. If the observed sensitivity or specificity was 100%, only the lower 95% confidence interval 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 exams with bowel prep separately from those without bowel prep. For each study that reported both sensitivity and specificity, we plotted results in ROC space (sensitivity versus 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 is dependent on the detection limit of the test. Many manufacturers express the test cutoff value in ng 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 extra-colonic findings with harms, we recognize that detection of extra-colonic 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 restricted maximum likelihood (REML) 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 the R version 3.0.2.

Expert Review and Public Comment

A draft research plan was available for public comment in January 2014 that included the analytic framework, KQs, and inclusion criteria. 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 (CDC), National Institutes of Health, Department of Veterans' Affairs, 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 full draft report will be posted for public comment along with the USPSTF draft recommendation statement.

USPSTF and AHRQ 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

KQ1. 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 Colorectal Cancer: Colonoscopy; Flexible Sigmoidoscopy; CT Colonography; Stool Screening Tests: Guaiac Fecal Occult Blood, Fecal Immunochemical, Stool-Based DNA, or Multi-Target Stool DNA Tests; Blood Screening Test: Methylated *SEPT9* DNA?

We included 26 unique fair- to good-quality studies[41,109-133] (published in 48 articles[41,109-155]) 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 of CRC (**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=442,088) 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 (RR 0.91 [95% CI, 0.84 to 0.98] at 19.5 years to RR 0.78 [95% CI, 0.65 to 0.93] at 30 years). Based on one of these trials, conducted in the US, 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 CRC-specific mortality rate was lower in persons with self-reported at least one screening colonoscopy (multivariate adjusted HR 0.32 [95% CI, 0.24 to 0.45]), compared with 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 for 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 for 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 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 were 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 (NHS) (57,166 women) and the Health Professionals Followup Study (HPS) (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 two 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., BMI, 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, non-steroidal 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 ITT 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 colonoscopies (multivariate HR 0.32 [95% CI 0.24, 0.45]) and screening FS (multivariate HR 0.59 [95% CI, 0.45 to 0.76]) compared with those who had never had 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 1815 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 with 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]).

Flexible Sigmoidoscopy

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 screening for CRC recommendation (**Table 6**).[109,123,125,144]

Population Characteristics

Only one included trial was conducted in the United States (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO]);[123,155] the remaining three trials were conducted in Norway (Norwegian Colorectal Cancer Prevention [NORCCAP]),[144] Italy (Screening for COlon Rectum [SCORE]),[125,150] and the United Kingdom (UK Flexible Sigmoidoscopy Screening Trial [UKFSST]).[109,134] All trials started in the 1990s and recruited average-risk adults between the ages of 50 and 74. The mean age at baseline across three of the trials was 56 to 60 (PLCO did not report mean age at baseline but included participants ages 55-74). Only two trials reported underlying percent 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 US trial, PLCO, reported the race/ethnicity of participants, and this trial included 14 percent nonwhite participants.[123]

FS Protocol

All four included trials evaluated screening FS with a limited bowel prep (i.e., not a full bowel prep required for colonoscopy). Two trials used a colonoscope instead of flexible sigmoidoscope to conduct the FS.[125,144] 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).[144] The other trials compared FS to a no-screening control group.[109,123,125] PLCO evaluated screening with followup FS at 3 to 5 years. SCORE and UKFSST evaluated one-time FS.[123] Referral to diagnostic colonoscopy varied across trials and was likely related to referral criteria:

- UKFSST (5.2 percent referred to colonoscopy), biopsy-based referral criteria: polyp 10 mm or larger, three or more adenomas, or high-risk findings (including tubulovillous, villous histology or severe dysplasia or malignancy, 20 or more hyperplastic polyps).[109]
- SCORE (8.6 percent referred to colonoscopy), biopsy-based referral criteria: UKFSST criteria plus adenomas 6–9 mm.[125]
- NORCCAP (20.4 percent 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.[144]
- PLCO (32.9 percent 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.[123]

Study Quality

All included trials were very large, fair-quality, randomized controlled trials. Only PLCO had a traditional randomized trial design in which the control group was consented and enrolled into 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 percent) was found to have had some type of lower GI endoscopy during the screening phase (0–5 years).[123] 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 in cancer incidence because of generally similar study design/methods, population characteristics, and length of followup (median followup of approximately 11–12 years). Based on intention-to-treat analyses across the four trials, one-time FS consistently decreased CRC-specific mortality. The pooled incident rate ratio

(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, 5**). In NORCCAP, FS plus FIT testing arm had lower CRC-specific mortality than the FS only arm (age-adjusted HR 0.62 [95% CI, 0.42 to 0.90] versus HR 0.84 [95% CI, 0.61 to 1.17], respectively).[144] 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]).[123]

Three of the four trials that reported relevant results did not find reductions in all-cause mortality. PLCO did not report all-cause mortality outcomes (**Figure 6**).[109,125,144]

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, 9**).

Subpopulations

Three trials (NORCCAP, PLCO, and UKFSST) reported CRC mortality estimated separately by age and/or sex (**Table 6**).[109,123,144] All of these trials suggest that the benefit in mortality reduction may be greater for men compared to women. PLCO also reported CRC mortality separately by age group. The finding of a greater CRC mortality reduction for older adults compared to middle-aged adults, however, was not statistically significant.

All four trials reported CRC incidence separately by age and/or sex.[109,123,125,144] Three of the four trials (NORCCAP, PLCO, UKFSST) estimated greater CRC incidence reduction for men compared to women.[109,123,144] Only PLCO reported statistic tests for differential effects of the intervention by sex, and these results showed borderline statistical significance (p=0.052).[123] 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 groupings.[123,125] Although trials were not powered to detect differential effects of FS across subgroups, results are suggestive of a stronger benefit in men than women, which may be due to the fact that women had lower proportion of screen-detected cancers and 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.

CT Colonography

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

mortality.

Stool Tests

gFOBT

We found six[114,118-120,124,128] fair- to good-quality large population screening trials (reported in 11 articles,[114,118-120,124,128,143,146-148,151] 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 US. Five of the six trials (conducted in France, Denmark, Sweden, UK, and the US) are older trials with longer-term followup of mortality reported,[114,118,119,124,128] while one newer trial in Finland has not yet reported mortality outcomes.[120]

Trials primarily evaluated biennial testing, although one also evaluated annual testing.[128] Overall, biennial screening with Hemoccult II (k=5, n=442,088) 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 onto 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.[124] This trial also had slightly lower adherence to testing and after adjustment for non-adherence (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).[119] 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.[118,124]

The Minnesota Colon Cancer Control Study trial 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.[128]

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.[118,124] 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 versus RR 0.92 [95% CI, 0.72 to 1.18] in women, interaction test p=0.04).[128]

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 [110,111,117,121,122,126,127,129-133] (published in 16 articles[110,111,117,121,122,126,127,129-133,138,139,149,153]) 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[113,115,116] in six articles[113,115,116,140-142] 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 6000 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 6000 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**.

KQ2. What Are the Test Performance Characteristics (e.g., Sensitivity and Specificity) of the Following Screening Tests (Alone or in Combination) for Detecting a) Colorectal Cancer, b) Advanced Adenomas, and/or c) Adenomatous Polyps Based on Size: Colonoscopy; Flexible Sigmoidoscopy; CT Colonography; Stool Screening Tests: High Sensitivity Guaiac Fecal Occult Blood, Fecal Immunochemical, Stool-Based DNA, or Multi-Target Stool DNA Tests; Blood Screening Test: Methylated *SEPT9* DNA?

We included 33 unique diagnostic accuracy studies[49-52,156-184] (published in 43 articles[49-52,156-194]) that evaluated colorectal cancer (CRC) screening tests compared to an adequate reference standard (i.e., colonoscopy for adenomas, and colonoscopy or robust clinical/registry followup

for colorectal cancer) (**Table 9**). We found no diagnostic accuracy studies that compared colonoscopy or FS to 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 computed tomography colonography (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 greater than just a limited number of endoscopists.[50,52,168,181] We found 23 unique studies evaluating high-sensitivity stool-based testing,[49,156-162,164,166,167,170-172,175-180,182-184] three evaluating high-sensitivity guaiac fecal occult blood tests (hsgFOBT),[156,157,171] 20 evaluating various different fecal immunochemical tests (FIT),[49,156-162,164,166,167,170-172,175-180,182-184] and one evaluating a mtsDNA test, which included a FIT component.[166] In addition, we used a good-quality AHRQ-funded systematic review to summarize older stool-based DNA screening tests,[173] which are no longer available. Finally, we identified only one diagnostic accuracy study that met our inclusion criteria that evaluated a blood test to detect circulating methylated *SEPT9* DNA (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) colorectal cancer or advanced neoplasia (a composite outcome of colorectal cancer plus advanced adenomas), 2) advanced adenomas (generally defined as adenomas ≥10 mm, or with villous components or with high-grade dysplasia), and 3) adenomatous polyps based on size (e.g., ≥10 mm, ≥6 mm). Results for adenomas <6 mm were not commonly reported.

Direct Visualization Tests

Only four fair- to good-quality studies (n=4821) 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=2290), the per-person sensitivity for adenomas ≥10 mm 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 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=6497), the 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 of 0 to 7 cancers). Based on seven studies of CTC with bowel preparation (prep) (n=5328), the per-person sensitivity and specificity to detect adenomas ≥10 mm 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 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=1044) 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) percent. Two studies (n=1169) evaluated CTC without using a bowel prep. Although data is much more limited, it appears that sensitivity of CTC without bowel prep to detect advanced adenomas, adenomas ≥10 mm, or adenomas ≥6 mm is lower than CTC protocols including bowel prep (**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 prep, CTC imaging itself, 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 guaiac fecal occult blood tests (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 versus differential reference standard followup). Fourteen fair- to good-quality studies (n=59,425) that used 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) had relatively high sensitivity and specificity, and are FDA-cleared tests. 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=9989) 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 percent, 95% CI, 96.6 to 98.0 percent) and as high as 40.3 percent (95% CI, 29.8 to 51.4; specificity 91.3 percent, 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 3

additional studies for non-comparable study design or few CRC cases).
Only one stool test using stool DNA testing, the mtsDNA assay Cologuard (Exact Sciences), is available for clinical use. One fair-quality study (n=9989) 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 percent [95% CI, 84.0 to 97.0]) and for advanced adenoma (42.4 percent [95% CI, 38.9 to 45.9]) compared to FIT is accompanied by reduced specificity (84.4 percent [95% CI, 83.6 to 85.1] for CRC and 86.6 percent [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=1516) that found that m*SEPT9* had a relatively low sensitivity to detect colorectal cancer, 48.2 percent (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=4821) included a larger number of endoscopists, and have greater applicability to colonoscopy performance in community practice (**Table 11**).[50,52,168,181]

Population Characteristics

All four of the included trials were conducted in the US. Three of these trials (n=4369) were multicenter trials.[50,52,181] All studies recruited similar populations of asymptomatic, average-risk adults age 50 years or older. Two studies also included persons ages 40 and older with or without a family history.[52,168] The mean age across studies ranged from 58 to 65. The baseline prevalence of cancer in the populations ranged from 0.16 percent to 1.1 percent. The highest prevalence was in the study by Johnson and colleagues with the highest mean age, 65.[168] Two studies included more than 15 percent nonwhite participants.[50,168]

Colonoscopy Details

Only one study actually reported the number of endoscopists (17 endoscopists). 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 report the cecal intubation rate, and both were ≥99 percent.[52,168]

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 adenomas ≥6 mm. Two studies used colonoscopy enhanced with CTC as their criterion standard.[52,181] 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 greater than 5 mm, which 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, persons could have a repeat colonoscopy if indicated by CTC.[50,168] Despite this approach, however, not all the persons 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 get a repeat colonoscopy for lesions detected on CTC actually received the second colonoscopy.[50]

Outcomes

For CRC. In two trials (n=1685), colonoscopy missed CRCs.[52,168] 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.[168] In this study, a repeat colonoscopy was performed in six persons in whom ≥10 mm lesions 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 CRCs. In another study (n=1233), 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 colorectal cancers.

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 ranged from 89.1 percent (95% CI, 77.8 to 95.7)[52] to 94.7 percent (95% CI, 74.0 to 99.9),[181] and the per-person sensitivity for adenomas ≥6 mm ranged from 74.6 percent (95% CI, 62.9 to 84.2)[181] to 92.8 percent (95% CI, 88.1 to 96.0).[52] The per-lesion (per person not reported) sensitivity of colonoscopy in ACRIN for adenomas ≥10 mm 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 of 88.7 percent (95% CI, 85.8 to 91.1) and for adenomas ≥6 mm, 94.2 percent (95% CI, 91.8 to 96.0).[181] None of these studies reported sensitivity or specificity for lesions <6 mm.

Flexible Sigmoidoscopy

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 exams (i.e., six large cohort studies 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.

CT Colonography

We found nine diagnostic accuracy studies[49-52,165,168,169,174,181] in 10 articles[49-52,165,168,169,174,181,193] that evaluated CTC as a screening test in asymptomatic average-risk persons (**Table 12**). Three of these studies were included in the prior review to support the 2008 USPSTF recommendation.[52,168,174] Two of the previously included studies were excluded from this review due to use of older, single-detector technology that are no longer applicable to current practice.[204,205]

Population Characteristics

Six (n=5453) of the nine studies were conducted in the US.[50,52,165,168,174,181] Three trials (n=4369) were multicenter trials.[50,52,181] The sample sizes for these nine studies ranged from 68 to 2531. The largest trial (n=2531) was a multicenter trial (15 centers), ACRIN National CT Colonography Trial, conducted in the US.[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.[52,165,168,169] The mean age across studies ranged from 55 years to 65 years. Only one study (n=452), which was conducted by Johnson and colleagues, had a mean age of 65 or greater.[168] All trials excluded persons with familial hereditary CRC syndromes. Two trials also explicitly excluded persons with family history of CRC in first-degree relatives.[49,174] The baseline prevalence of cancer in the populations ranged from 0.16 percent to 1.1 percent. The highest prevalence was in the study conducted by Johnson and colleagues that also had the highest mean age, 65.[168] 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.[174] 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 US,[50,168] and one study was conducted in South Korea.[169]

CTC Protocol

All included studies evaluated multi-detector CTC using two exams (supine and prone), although protocols for bowel prep, imaging, and reading images varied across studies. Seven studies (n=5328) evaluated CTC with bowel prep with[50-52] or without fecal tagging,[49,168,169,174] and two more recent studies (n=1169) evaluated CTC without bowel prep and with fecal tagging.[165,181] Studies using a bowel prep varied in the types of bowel prep from full prep with PEG to more limited preps using only sodium phosphate or sodium picosulfate. Only one study (n=241),

which was conducted by Kim and colleagues, administered IV contrast as part of the CTC protocol.[169] 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 persons. Seven studies used three or fewer highly trained radiologists,[49,51,165,168,169,174,181] and only one trial (n=2531), ACRIN, used a larger sample of CTC readers (15 radiologists).[50] While readers generally used a combination of 2D and 3D 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.[49,50,52,165,181] Limitations of fair-quality studies included limited reporting on study details (e.g., on attrition, exclusions due to inadequate CTC or colonoscopy), small number of included participants, and, in one study, attribution of lesions seen on CTC as false positives, but not colonoscopy. While the followup (n analyzed/n screened) was generally high (>97 percent) However, reasons for attrition were not consistently reported, in at least five studies, it appears that some of the attrition was due to incomplete or non-diagnostic CTC (e.g., non-adherence, issues with prep or CTC exam, technical error).[50-52,168,181] Only three studies used the best choice of reference standard (i.e., colonoscopy with segmental unblinding (CTC-enhanced colonoscopy).[49,52,181] 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.[165,168,169,174] Details about the number, training, or quality parameters of the endoscopists or colonoscopy itself was 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, non-advanced adenomas) and size (i.e., 6–9 mm, ≥6 mm, ≥10 mm). The test positivity for CTC ranged from 10 to 30 percent of persons undergoing screening CTC. Test positivity is defined as having at least one lesion ≥5 or 6 mm and therefore would have resulted in a followup colonoscopy for polypectomy, or at minimum required surveillance CTC. [50-52,165,168,169,174,181] Three studies reported on detection of lesions smaller than 6 mm.[49,169,174]

Sensitivity and specificity of CTC with bowel prep.

For CRC. Overall the number of cancers (20 cancers) detected in seven studies that evaluated CTC with bowel prep (n=5328) was low, and the actual number of cancers detected ranged from 0 to 7 (**Table 12**). In only one study, ACRIN (n=2531), 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 a bowel prep (n=1044), 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**).[49,51,169] 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 prep (n=4764), the per-person sensitivity for adenomas ≥10 mm ranged from 66.7 percent (95% CI, 45.4 to 83.7) to 93.5 percent (95% CI, 83.6 to 98.1).[49,50,52,168,169] Across four studies using bowel prep (n=4523), the per-person specificity for adenomas ≥10 mm ranged from 86.0 percent (95% CI 84.6, 87.3) to 97.9 percent (95% CI, 95.7, 99.1).[49,50,52,168] The pooled estimate for sensitivity was 89.2 percent (95% CI, 82.0, 96.4; I^2 = 56.9%), and for specificity was 94.4 percent (95% CI, 88.9, 1.00; I^2 = 98.4 percent) (**Figure 11**).

The per-person sensitivity for adenomas ≥6 mm across five included studies using a bowel prep (n=4808) ranged from 72.7 percent (95 % CI, 58.4 to 84.1) to 98.0 percent (95 % CI, 90.9 to 99.8).[49-52,169] Across four studies using bowel prep (n=4567), the per-person specificity for adenomas ≥6 mm 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%). The pooled estimate 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.[49,169,174] We could not calculate per-person sensitivity or specificity using reported data. In two studies (n=548), the per-lesion sensitivity for adenomas <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).[49,169] In two studies (n=375), the per-lesion sensitivity for any polyp (regardless of histology) <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).[169,174]

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 3D, primary 2D, 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.[49,51,169] 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 primary 3D 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. This study also showed relatively high corresponding sensitivities for the detection of all types of lesions. Identification of more sub-centimeter lesions, which will necessarily have a lower prevalence of advanced histology, resulted in lower specificity for advanced neoplasia.

For adenomas ≥10 mm, one study conducted by Johnson and colleagues observed lower sensitivity than the other studies.[168] This fair-quality study was conducted in a somewhat older population (mean age 65), with a higher prevalence of cancer, using a limited number of CTC readers using primary 3D reading strategy. The CTC protocol did not use fecal tagging. The authors reported that the CTC exams were conducted prior to standard fecal tagging and insufflation practices. For adenomas ≥6 mm, 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 or CTC readers found lower specificities for adenoma ≥10 mm[50] and adenomas ≥6 mm.[52] The lower specificities did not correlate with higher sensitivities in these studies. Both of these studies used fecal tagging and primary 3D 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 prep reported on the distribution of lesions in the colon.[49-52] The percent of ≥10 mm adenomas in the distal colon was 49 to 73, and the percent of 6–9 mm adenomas was 48 to 66. 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 prep and without fecal tagging against colonoscopy with segmental unblinding. The sensitivity for advanced adenomas did not vary significantly by location (proximal 88.9 percent [95% CI, 58.6 to 98.8] versus distal 91.7 percent [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=2531) evaluated CTC with bowel prep 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 65 years and older (n=477), compared with those younger than 65 years (n=2054). The per-person sensitivity for adenomas or cancers ≥10 mm 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 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 prep and distention by age group.

Sensitivity and specificity of CTC without bowel prep. Only two studies (n=1169) evaluated CTC performance without bowel prep but using fecal tagging (**Table 12**).[165,181] Both studies were good quality and conducted in the US. Neither study was designed to estimate the diagnostic accuracy to detect CRC, as the total number of CRCs was very low (four cancers). One study (n=564), conducted by Fletcher and colleagues, reported a per-person sensitivity and specificity for detection of adenomas ≥10 mm and ≥6 mm that appeared comparable to those studies using a bowel prep, 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 appeared comparable to those studies using a bowel prep, although the sensitivity for adenomas ≥6 mm was lower: 57.7 percent (95% CI, 45.4 to 69.4).[181] This study did not report test performance for advanced adenomas or advanced neoplasia. Given the clinical heterogeneity among studies with and without bowel prep, it is unclear from these two studies if lower sensitivities for detection of certain lesions are due to lack of bowel prep use or other differences in study design, population, or CTC protocol.

High Sensitivity Stool Tests: Guaiac Fecal Occult Blood Tests (gFOBT)

Study Details

Three fair-quality trials (n=15,969) reported results of a high sensitivity guaiac fecal occult blood test (gFOBT; Hemoccult Sensa) in adults at average risk for CRC (**Table 13**).[156,157,171] Two of these studies were included in the previous systematic review.[156,157] Two were multicenter studies,[156,171] and one was conducted at a single medical center.[157] Two studies were conducted in the US,[156,157] and one was conducted in Israel.[171] 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.[157] In another study, gFOBT-negative patients were recommended to have sigmoidoscopy.[156] Mean or median age was not reported, but studies included individuals 50 years or older; 50 to 60 percent of the enrolled population were female in two reporting studies.[156,157] 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**).[156]

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**).[171] 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.[157] The 95 percent confidence intervals 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).[156]

High Sensitivity Stool Tests: Fecal Immunochemical Test

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 vary 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 Methods). 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[49,158,161,162,164,166,172,175,176,178-180,183,184] (published in 20 articles[49,158,161,162,164,166,172,175,176,178-180,183,184,186,187,189,191,194,206]) that evaluated FIT as a screening test in asymptomatic average-risk persons and followed all screenees (both screen negatives and positives) with a diagnostic colonoscopy (**Table 15**). Three of these studies were included in the review to support the 2008 USPSTF recommendation.[161,175,176] We excluded one of the previously included studies from this review because the study was conducted in high-risk patients.[207] 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.[158,186]

Population characteristics. Of the 14 included studies of FITs, eight were conducted in Asia (Japan, Taiwan, Hong Kong, or South Korea),[161,162,175,176,178-180,184] four were conducted in Europe (Germany, Netherlands),[49,158,164,183] one was conducted in the US,[172] and one, which compared a FIT to the mtsDNA test (includes a FIT), was conducted in the US and Canada.[166] Five of these studies were single-center studies,[161,162,175,178,180] six were multicenter studies,[158,164,166,179,183,184] and three studies did not provide sufficient description.[49,172,176] 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, but when reported, was 40 in two studies.[172,176] Reported mean age varied from 46.8 to 64.2. The proportion of females enrolled in these studies ranged from about 40 to 60 percent, except for 28 percent in one study.[175] Baseline prevalence of cancer ranged from 0.15 to 1.7 percent and appeared 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 US,[164,172] and one study (conducted in the US and Canada) reported 16 percent nonwhite participants.[166]

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 versus various options for automation) or in combination with assays for other analytes. Not all FITs have been reviewed or cleared for marketing in the US by the FDA, and some FITs have since been discontinued by the manufacturer. One study (in multiple publications, BliTz) compared multiple FITs across the same participant population (**Table 15**),[158,186] one study utilized four different FITs over time in different study subgroups,[172] and one study compared a FIT to the mtsDNA assay, which includes a FIT (see "Stool-based DNA and multi-target stool DNA tests" section).[166] 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[49,158,162,164,183] and nine studies were rated fair quality.[161,172,175,176,178-180,184,208] 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 less than 50 years of age and the study enrolled 2.5 times as many men as women, making the study less representative.[175] In

another study, only 78 percent of enrolled participants had results that were evaluable.[166] 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 adenoma. 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.[158,162,166,175,186] Three studies reported results by sex[158,175,180]and two studies by age groups.[175,180] 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, Monohaem), reported diagnostic accuracy for CRC outcomes (**Table 16**).[161,162,176,178] 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 (95% CI, 90.3 to 91.6) percent,[161] although another study using the same assay reported somewhat poorer sensitivity at 78.6 percent.[162] Confidence intervals were widely overlapping between the two studies. The lowest sensitivity was for Hemosure (assay cutoff 50 µg Hb/g feces) and manufacturer-recommended for a single sample. The Monohaem FIT had the highest sensitivity in this group, even though it has the highest cutoff (~1,000 µg Hb/g feces), due to the recommended testing of three different stool samples. Monohaem sensitivities for CRC using one and two-stool samples were 55.6 and 83.3 percent (data not shown).

For advanced adenomas. Four studies (n=31,576) using eight qualitative FITs (OC-Light, Hemosure, Bionexia FOBplus; Bionexia Hb/Hp Complex; FOB advanced; immoCARE-C; PreventID CC; QuickVue) reported diagnostic accuracy outcomes for advanced adenoma (**Table 16**).[161,162,178,186] Two of these studies utilized OC-Light.[161,162] 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**).

For advanced neoplasia. Six studies (n=36,808) that assessed 11 qualitative FITs (Clearview iFOB complete [cassette]; Clearview ULTRA iFOB [test strip]; OC-Light; QuickVue; Hemosure; Bionexia FOBplus; Bionexia Hb/Hp Complex; FOB advanced; immoCARE-C; PreventID CC; Monohaem) with cutoff ranges from 6 to 50 µg Hb/g feces reported diagnostic accuracy results for advanced neoplasia (**Table 16**).[161,162,172,176,178,186] Six of these FITs have been cleared by the FDA. Among only those 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) (**Figure 15**). The lowest sensitivities were obtained in a study of very small sample sizes for a succession of four FITs.[172] Brenner and colleagues compared six FITs within a screening program (n=1330).[186] Of the FDA-cleared tests in these rare FIT comparison studies, the highest and most consistent sensitivities were obtained by QuickVue (50.0 percent [95% CI, 1.0 to 99.0] and 59.6 percent [99% CI, 51.3 to 67.4]) but at a loss of corresponding specificity (88.0 percent [95% CI, 76.0 to 95.0] and 69.6 percent [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).[161,162] 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 Hemoglobin; RIDASCREEN Hemoglobin-Haptoglobin Complex; FOB Gold; Magstream 1000/Hem SP; OC-hemodia; Hemo Techt NS-Plus C) reported diagnostic accuracy for CRC outcomes (**Table 17**).[49,158,164,166,175,179,180,183,184] CRC prevalence in these studies ranged from 0.3 to 1.7 percent, and the number of CRC cases detected ranged from one to 79. Five studies used a version of the FDA-cleared OC FIT-CHEK assay.[158,164,166,179] 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 percent [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 percent [95% CI, 84.7 to 89.4]).[179] Other assays generally had lower sensitivities (or were tested on few cancer cases) and are either discontinued or otherwise not available in the US.

For advanced adenomas. Six studies (n=18,329) using six quantitative FITs (OC FIT-CHEK/OC-Sensor/OC-SENSOR MICRO; RIDASCREEN Hemoglobin; RIDASCREEN Hemoglobin-Haptoglobin Complex; FOB Gold; OC-hemodia) reported diagnostic accuracy outcomes for advanced adenoma (**Table 17**).[49,158,164,179,180,184,208] Four of these studies used OC FIT-CHEK (on different or unspecified automated analyzers).[158,164,166,179] 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 advanced adenoma prevalence (1.8 percent) used the now discontinued OC-Hemodia and reported the lowest sensitivity of 6.0 percent (no corresponding specificity reported).[180] 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 percent [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.[179]

For advanced neoplasia. Nine studies (n=42,310) that used seven quantitative FITs (OC FIT-CHEK/OC-Sensor/OC-SENSOR MICRO; RIDASCREEN Hemoglobin; RIDASCREEN Hemoglobin-Haptoglobin Complex; FOB Gold; OC-hemodia; Magstream 1000/Hem SP; Hemo Techt NS-Plus C) with cutoff ranges from 2 to 100 µg Hb/g feces reported diagnostic accuracy results for advanced neoplasia (**Table 17**).[49,158,164,175,179,180,183,184,208] Only one of the FITs (OC FIT-CHEK family) is currently available and FDA-cleared. 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.[179] Overall, the highest sensitivity for advanced neoplasia, 76.2 percent, was obtained using Hemo Techt NS-Plus C, a FIT that is not available in the US.

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 they did for proximal lesions, but differences were not consistently apparent or statistically significant. Sensitivities for the reported outcomes tended to be higher in males than in females. 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 percent) versus proximal (72.7 percent; p=0.44) location.[162] The difference was statistically significantly different, however, for advanced adenoma, with a sensitivity for distal lesions of 31.6 percent versus sensitivity for proximal lesions of 22.5 percent (p<0.001). The BliTz study evaluated six qualitative tests, two of which are FDA-cleared (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,[158,186,187,189,191] is presented twice since it has a subsample of the population with different FITs).[175,180,194] Morikawa and colleagues reported FIT (Magstream 1000/Hem SP) 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 Hemoglobin) sensitivity was higher for distal (43.9 percent) than for proximal (29.6 percent) lesions (p=0.04).[189] The latter study also reported a

sensitivity for advanced neoplasia that was higher for men (47.7 percent; 95% CI, 40.0 to 55.6) than for women (30.7 percent; 95% CI, 21.8 to 40.8).[187] Morikawa and colleagues reported that FIT sensitivity for advanced adenoma was higher for males (23.9 percent) than for females (16.7 percent), 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) sensitivities by sex and age categories, but the specific FIT used had poor sensitivity in general and was discontinued, and results were inconclusive.[180] 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) [156,157,159,160,167,170,171,177,182] in 10 articles[156,157,159,160,167,170,171,177,182,188] evaluated FIT as a screening test in asymptomatic average-risk persons and followed screen-positive participants with diagnostic colonoscopy (or FS plus barium enema[182]), 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.[156] 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**).[156,157,159,160,167,170,171,177,182] Four studies were conducted in Asia (Japan, Taiwan),[160,167,177,182] two were conducted in Europe (France, Italy),[159,170] two were conducted in the US by the same group,[156,157] and one study was conducted in Israel.[171] Five studies reported results from screening programs,[159,160,167,177,182] three from multicenter designs,[156,170,171] and one from a single medical center.[157]

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[157,159,177] (**Table 19**), which were OC-Hemodia and HemeSelect, 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[177]). Specificity ranged from 94.4 to 96.3 percent across all tests. Allison and colleagues reported sensitivity (81.8 percent) and specificity (96.9 percent) only for distal CRC using Flexure OBT, with an assay cutoff of 300 µg Hb/g feces (n=5356, data not shown).[156]

Five studies (n=82,840) utilized quantitative FITs (**Table 20**).[160,167,170,171,182] Three of these studies used the FDA-cleared OC FIT-CHEK family of FITs;[160,171,182] one of these studies compared OC FIT-CHEK to HM-JACK in the context of a nationwide screening program linked to a cancer registry.[182] A third study used OC-Hemodia FIT (discontinued).[167] All of these FITs have cutoffs in the range of 10–20 µg Hb/g feces. A fourth study used the non-FDA-cleared Magstream 1000 FIT, with a cutoff of 100–200 µg Hb/g feces.[170] 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.[167,170,171] Chen and colleagues[160] 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.[167,170] 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.[182] Levi and colleagues, also using OC-Sensor but evaluating three stool samples, detected all of the CRC cases (n=6) in their study.[171]

High Sensitivity Stool Tests: Stool-Based DNA and Multi-Target Stool DNA Tests

In 2012, we published a systematic review on stool-based DNA (sDNA) testing to screen for CRC cancer in average risk adults.[173] 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.[166] 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 sDNA tests in asymptomatic persons.[185,190,192] Because the sDNA 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=5004) that evaluated a multi-marker sDNA test, a prototype to a later version that was clinically available as PreGen Plus.[185,192] The sensitivity to detect CRC for this prototype was discordant between the two studies (25 percent [95% CI, 5 to 57] versus 51.6 percent, [95% CI, 34.8 to 68.0]), although the confidence intervals overlapped. Sensitivity for advanced adenomas was similarly poor in both studies (19 percent [95% CI, 5 to 42] and 15.1 percent [95% CI, 12.0 to 19.0]). Between-study differences, such as differences in study populations, do not clearly account for differences in test sensitivities. 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 2322**). From that review we concluded that there was insufficient evidence regarding the clinical accuracy for sDNA tests in persons at average risk for CRC.

The same manufacturer of sDNA tests included in the prior review reconfigured its sDNA test 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.[166,209] 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 (Exact Sciences), is substantially different from previous sDNA tests by this manufacturer.

One fair-quality diagnostic accuracy study (evaluable n=9989) conducted at 90 clinical sites in the US and Canada compared the results of the mtsDNA test to colonoscopy and a commercially available FIT (OC FIT-CHEK) (**Tables 15, 17**).[166] Participants were asymptomatic individuals aged 50-84 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 65 years and older and as a result, 63 percent of

the evaluable participants were in this age category. Of the participants originally consented for the mtsDNA study, 13.8 percent could not be evaluated because they withdrew consent (3.6 percent), did not have colonoscopy (9.1 percent), or did not submit a stool sample (1 percent). 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 percent), or had technical failure (1.9 percent). 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 test, and slight differences between the evaluable and non-evaluable populations.

mtsDNA testing detected 60 of 65 patients with cancer who were identified by colonoscopy. The sensitivity of the mtsDNA test for CRC was significantly improved statistically compared to the FIT, 92.3 percent (95% CI, 84.0 to 97.0) compared to 73.8 percent (95% CI, 62.3 to 83.3; p=0.002), respectively (**Table 17**).[166] Specificity for CRC, however, was significantly lower statistically by mtsDNA than by the commercial FIT (84.4 percent, 95% CI, 83.6 to 85.1; 93.4 percent, 95% CI, 92.9 to 93.9, respectively), indicating a higher false positive rate by mtsDNA. The pattern of results was similar for advanced adenoma (**Table 17**), with noticeably improved sensitivity for advanced adenoma by mtsDNA, but also with a consequent reduction in specificity.

Blood Test: Methylated *SEPT9* DNA Test

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

This study initially included 7920 asymptomatic individuals from 32 clinical sites in the US and Germany who met inclusion criteria, were aged 50 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=6874), the mean age was 61, 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 prep, with an average of 14 days prior to prep. All patients included in the analyses had colonoscopies from 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=1516) using random sampling stratified by colonoscopy findings, including all 53 cancers, 315 of 666 advanced

adenomas, 210 of the 2359 non-advanced adenomas, and 938 of the 3796 persons without evidence of disease. The test positivity rate in this subset was 10.1 percent (153/1510). 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 by increasing CRC tumor stage. Sensitivity for distal (53.3 percent [95% CI, 34.7 to 72.4]) and proximal CRC (39.4 percent [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.

KQ3. a) What Are the Adverse Effects (i.e., Serious Harms) of the Different Screening Tests (Either as Single Application or in a Screening Program)? b) Do Adverse Effects Vary by Important Subpopulations (e.g., Age)?

We included 97 fair- to good-quality studies[48-50,111,114,161,162,165,168,169,210-249,51,52,121-123,129,132,148,150,173,174,178,181,250-283] (in 111 articles[33,48-50,111,114,134,137,161,162,165,168,193,210-243,284-28651,52,119,121-123,128,129,148,150,169,173,174,178,244-275,287-290,17,132,154,181,276-283]) 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 per exam, and 21 CTC studies reported information on extra-colonic findings. Although extra-colonic findings can be either a benefit or harm, a summary of extra-colonic findings is included in this section. While we found no additional studies examining the harms of stool studies, we did not hypothesize any harms for these noninvasive tests other than diagnostic inaccuracy (i.e., false positive or negative testing) or downstream harms of diagnostic followup seen in "program of screening." We also found no empiric studies that directly addressed issues of harms related to over diagnosis. 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 cancers or interval cancers.

Overall Summary

Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons is estimated at four perforations (k=26) per 10,000 procedures (95% CI, 2 to 5 per 10,000), and eight major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14 per 10,000). Serious adverse events from screening FS are even less common, with a pooled estimate of one perforation (k=17) per 10,000 procedures (95% CI, 0.6 to 3 per 10,000), and three major bleeds (k=11) per 10,000 procedures (95% CI, 1 to 9 per 10,000). FS, however, may require followup diagnostic or therapeutic colonoscopy. From six FS screening trials, the pooled estimate was 14 perforations per 10,000 (95% CI, 9 to 26 per 10,000), and 34 major bleeds per 10,000 (95% CI, 5 to 63 per 10,000) for followup colonoscopy 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 in colonoscopies for stool-positive testing may be higher—the pooled estimate was eight perforations (k=6) per 10,000 (95% CI, 2 to 32 per 10,000) diagnostic colonoscopy.

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 MI, 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 extra-colonic findings, which could be a benefit or harm. Extra-colonic findings are very common and are estimated to occur in 41 to 69 percent of examinations, although approximately 5 to 37 percent of exams have extra-colonic findings that necessitate actual diagnostic followup. An even smaller proportion of exams have findings that require any type of definitive treatment (up to 3 percent). From empiric evidence to date, it remains unclear if detection of extra-colonic findings represents a net benefit or harm.

Detailed Results

Screening Programs

gFOBT or FIT

Based on included studies for KQ1 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 US, the Minnesota Colon Cancer Control Study, which evaluated Hemoccult II.[148] 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 for perforation was 8 per 10,000 (95% CI, 2 to 32 per 10,000), I^2 60% (**Figure 16**); and for major bleeding was 1.9 per 1000 (95% CI, 5 to 64 per 10,000), I^2 83% (**Figure 17**), following

diagnostic colonoscopy. From a single round of stool-based screening, assuming a 5-percent test positivity rate and a 100-percent adherence to recommended followup colonoscopy, one to 16 persons would have a perforation and two to 32 persons would have major bleeding per 100,000 people 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/therapeutic colonoscopy. For harms of screening attributed to FS alone, please see the section below. Five included trials for KQ1 evaluating FS screening reported harms from followup colonoscopies (**Table 23**). Only one trial, PLCO, was conducted in the US.[123] This was also the only trial that evaluated more than a single round of screening. Based on these trials, 5 to 33 percent went on for diagnostic/therapeutic colonoscopy. Again, given the limited number of studies (k=5), the estimates of harms are imprecise. The pooled estimate for perforation was 1.4 per 1000 (95% CI, 9 to 26 per 10,000), I^2 0% (**Figure 18**), and for major bleeding was 3.4 per 1000 (95% CI, 5 to 63 per 10,000), I^2 8% (**Figure 19**) for followup colonoscopy for positive screening FS. Therefore, from one round of FS screening, assuming a 25 percent referral onto colonoscopy and 100 percent adherence to recommended followup, approximately 22 to 65 persons would have a perforation, and 12 to 158 persons would experience major bleeding per 100,000 people screened; this is in addition to harms accrued directly from FS, six 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/therapeutic colonoscopy harms by age (groups).

Flexible Sigmoidoscopy

We found 18 fair- or good-quality studies[111,122,123,127,132,134,150,236,239,244,251,256,270,277,279,280,284,291] (in 21 articles[17,33,111,122,123,127,132,134,150,236,239,244,251,256,270,277,279,280,284,285,291]) 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;[239,244,251,277,279] the remaining 13 were prospective.[111,122,123,127,132,134,150,236,256,270,280,284,291] Five studies were conducted in the US.[123,239,251,277,280] The length of followup to determine harms was not commonly reported, but when reported, approximated one month. Despite some clinical heterogeneity, given the stringency of our inclusion criteria, 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),[122,123,127,132,134,150,236,239,244,251,270,277,279,280,284,291] we found that perforations from FS in average-risk screening populations were relatively uncommon, with a pooled point estimate of 1 per 10,000 procedures (95% CI, 0.4 to 1.4 per 10,000), I^2 18.4% (**Figure 20**). Based on 10 studies (n= 137,987),[111,122,132,134,150,236,239,251,279,280] we found that major bleeding episodes from FS were also relatively uncommon, with a pooled point estimate of 2 per

10,000 procedures (95% CI, 0.7 to 4 per 10,000), 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, this study 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.[251]

Colonoscopy

We found 55 fair- or good-quality studies that evaluated serious harms from colonoscopy (**Table 25**).[48,50,121,129,161,162,178,181,210,211,213,215-218,222-225,227,233,235,237,240,241,243,244,247-249,252,253,255-257,264-267,269-272,274-277,281,282214,220,246,250,268,283] Twenty-four studies were conducted explicitly and exclusively in screening populations (or reported the harms specific to the screening subgroup);[48,50,121,129,161,162,178,181,211,215,218,224,225,243,249,256,257,264,270,274-276,282,283] five studies we conducted in asymptomatic (but not necessarily screening) populations,[214,220,246,250,268] and 26 studies were conducted in mixed populations (including nonscreening colonoscopies).[210,213,216,217,222,223,227,233,235,237,240,241,244,247,248,252,253,255,265-267,269,271,272,277,281] Thirty-one of these 54 studies were retrospective cohort studies,[210,213,215-217,222,223,225,227,233,235,237,240,241,244,248-250,253,255,266-269,272,274,275,277,281-283] while the other 24 were prospective study designs.[48,50,121,129,161,162,178,181,211,214,218,220,224,243,246,247,252,256,257,264,265,270,271,276] Twenty-six studies were conducted in the US.[50,181,210,213,215,216,220,222,223,227,233,240,243,246-250,257,265,267,268,277,281-283] 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, ED 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,[48,50,121,129,161,162,178,181,214,215,218,220,224,225,243,246,250,257,264,268,270,274-276,282,283] we found that perforations from colonoscopy were relatively uncommon, with a point estimate of 4 per 10,000 procedures (95% CI, 2 to 5 per 10,000), I^2 86% (**Figure 22**). Based on 22 studies (n=3,347,101),[50,121,129,161,178,181,214,215,218,220,224,225,246,250,257,264,268,274-276,282,283] we found that the risk of major bleeding from colonoscopy was 8 per 10,000 procedures (95% CI, 5 to 14 per 10,000), 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.[48,50,129,214,252,267,271,272] 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).[121,213,274,281]The risk of perforation and bleeding was statistically significantly higher in the colonoscopy group in three of the four studies.[121,213,281]

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 events, and GI 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.[274,281] 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)[240] and comparative harms of different bowel preps (k=2).[235,249] Splenic injury (rupture) is a rare, but serious, event previously described as case-reports following colonoscopy. This large retrospective study found splenic injury in 0.002 percent (7/296,248) of colonoscopies, only one of which happened during a screening colonoscopy.[240] Two studies that assessed harms compared polyethylene glycol (PEG) versus sodium phosphate (SP) bowel prep found greater risk of serious harm, including acute kidney injury for PEG compared to SP, especially in older adults (age ≥65).[235,249]

Nineteen studies provided differential harms of colonoscopy by age (groups) (**Appendix E**).[48,210,213,216,217,222,223,225,233,246,248,250,253,255,264,266,268,281,283] Only two studies provided differential harms limited to screening populations: one in Australia (n=44,350)[48] and another in the US (n=55,423).[283] The Australian study found that cardiopulmonary adverse events increased with age, from 0.05 percent in ages 50–60 to 0.25 percent in ages 70–80 ($p<0.001$), whereas bleeding events were similar ($p=0.23$).[48] The American 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=1384), although only cardiovascular events were statistically significant.[283] The remaining 17 studies were large studies of colonoscopy harms in mixed populations (n>10,000), including, but not limited to, screening colonoscopies. Serious adverse events were not reported by age for the screening subgroups in these studies. In general, studies of colonoscopies performed for mixed indications found increasing risk of serious adverse events, including bleeding, perforation, and serious 30-day serious adverse events, with increasing age. Seven studies reported increasing age as risk factor for serious adverse events after adjusting for potential confounders.[216,217,222,223,246,268,281] Only two studies explicitly include 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.[216,268] 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) or had a mean age ≥65.[223,227,235,264,274,281]

CT Colonography

Serious Adverse Events

We found 15 fair- to good-quality studies that addressed serious adverse effects of screening CTC (**Table 26**).[49-51,129,165,169,181,212,229,238,243,256,263,273] 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 exams),[238,263,273] and one was a retrospective study conducted in a mixed population that presented screening results separately.[283] 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 prep or the CTC exam itself, and vasovagal syncope or pre-syncope. The mean age ranged from 51 to 77, 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.[49-51,129,165,169,181,212,229,238,243,256,263,273] Evidence of any clinically significant adverse effects primarily came from four retrospective studies (n=65,082), which included both asymptomatic and symptomatic populations.[238,263,273] These four studies suggested an increased risk of perforation in symptomatic compared with asymptomatic persons. Three of these studies specified perforation rates in the screening CTC subgroup.[263,273,283] No perforations were reported in one study's screening subgroup of 11,707 procedures.[263] In the study by Sosna, there was one screening-related perforation in 11,870 procedures (number of CTC screening procedures not reported).[273] In one small study using Medicare claims data, 1 perforation was found among 1384 screening CTC exams.[283] While there were seven perforations in 40,121 procedures in a fourth study, the author states than none was due to mechanical insufflation and five of the seven perforations were following persons who also had colonoscopy within 2 weeks.[238] Results were not reported for screening only exams in this study. Limited data suggest that not all CT-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.[273] In the study by Pickhardt and colleagues, only one of the two perforations was clinically symptomatic and required treatment.[263]

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

Radiation Exposure per Exam

Many of the CTC diagnostic accuracy studies in this review did not report actual radiation exposure or provide sufficient information to calculate the radiation exposure (**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 exam (dual positioning supine and prone) was about 4.5 to 7 mSv.[49,50,165,181] 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.[212,229,256] A recent survey of academic and nonacademic institutions (62 of 109 responding) found that the median radiation dose per screening CTC exam was 4.4 mSv.[292] In contrast, two older reviews provided estimates of radiation exposure and found a dose range per CTC exam (not limited to screening exams) from 1.6 to 24.4 mSv, with a median dose estimate of 8.8 mSv or 10.2 mSv.[293,294] Overall, the body of evidence reflects a decrease in radiation exposure for CTC exams 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.

Extra-Colonic Findings

Incidental extra-colonic findings detected on CTC can be a benefit or a harm, depending on the finding itself. CT Colonography Reporting and Data System (C-RADS) is a well-recognized standard for reporting findings at CTC. Under C-RADS, extra-colonic findings are categorized into five categories: E0 = limited exam, E1 = normal exam or normal variant, E2 = clinically unimportant finding in which no work-up is required, E3 = likely unimportant or incompletely characterized in which work-up may be required, and E4 = potentially important finding requiring followup.[295] Some studies examining extra-colonic 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 or larger, aneurysms of the splenic or renal arteries, adenopathy greater than 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) [50,52,129,181,219,221,228,230-232,234,243,245,254,258,260-262,278,286,289] (seven studies with overlapping populations reported different extra-colonic findings) in 22 articles[50,52,129,181,193,219,221,228,230-232,234,243,245,254,258,260-262,278,286,289] reporting on extra-colonic findings in asymptomatic persons, 16 studies (n=35,409) in screening populations,[50,52,129,181,221,228,230,243,245,258,260-262,278,286,289] and five studies (n=2884) in mixed asymptomatic populations (including those undergoing surveillance, those with positive stool testing or iron deficiency anemia, and family history) (**Table 28**).[219,231,232,234,254] The number of exams 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 extra-colonic malignancies only.[261] In general, these studies that reported extra-colonic findings varied greatly in their ability to accurately assess followup and the duration of followup. The longest duration of followup was 5 years, but often the duration of followup was not reported. Thus, none of these studies is able to articulate the true net health benefit or harm due to extra-colonic findings for individuals undergoing CTC.

Overall, extra-colonic findings were common among screening or surveillance CTC exams and ranged from 27 to 69 percent with any extra-colonic findings. Similarly, available studies suggested a very wide range of findings needing additional workup; 5 to 37 percent with E3 or E4 category findings, and 1.7 to 12 percent with E4 category findings. Because E3 or E4, as well as well as those findings 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 extra-colonic 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 (up to 3 percent) required definitive medical or surgical treatment. Extra-colonic cancers were not common and occurred in only 0.5 percent of persons undergoing CTC exams. In the largest series of exams (n=10,286), with about 4 years followup, 36 (0.35 percent) of exams found an extracolonic malignancy, 32 of which received definitive treatment.[261] 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 extra-colonic findings (any or clinically significant) between studies limited to screening populations and those in asymptomatic persons. Extra-colonic findings, however, may be more common with increasing age. The mean age in these studies ranged from 57 to 75. In the two studies with mean age ≥65, the percent with E3/E4 extra-colonic findings was on average higher than studies with younger mean ages.[219,286] Two studies compared extra-colonic findings in persons under age 65 to those 65 and older.[50,254] Both studies found a higher prevalence of both any extra-colonic finding and extra-colonic findings that warranted further workup (E3/E4).[50,254]

Chapter 4. Discussion

Summary of Evidence

Overall

We conducted this review to support the USPSTF in updating its screening for colorectal cancer recommendation. 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 on harms.

A number of tests have been studied for their use in screening average-risk adults for CRC, including: colonoscopy, FS, CT colonography, high sensitivity gFOBT, various qualitative and quantitative FITs, and a multi-target stool DNA 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 (trade-offs) 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 US. Therefore, we have limited empiric data on both 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 stool sample using OC-Light or OC FIT-CHEK. Stool tests that maximize sensitivity, e.g., mtsDNA, multiple sample FITs, or quantitative FIT using lower cut-offs, have lower specificity and therefore need new trials or modelling exercises to understand the tradeoff of higher false positives. Although imperfect, colonoscopy remains the criterion standard for assessing the test performance for 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 extra-colonic findings. Although a blood test would undoubtedly increase screening rates, the Epi proColon® test for circulating m*SEPT9* was not FDA approved for CRC screening because of test performance for the detection of CRC. Instead, the FDA has requested additional data demonstrating that the test will increase adherence to CRC screening in patients who are currently noncompliant with recommended screening.

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 US, 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; however, that compared a single FIT screen to no screening because of the setting (i.e., inclusion limited to those countries with similar achievement in key dimensions of human development as determined by the United Nations).[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 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 testing. 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. Qualitative OC-Light (n=25,707) and the quantitative OC FIT-CHEK (n=15,029) tests, both available in the US 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 US, 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=9989) 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] percent; specificity 87.2 [95% CI, 84.7 to 89.4] percent) or lowered the assay cutoff value (sensitivity 87.5 percent; specificity 90.9 percent). Specificity decreased with increasing sensitivity. The range of sensitivity and specificity estimates for these selected FITs are similar to the results of a meta-analysis of all FIT types, where 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 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=9989), mtsDNA was statistically significantly more sensitive for CRC at 92.3 percent than OC FIT-CHEK (73.8 percent) using a recommended single stool sample for each test. In other included FIT studies, OC FIT-CHEK had higher estimated sensitivity than observed in this study, when multiple samples or lower assay cutoff was 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 percent), for example, was lower than all FIT assays, resulting in the highest false positive rate.

The high rate of unsatisfactory samples for the mtsDNA test (6.25 percent) was concerning when compared to these rates for FITs (0.3 percent). 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.[166] 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 stool positive testing may be higher than perforations for colonoscopies in average risk screening populations (see below); the pooled estimate was eight perforations per 10,000 diagnostic colonoscopies (95% CI, 2 to 32 per 10,000).

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-scheduled FS in PLCO) 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 US suggest that FS (in combination with stool testing) is very uncommon (less than 1 percent).[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 cancers (and advanced adenomas) are dependent on whether the screening FS used biopsy, and the referral criteria used to progress cases onto diagnostic/therapeutic colonoscopy. Screening FS with biopsies do not appear to be commonplace in US practice. The PLCO trial used nonbiopsy referral-based criteria onto followup colonoscopy and had the highest referral onto colonoscopy (about 33 percent) of all the trials.

Colonoscopy

One fair-quality large cohort study using data from the NHS and the HPS found that persons with a 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 cancers than proximal cancers 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 with the magnitude of effect of CRC mortality reduction observed in ITT analyses of RCTs for FS and Hemoccult II. Three large RCTs of screening colonoscopy in average-risk adults are underway that are examining the long-term outcomes on CRC incidence and mortality. The first is the Northern European Initiative on Colorectal Cancer (NordICC) 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 comparing colonoscopy to biennial FIT in Spain[121,312,313] and CONFIRM comparing colonoscopy versus annual FIT in the US.[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 had colonoscopies conducted by more than a handful of expert endoscopists, reported sufficient data 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 of CRC. Based on three studies, the per-person sensitivity for colonoscopy to detect adenomas ≥10 mm ranged from 89.1 to 94.7 percent, and the per-person sensitivity to detect adenomas ≥6 mm ranged from 74.6 to 92.8 percent. Test performance of screening colonoscopy will vary in clinical practice because of bowel prep and colonoscopist performance/experience. The ASGE, ACG, and USMSTF 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 that was conducted by VanRijn and colleagues to assess miss rate determined by tandem colonoscopy (k=6, n=465) found that colonoscopy rarely misses adenomas ≥10mm (2.1%; 95% CI, 0.3 to 7.3) but miss rate increases with smaller-sized adenomas: 5–10mm (15%; 95% CI, 8.0 to 18), and 1–5mm (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 upon adenoma detection, namely chromoendoscopy or digital/virtual chromoendoscopy (e.g., narrow band imaging, flexible spectral imaging CE [FICE], I-scan) or endoscopic technologies to increase mucosal surface area inspection (e.g., wide-angle lens or full spectrum endoscopy, and cap fitted colonoscopy, through-the-scope retrograde viewing device [Third-Eye Retroscope]). The vast majority of the studies that evaluated these technological advancements were small, single-center studies that employed a small number of expert endoscopists. Multi-center trials of back-to-back colonoscopy evaluating the Third-Eye Retroscope or wide-angle lens endoscopy demonstrate fewer missed adenomas with enhanced technologies.[317,318] To date, based on very limited multi-center randomized trials, it appears that although technological advancements can improve detection, data are limited to support widespread adoption (of chromoendoscopy, NBI, or Third-Eye Retroscope) 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 four perforations (k=26) per 10,000 procedures (95% CI, 2 to 5 per 10,000) and eight major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14 per 10,000). 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 one perforation (k=17) (CI: 0.6, 3 per 10,000) and three major bleeds (k=11) per 10,000 procedures (95% CI, 1 to 9 per 10,000). 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 per 10,000) and 34 major bleeds per 10,000 (95% CI, 5 to 63 per 10,000) for followup colonoscopy for positive screening

FS. Other serious harms (e.g., cardiopulmonary and other GI events) are 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,[242,328,329] 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., HCV, HPV) using unsanitized colonoscopies[333-335] and chemical colitis from glutaraldehyde, which is used to disinfect endoscopes.[336]

Harms of Bowel Prep

Common bowel preparation agents for FS include enemas and occasionally oral laxatives. Common bowel preparation agents for colonoscopy or CTC include polyethylene glycol (PEG) solution, oral sodium phosphate (NaP) 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, NaP is generally avoided in persons with renal impairment (includes older patients with reduced glomerular filtration rates [GFR]), cardiovascular impairment (e.g. CHF, recent myocardial infarction), major upper or lower GI motility disturbances, GI 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 CT colonography, except for one person with "water intoxication" due to "over anxious bowel cleansing" in preparation for FS[17] and another person with severe diarrhea.[339] Two included studies that compared PEG versus sodium picosulphate bowel prep found greater risk of serious harm, including acute kidney injury, especially in older adults (age≥65 years) for PEG compared to sodium picosulphate.[235,249] In one large, recent, 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 with PEG in adults older than 66 years.[340] Overall, existing systematic reviews on bowel prep for endoscopy suggest similar tolerability as a number of minor adverse events, no difference in efficacy of prep, and no clinically significant adverse events from PEG or NaP.[341,342] Low-volume PEG (2 liters) with bisacodyl may be better tolerated than full-volume PEG (4 liters), again with no difference in the efficacy of prep.[343] 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 NaP or PEG,[337,344-346] one person with ischemic colitis who received bowel preparation with NaP,[337] one person with symptomatic hypokalemia with

NaP,[337] one person with Boerhaave's syndrome (barogenic esophageal rupture) with PEG,[347] and one person with a seizure secondary to hyponatremia with PEG.[348]

CT Colonography

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 prep (k=7) the per-person sensitivity and specificity to detect adenomas ≥10 mm 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 prep to detect adenomas ≥6 mm 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 percent. Based on very limited data (k=2), it appears that sensitivity of CTC without bowel prep to detect advanced adenomas, adenomas ≥10 mm, or adenomas ≥6 mm is lower than CTC protocols including bowel prep. Our findings are consistent with an existing systematic review by de Haan and colleagues of five prospective CT colonography screening studies in average-risk adults, which found that the per-person sensitivity and specificity for large adenomas (> 10mm) was 83.3 to 87.9 percent and 97.6 to 98.7 percent, respectively.[349] However, per-person sensitivity and specificity for smaller adenomas (≥6 mm) were lower, 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 due to differences in bowel prep, CTC imaging itself, reading protocols, and radiologist experience. In the included studies and current practice there is variation in bowel prep (e.g., full, partial, none) and CTC technical enhancements (e.g., increasing detectors, fecal tagging, electronic cleansing, computer aided detection [CAD], insufflation techniques). Because some variation in accuracy is likely due to CTC protocol and/or radiologists ability, both American College of Radiology and International CTC Standards collaboration have recommended practice guidelines and quality metrics, as well as specification around training and certification.[350-352] In practice, the standard appears to be a dry prep (NaP, Mag citrate, bisacodyl) over standard wet prep (PEG) because of patient preferences and because PEG can leave liquid in the colon that can potentially obscure lesions.[353] 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 prep. Additionally, there are different contrast agents, barium based or iodine based (ionic and nonionic), and the choice for which to use is largely based on local experience. Current practice uses multi-detector row CT scanners, using much thinner slices, with faster scan times, resulting in better imaging and decreased radiation dose. Finally, differences in reading software exist. Currently, V3D® software by Viatronix is the only FDA-cleared software for CTC CRC screening.[354] Commonly used reading software allows for both 2D and 3D 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) go onto colonoscopy for polypectomy. There is variation in practice around smaller lesions, such that 6-9mm lesions may go onto 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 6–9 mm should be offered colonoscopy and lesions less than 5 mm need not be reported.[295,350,355,356] Ultimately, referral and/or surveillance criteria should be dependent on the risk of indwelling cancer in (small) 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 prep. Ideally, while same-day colonoscopy could avoid duplicate prep, it may result in suboptimal colonoscopy if limited bowel prep 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 for screening CTC was less than two per 10,000 exams. 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. There was one case of acute appendicitis in an average-risk adult undergoing routine screening.[357]

Potential harms from CTC include exposure to radiation, especially if used in a program of screening that requires repeated exams. 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 exam (dual positioning). For radiation produced in CT scanners, the effective dose equivalent (Sv) is the same as absorbed dose (Gy) (i.e., 1 mSv = 1mGy).[192] Given that the average amount of radiation that one is exposed to from background sources in the US is about 3.0 mSv per year,[358] ionizing radiation from a single CTC exam is low. Even low doses of ionizing radiation, however, may convey a small excess risk of cancer.[359,360] 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 estimate for lifetime attributable risk of malignancy (i.e., all solid cancers and leukemia) based on the National Research Council's BEIR VII- Phase 2 report findings.[358] Data are inadequate to quantify whether risk for noncancer diseases exists for low-dose radiation exposure.

Most experts in radiation exposure consider the current report from the National Academy of Sciences' National Research Council's (NRC) on the impact of low-emission radiation on human health the definitive resource of radiation risk.[358] Based on this report, the committee predicts that approximately one additional individual per 1,000 would develop cancer (solid cancer or leukemia) from an exposure to 10 mSv above background using the linear no-threshold model (LNT). 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.[358] Multiple organizations support the LNT model to estimate potential harms for radiation

exposures less than 100mSv, including the NRC, the International Commission on Radiological Protection (ICRP), the US National Council on Radiation Protection and Measurements, the United Nations (UN) Scientific Committee on the Effects of Atomic Radiation, and the UK National Radiological Protection Board. Other organizations, however, believe that the LNT model is an oversimplification and likely overestimates potential harms for low-dose radiation exposures, including the Health Physics Society (HPS), the France Academy of Sciences/National Academy of Medicine, and the American Nuclear Society.[361] 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 computed tomography.[360,362]

Modeled data based on the NRC's assumptions, and using a mean dose of 8 mSv for women and 7 mSv for men per CTC exam, found that the benefits of CTC screening every 5 years (from age 50 to 80) far outweigh any potential radiation risks, with 15 cases of radiation-related cancers per 10,000 persons screening (95% CI, 8 to 28) versus 358 to 519 CRC cases prevented per 10,000 persons screened.[363]

Extra-Colonic Findings

CTC also detects extra-colonic findings, which could be a benefit (e.g., detection of intervenable extra-colonic cancer, AAA) or harm (e.g., overdiagnosis, procedural harms from subsequent testing). Extra-colonic findings are very common, estimated to occur in 41 to 69 percent of examinations. Despite this, only approximately 5 to 37 percent of exams have extra-colonic findings that necessitate actual diagnostic followup. An even smaller proportion of exams has findings that require any type of definitive treatment (up to 3 percent). Therefore, judicious handling of the reporting and diagnostic workup around extra-colonic 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 exams to obtain bone mineral density from the lumbar spine to screen of osteoporosis if desired/indicated.[364,365] It remains unclear if detection of extra-colonic findings represents a net benefit or harm based on empiric 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 appears varies widely. Preference for which screening test is multifactorial, based on the individual test's ability to detect and/or prevent cancer, the test's side effects or adverse effects (including prep and test itself), the risk of false positive, and the screening frequency (interval of testing).[366] Several patient factors may affect uptake and adherence to screening, including age, sex, socio-economic 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).[367]

Recent estimates of prevalence of CRC screening in the US, based on BRFSS survey data, show that the overall proportion of adults "up to date" on CRC screening increased from 54 percent in 2002 to 65 percent in 2010.[70] About 28 percent of US adults, however, still had never been screened. Colonoscopy remains the most commonly used screening test (about 62 percent) followed by stool tests (about 10 percent). 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 US.[308] Additionally, uptake may be higher in health systems, and health systems with robust IT infrastructure. In the Veterans Health Administration, for example, 80 percent were "up to date" on CRC screening in 2008-2009.[368] Uptake of CRC screening also appears to be higher in the US than in most European countries, such that it may not be fair to extrapolate from CRC screening studies conducted outside the US. Based on comparative utilization data across 11 European countries (i.e., Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland) in 2004 to 2005, the overall proportion of adults "up to date" on CRC screening using endoscopy varied from 6 to 25 percent, and using stool tests ranged from 4 to 61 percent.[369]

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 versus gFOBT testing, greater adherence to single application of stool based testing versus a single application of endoscopy, and greater adherence to FS versus colonoscopy. Data to estimate the adherence to CTC in relationship to other screening tests are limited; however, this data suggest that adherence to CTC adherence may be greater than to colonoscopy. Overall, there are very limited data on adherence within US-based screening programs and adherence to repeated screening over subsequent screening rounds. Additionally, tests other than colonoscopy may require followup diagnostic/therapeutic colonoscopy, and adherence to subsequent colonoscopy also varies and is suboptimal.

Adherence to Screening

We can estimate adherence to initial screening and subsequent testing in the US 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 US; only two have been conducted in the US.[123,128] One of these, the Minnesota trial of screening Hemoccult II, had a 90 percent adherence to at least one round (not reported for individual rounds), which was higher than Hemoccult II trials conducted outside the US (range 60 to 70 percent) (**Table 7**). The other, the PLCO trial of screening FS, had an 84 percent adherence in the first round and 54 percent in the second round, which was higher than the FS trials conducted outside the US (range 58 to 67 percent in the first round). None of the comparative effectiveness screening trials designed to evaluate comparative adherence was conducted in the US (**Appendix D**). Based on these trials conducted in Western European countries, adherence to a single round of gFOBT ranged from 32 to 59 percent, FIT from 32 to 65 percent, FS from 28 to 47 percent, FS plus stool testing from 20 to 39 percent, colonoscopy from 17 to 27 percent, and CTC approximately 34 percent. One Dutch trial found greater adherence to CTC than colonoscopy.[129] However, estimates of adherence to colonoscopy and CTC are based on limited number of studies, again none of which was conducted in the US.

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 US.[370] 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 3 decades. They found that overall adherence for gFOBT was 47 percent; for FIT, 42 percent; for FS, 35 percent; for colonoscopy, 28 percent; and for CTC, 22 percent. One review of screening trials (k=14), again most not conducted in the US, found that the overall adherence to testing was about 33 percent, adherence to FIT was higher than gFOBT (k=5, RR 1.16 [95% CI 1.03 to 1.3]), and adherence to endoscopy was lower than 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 significantly lower statistically than stool tests (RR 0.78 [95% CI, 0.59 to 1.04]), and adherence to stool tests higher than colonoscopy (RR 0.57, [95% CI, 0.42 to 0.78]).[371] Another existing systematic review of 14 FS studies confirmed that the uptake of FS was lower than stool-based testing (i.e., gFOBT or FIT).[372] One comprehensive systematic review on enhancing the use and quality of CRC screening conducted by Holden and colleagues found a wide variation in adherence to screening in studies designed to improve adherence to CRC screening.[367] The range of adherence in the usual care group (no intervention to improve adherence to screening) for stool tests ranged from 17 to 51 percent; for colonoscopy, from 5 to 59 percent; and for any CRC screening test, from 23 to 55 percent. 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 US practice. We did not find published adherence rates for Hemoccult II testing over the multiple rounds of screening from the Minnesota trial. In the UK, adherence to initial gFOBT was 57 percent in the National Health Service Bowel Cancer Screening Programme, but over three rounds, only 44 percent completed all three screening rounds.[373] One study of adherence to stool testing within an integrated health system, Kaiser Permanente in the US, showed that the initial adherence to FIT was 47 percent, but only 24 percent were adherent to annual testing over four rounds.[374] A retrospective analyses 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.[375] Another study comparing the adherence of colonoscopy to gFOBT in the US found that 85 percent received a one-time colonoscopy, compared to 41 percent who were adherent to three rounds of screening with gFOBT.[376] We found even less data on adherence to followup screening colonoscopy. One small study from the Veterans Health Administration during the 1990s demonstrated 57 percent of persons with a normal screening colonoscopy returned for a repeat screening colonoscopy (at 5.5 year interval).[377] 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/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=2410) in VA patients ages 70 or older found that only 42% of those who had a positive stool test (9%) received a complete colon evaluation within 1 year.[378] 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 one year) in integrated health systems ranged from 44 to 86 percent.[367] This review also found that three older single-institution studies from the 1980s-90s had similar findings of incomplete followup.

Differential Adherence by Age, Sex, Race/Ethnicity

Based on an existing systematic review, national US survey data, and national Medicare data, it appears the 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, and whites more likely than blacks or Latinos.[367,379,380] 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 CRC screening in the US and often explains observed racial/ethnic differences in screening uptake.[381] Additionally, data were much more limited for Asians. Based on one recent study using US California Health Interview Survey (CHIS) 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.[382] 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.[370] One recent cluster RCT (n=997) found that adherence to cancer gFOBT and colonoscopy or choice of gFOBT or colonoscopy increased with age and was higher in Latinos and Asians as compared to blacks.[383] One VA study found overall high adherence to CRC screening, and although blacks had slightly lower adherence (72 percent) compared to whites (77 percent), the disparity was attenuated (compared to national averages) and the disparity was accounted for by confounders of being unmarried and with lower levels of education.[384] 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 percent) to follow-up diagnostic colonoscopy after screening FS, as compared to whites (72 percent).[385]

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.[367] However, one recent study using 2007 data from the US CHIS found that women were less likely to undergo CRC screening than men.[386] Uptake of FOBT was about 26 percent in men versus 24 percent in women, FS was 18 percent in men and 15 percent in women, and colonoscopy was 50 percent in men and 48 percent in women. One recent study using Medicare data from 2001-2005 also found lower colonoscopy screening uptake in women.[387] One comprehensive existing review focusing on adherence to screening (mainly stool testing) found no consistent pattern or difference by sex.[370] Another

meta-analyses of FIT screening studies demonstrated lower uptake in men compared to women.[388]

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 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.[59,389-391] 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 empiric data to support this exist at this time. Modelling exercises may be helpful in understanding the net benefit of earlier screening or different preferred screening modalities by age, sex, and/or race/ethnicity.

Despite the large range in risk and known risk factors for colorectal cancer, risk prediction for CRC is suboptimal, and to date, there is no accepted risk assessment tool to help tailor colorectal 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 blacks beginning at age 45.[392,393] One microsimulation model evaluated tailored screening race/ethnicity and sex, and found that earlier screening in Black men and women (age 47 compared to age 53 in Whites) could marginally improve life expectancy.[394]

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.[38-42,395] FS is no longer commonly used in the US, 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,[162,186,191,396,397] 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/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 proximal cancers specifically, are more common with advancing age. Evidence from our review, as well as others, however, suggests that colonoscopy has increasing serious harms with advancing age. The greatest evidence for harms and inadequate bowel prep is in the very old (>=80 years).[398] The optimal screening modality for older adults and age to stop screening are beyond the scope of this review. Again, modelling exercises may be helpful in understanding the tradeoff between the different screening modalities as both cancers and harms from colonoscopy become more common. Modeled data show that the net benefit of screening diminishes with age due to competing comorbidities, harms associated with screening, and natural life expectancy.[398-400] In 2008, the USPSTF considered modeled data

showing that while increases in life expectancy were considerably lower in adults ages 75 and older,[399,401] the number and severity of co-morbid medical conditions (or co-morbidity index) are equally as important factors influencing decision on when to stop screening as these co-morbidities adversely affect one's prognosis after discovery of CRC (e.g., competing source of mortality, worse survival after cancer treatment).[398]

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 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 another report of microsimulation decision models from CISNET, which will 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 US 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 (less than 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 cut-off 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 US and not FDA-cleared. 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 US. Several ongoing trials may fill this evidence gap for currently used tests (**Appendix F**). This complexity is compounded by technologic advancements over time (i.e., to existing tests like 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 (rectal, distal colon and proximal colon), and variation in the disease process across individuals by age, sex, and race/ethnicity.

We need empiric studies, trials or well-designed cohort studies, in average risk populations to evaluate programs of screening using colonoscopy, the best-performing FITs, and CTC on cancer mortality and cancer incidence. These studies should report (if applicable) on the number of rounds, intervals of testing, test positivity (with explicit criteria or cutoff used to define test positivity), adherence to screening and followup studies, and harms or other burden of testing incurred. In addition, 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 limited evidence base (e.g., mtsDNA, serum m*SEPT9*) is also needed, with reporting of percent inadequate or indeterminate 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 prep). Last, the clinical impact of the identification of extra-colonic findings remains unknown. More complete and consistent reporting around the downstream benefits and harms from the initial detection (subsequent work-up and definitive treatment) of C-RADS E3 and E4 findings need to be published in observational studies or trials with longer-term followup.

Conclusion

Colorectal cancer 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 US and FDA approved for screening. Currently used screening modalities including colonoscopy, FS, CTC, and various high sensitivity stool-based tests each has 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 decisionmakers' 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.

References

1. American Cancer Society. Cancer Facts and Figures 2013. Atlanta: American Cancer Society; 2013.
2. U.S.Cancer Statistics Working Group. United States Cancer Statistics: 1999-2011 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2014.
3. National Cancer Institute. SEER Cancer Statistics Factsheets: Colon and Rectum Cancer. Bethesda, MD: 2014.
4. Cress RD, Morris CR, Wolfe BM. Cancer of the colon and rectum in California: trends in incidence by race/ethnicity, stage, and subsite. Prev Med 2000 Oct;31(4):447-53. PMID: 11006071.
5. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 2004 Mar;54(2):78-93. PMID: 15061598.
6. Irby K, Anderson WF, Henson DE, et al. Emerging and widening colorectal carcinoma disparities between Blacks and Whites in the United States (1975-2002). Cancer Epidemiol Biomarkers Prev 2006 Apr;15(4):792-7. PMID: 16614125.
7. Whitlock EP, Lin JS, Liles E, et al. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008 Nov 4;149(9):638-58. PMID: 18838718.
8. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008 Mar 5;299(9):1027-35. PMID: 18319413.
9. Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review. JAMA 289(10):1288-96, 2003 Mar 12 PMID: 12633191.
10. Chen CD, Yen MF, Wang WM, et al. A case-cohort study for the disease natural history of adenoma-carcinoma and de novo carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy. Br J Cancer 2003 Jun 16;88(12):1866-73. PMID: 12799628.
11. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006 Feb;101(2):385-98. PMID: 16454848.
12. Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review. Cancer 1996 Sep 15;78(6):1149-67. PMID: 8826936.
13. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc R Soc Med 1974 Jun;67(6 Pt 1):451-7. PMID: 4853754.
14. Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 1995 May;108(5):1405-11. PMID: 7729632.
15. Citarda F, Tomaselli G, Capocaccia R, et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001 Jun;48(6):812-5. PMID: 11358901.
16. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993 Dec 30;329(27):1977-81. PMID: 8247072.

17. Thiis-Evensen E, Hoff GS, Sauar J, et al. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999 Apr;34(4):414-20. PMID: 10365903.
18. Selby JV, Friedman GD, Quesenberry CP, Jr., et al. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992 Mar 5;326(10):653-7. PMID: 1736103.
19. 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.
20. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995 Dec 15;123(12):904-10. PMID: 7486484.
21. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012 Feb 23;366(8):687-96. PMID: 22356322.
22. Heitman SJ, Ronksley PE, Hilsden RJ, et al. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. Clinical Gastroenterology & Hepatology 2009 Dec;7(12):1272-8. PMID: 19523536.
23. Hofstad B, Vatn MH, Andersen SN, et al. Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. Gut 1996 Sep;39(3):449-56. PMID: 8949653.
24. Bersentes K, Fennerty MB, Sampliner RE, et al. Lack of spontaneous regression of tubular adenomas in two years of follow-up. Am J Gastroenterol 1997 Jul;92(7):1117-20. PMID: 9219781.
25. Young GP, Bosch LJ. Fecal Tests: From Blood to Molecular Markers. Curr Colorectal Cancer Rep 2011 Mar;7(1):62-70. PMID: 21423316.
26. Crockett SD, Snover DC, Ahnen DJ, et al. Sessile serrated adenomas: an evidence-based guide to management. Clin Gastroenterol Hepatol 2015 Jan;13(1):11-26. PMID: 24216467.
27. Schoenfeld P. Small and diminutive polyps: implications for colorectal cancer screening with computed tomography colonography. Clinical Gastroenterology & Hepatology 4(3):293-5, 2006 Mar PMID: 16527690.
28. Schoen RE, Weissfeld JL, Pinsky PF, et al. Yield of advanced adenoma and cancer based on polyp size detected at screening flexible sigmoidoscopy. Gastroenterology 131 (6):1683 -9, 2006 Dec PMID: 17188959.
29. Coe SG, Wallace MB. Management of small and diminutive colorectal polyps: a review of the literature. Minerva Gastroenterologica e Dietologica 2011 Jun;57(2):167-76. PMID: 21587146.
30. Hassan C, Repici A, Zullo A, et al. Colonic polyps: are we ready to resect and discard? Gastrointestinal Endoscopy Clinics of North America 2013 Jul;23(3):663-78. PMID: 23735109.
31. Hassan C, Pickhardt PJ, Kim DH, et al.Alimentary Pharmacology & Therapeutics 2010 Jan 15;31(2). PMID: 19814745.
32. Lieberman D, Moravec M, Holub J, et al. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology 2008 Oct;135(4):1100-5. PMID: 18691580.

33. Hoff G, Sauar J, Vatn MH, et al. Polypectomy of adenomas in the prevention of colorectal cancer: 10 years' follow-up of the Telemark Polyp Study I. A prospective, controlled population study. Scand J Gastroenterol 1996 Oct;31(10):1006-10. PMID: 8898422.
34. Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: A longitudinal study of natural history. The lancet oncology 2013;14:711-20. PMID: 23746988.
35. Phipps AI, Scoggins J, Rossing MA, et al. Temporal trends in incidence and mortality rates for colorectal cancer by tumor location: 1975-2007. American Journal of Public Health 2012 Sep;102(9):1791-7. PMID: 22873481.
36. Siegel RL, Ward EM, Jemal A. Trends in colorectal cancer incidence rates in the United States by tumor location and stage, 1992-2008. Cancer Epidemiology, Biomarkers & Prevention 2012 Mar;21(3):411-6. PMID: 22219318.
37. Rabeneck L, Davila JA, El-Serag HB. Is there a true "shift" to the right colon in the incidence of colorectal cancer? Am J Gastroenterol 2003 Jun;98(6):1400-9. PMID: 12818288.
38. 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.
39. 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.
40. Brenner H, Chang-Claude J, Seiler CM, et al. Protection From Colorectal Cancer After ColonoscopyA Population-Based, CaseΓÇôControl Study. Ann Intern Med 2011 Jan 4;154(1):22-30. PMID: 21200035.
41. Nishihara R, Wu K, Lochhead P, et al. Long-Term Colorectal-Cancer Incidence and Mortality after Lower Endoscopy. N Engl J Med 2013 Sep 18;369(12):1095-105. PMID: 24047059.
42. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. Ann Intern Med 2013 Mar 5;158(5 Pt 1):312-20. PMID: 23460054.
43. Yamauchi M, Lochhead P, Morikawa T, et al. Colorectal cancer: a tale of two sides or a continuum? Gut 2012 Jun 1;61(6):794-7. PMID: 22490520.
44. Azzoni C, Bottarelli L, Campanini N, et al. Distinct molecular patterns based on proximal and distal sporadic colorectal cancer: arguments for different mechanisms in the tumorigenesis. Int J Colorectal Dis 2007;22(2):115-26. PMID: 17021745.
45. O'Brien MJ, Winawer SJ, Zauber AG, et al. Flat adenomas in the National Polyp Study: is there increased risk for high-grade dysplasia initially or during surveillance? Clinical Gastroenterology & Hepatology 2(10):905-11, 2004 Oct PMID: 15476154.
46. Siegel R, DeSantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014 Mar 1;64(2):104-17.
47. Henry KA, Sherman RL, McDonald K, et al. Associations of census-tract poverty with subsite-specific colorectal cancer incidence rates and stage of disease at diagnosis in the United States. J Cancer Epidemiol 2014;2014:823484. PMID: 25165475.

48. Ferlitsch M, Reinhart K, Pramhas S, et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. JAMA 2011 Sep 28;306(12):1352-8. PMID: 21954479.
49. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009 Feb;58(2):241-8. PMID: 18852257.
50. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008 Sep 18;359(12):1207-17. PMID: 18799557.
51. Lefere P, Silva C, Gryspeerdt S, et al. Teleradiology based CT colonography to screen a population group of a remote island; at average risk for colorectal cancer. European Journal of Radiology 2013 Jun;82(6):e262-e267. PMID: 23473734.
52. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003 Dec 4;349(23):2191-200. PMID: 14657426.
53. Nusko G, Mansmann U, tendorf-Hofmann A, et al. Risk of invasive carcinoma in colorectal adenomas assessed by size and site. Int J Colorectal Dis 1997;12(5):267-71. PMID: 9401839.
54. Gupta S, Balasubramanian BA, Fu T, et al. Polyps with advanced neoplasia are smaller in the right than in the left colon: implications for colorectal cancer screening. Clinical Gastroenterology & Hepatology 2012 Dec;10(12):1395-401. PMID: 22835574.
55. Wong RJ. Marked variations in proximal colon cancer survival by race/ethnicity within the United States. Journal of Clinical Gastroenterology 2010 Oct;44(9):625-30. PMID: 19996985.
56. Lieberman DA, Holub JL, Moravec MD, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. JAMA 2008 Sep 24;300(12):1417-22. PMID: 18812532.
57. Thornton JG, Morris AM, Thornton JD, et al. Racial variation in colorectal polyp and tumor location. Journal of the National Medical Association 2007 Jul;99(7):723-8. PMID: 17668638.
58. Schroy PC, III, Coe A, Chen CA, et al. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. Ann Intern Med 2013 Jul 2;159(1):13-20. PMID: 23817700.
59. Lieberman DA, Williams JL, Holub JL, et al. Race, ethnicity, and sex affect risk for polyps >9 mm in average-risk individuals. Gastroenterology 2014;147(2):351-8. PMID: 24786894.
60. Lee B, Holub J, Peters D, et al. Prevalence of colon polyps detected by colonoscopy screening of asymptomatic Hispanic patients. Digestive Diseases & Sciences 2012 Feb;57(2):481-8. PMID: 21918852.
61. Eaden JA, Mayberry JF. Colorectal cancer complicating ulcerative colitis: a review. Am J Gastroenterol 2000 Oct;95(10):2710-9. PMID: 11051339.
62. Schoen RE. Families at risk for colorectal cancer: risk assessment and genetic testing. J Clin Gastroenterol 2000 Sep;31(2):114-20. PMID: 10993425.
63. Weitz J, Koch M, Debus J, et al. Colorectal cancer. Lancet 2005 Jan 8;365(9454):153-65.
64. Winawer SJ. Screening of colorectal cancer: progress and problems. Recent Results Cancer Res 2005;166:231-44. PMID: 15648193.

65. Taylor DP, Burt RW, Williams MS, et al. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology 2010 Mar;138(3):877-85. PMID: 19932107.
66. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 2001 Oct;96(10):2992-3003. PMID: 11693338.
67. Baglietto L, Jenkins MA, Severi G, et al. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. Journal of Clinical Epidemiology 2006 Feb;59(2):114-24. PMID: 16426946.
68. Hopper JL. Disease-specific prospective family study cohorts enriched for familial risk. Epidemiol Perspect Innov 2011;8(1):2. PMID: 21352566.
69. Win AK, Macinnis RJ, Hopper JL, et al. Risk prediction models for colorectal cancer: a review. Cancer Epidemiol Biomarkers Prev 2012 Mar;21(3):398-410. PMID: 22169185.
70. Vital signs: colorectal cancer screening test use - United States, 2012. MMWR Morb Mortal Wkly Rep 2013 Nov 8;62(44):881-8. PMID: 24196665.
71. Prevlance of colorectal cancer screening among adults--Behavioral Risk Factor Surveillance System, United States, 2010. MMWR: Morbidity & Mortality Weekly Report 2012;61(suppl):51-6. PMID: 22695464.
72. Holden DJ, Jonas DE, Porterfield DS, et al. Systematic review: enhancing the use and quality of colorectal cancer screening. Ann Intern Med 2010 May 18;152(10):668-76. PMID: 20388703.
73. Whitlock EP, Lin J, Liles E, et al. Screening for Colorectal Cancer: An Updated Systematic Review. 2008. PMID: NBK35179 [bookaccession].
74. U.S.Food and Drug Administration. Clinical Laboratory Improvement Amendments: Fecal Occult Blood. 2015.
75. Ashraf I, Paracha SR, Arif M, et al. Digital rectal examination versus spontaneous passage of stool for fecal occult blood testing. Southern Medical Journal 2012 Jul;105(7):357-61. PMID: 22766663.
76. Nakama H, Zhang B, Abdul Fattah AS, et al. Does stool collection method affect outcomes in immunochemical fecal occult blood testing? Dis Colon Rectum 2001 Jun;44(6):871-5. PMID: 11391151.
77. Klabunde C, Breen N, Meissner H, et al. Use of colonoscopy for colorectal cancer screening. Cancer Epidemiol Biomarkers Prev 2005 Sep;14(9):2279-80.
78. Zapka J, Klabunde CN, Taplin S, et al. Screening colonoscopy in the US: attitudes and practices of primary care physicians. J GEN INTERN MED 2012 Sep;27(9):1150-8. PMID: 22539065.
79. 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.
80. 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.
81. Lakoff J, Paszat LF, Saskin R, et al. Risk of Developing Proximal Versus Distal Colorectal Cancer After a Negative Colonoscopy: A Population-Based Study. Clinical Gastroenterology and Hepatology 2008 Oct;6(10):1117-21. PMID: 18691942.
82. Rim SH, Joseph DA, Steele CB, et al. Colorectal cancer screening - United States, 2002, 2004, 2006, and 2008. MMWR Surveill Summ 2011 Jan 14;60 Suppl:42-6. PMID: 21430619.

83. Meissner HI, Breen N, Klabunde CN, et al. Patterns of colorectal cancer screening uptake among men and women in the United States. Cancer Epidemiology, Biomarkers & Prevention 15(2):389 -94 , 2006 Feb PMID: 16492934.
84. McNamara D. FDA Panel: Most favor CTC colorectal cancer screen. Medscape; 2013. http://www.medscape.com/viewarticle/810740. Accessed December 18, 2014.
85. Zijta FM, Bipat S, Stoker J. Magnetic resonance (MR) colonography in the detection of colorectal lesions: a systematic review of prospective studies. European Radiology 2010 May;20(5):1031-46. PMID: 19936754.
86. Spada C, Hassan C, Marmo R, et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clinical Gastroenterology & Hepatology 2010 Jun;8(6):516-22. PMID: 20215066.
87. U.S.Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008 Nov 4;149(9):627-37. PMID: 18838716.
88. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008 May;58(3):130-60. PMID: 18322143.
89. Fitzpatrick-Lewis D. Protocol: Screening for colorectal cancer. 2013. http://canadiantaskforce.ca/methods/protocols/. Accessed November 6, 2013.
90. Whitlock, EP, Lin, J, Liles, E, et al. Screening for Colorectal Cancer: An Updated Systematic Review. 2008. PMID: 20722162.
91. Wallace BC, Small K, Brodley CE, et al. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. Proceedings of the ACM International Health Informatics Symposium 2012:819-24. PMID: None.
92. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999 Sep 15;282(11):1061-6. PMID: 10493205.
93. Whiting P, Rutjes AW, Reitsma JB, et al. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004 Feb 3;140(3):189-202. PMID: 14757617.
94. Leeflang MM, Bossuyt PM, Irwig L. Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis. J Clin Epidemiol 2009 Jan;62(1):5-12. PMID: 18778913.
95. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1978 Oct 26;299(17):926-30. PMID: 692598.
96. Rutjes AW, Reitsma JB, Di NM, et al. Evidence of bias and variation in diagnostic accuracy studies. CMAJ 2006 Feb 14;174(4):469-76. PMID: 16477057.
97. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
98. National Institute for Health and Clinical Excellence. *'The guidelines manual'*. London: National Institute for Health and Clinical Excellence; 2006.
99. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10. PMID: 17302989.

100. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. Ottawa: Ottawa Hospital Research Institute; 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 21, 2014. PMID: None.
101. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011 Oct 18;155(8):529-36. PMID: 22007046.
102. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003 Nov 10;3:25. PMID: 14606960.
103. de Groot JA, Bossuyt PM, Reitsma JB, et al. Verification problems in diagnostic accuracy studies: consequences and solutions. BMJ 2011;343:d4770. PMID: 21810869.
104. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: A comparison of methods. Statistics in Medicine 1999;18:2693-708. PMID: 10521860.
105. Guolo A, Varin C. Package 'metaLik'. 2014.
106. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 2001 Oct 15;20(19):2865-84. PMID: 11568945.
107. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 2010;36(3)
108. Fraser CG, Allison JE, Halloran SP, et al. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. J Natl Cancer Inst 2012 Jun 6;104(11):810-4. PMID: 22472305.
109. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010 May 8;375(9726):1624-33. PMID: 20430429.
110. Berry DP, Clarke P, Hardcastle JD, et al. Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening. Br J Surg 1997 Sep;84(9):1274-6. PMID: 9313712.
111. Brevinge H, Lindholm E, Buntzen S, et al. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55-56 years' old population. Int J Colorectal Dis 1997;12(5):291-5. PMID: 9401844.
112. Elwood JM, Ali G, Schlup MM, et al. Flexible sigmoidoscopy or colonoscopy for colorectal screening: a randomized trial of performance and acceptability. Cancer Detect Prev 1995;19(4):337-47. PMID: 7553676.
113. Faivre J, Dancourt V, Denis B, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. European Journal of Cancer 2012 Nov;48(16):2969-76. PMID: 22572481.
114. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology 2004 Jun;126(7):1674-80. PMID: 15188160.
115. Guittet L, Bouvier V, Mariotte N, et al. Comparison of a guaiac and an immunochemical faecal occult blood test for the detection of colonic lesions according to lesion type and location. British Journal of Cancer 2009 Apr 21;100(8):1230-5. PMID: 19337253.
116. Hamza S, Dancourt V, Lejeune C, et al. Diagnostic yield of a one sample immunochemical test at different cut-off values in an organised screening programme for

colorectal cancer. European Journal of Cancer 2013 Aug;49(12):2727-33. PMID: 23601670.
117. Hol L, van Leerdam ME, van BM, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010 Jan;59(1):62-8. PMID: 19671542.
118. Kronborg O, Jorgensen OD, Fenger C, et al. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004 Sep;39(9):846-51. PMID: 15513382.
119. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. British Journal of Surgery 2008 Aug;95(8):1029-36. PMID: 18563785.
120. Malila N, Palva T, Malminiemi O, et al. Coverage and performance of colorectal cancer screening with the faecal occult blood test in Finland. Journal of Medical Screening 2011;18(1):18-23. PMID: 21536812.
121. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012 Feb 23;366(8):697-706. PMID: 22356323.
122. Rasmussen M, Kronborg O, Fenger C, et al. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study. Scand J Gastroenterol 1999 Jan;34(1):73-8. PMID: 10048736.
123. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012 Jun 21;366(25):2345-57. PMID: 22612596.
124. Scholefield JH, Moss SM, Mangham CM, et al. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012 Jul;61(7):1036-40. PMID: 22052062.
125. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst 2011 Sep 7;103(17):1310-22. PMID: 21852264.
126. Segnan N, Senore C, Andreoni B, et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007 Jun;132(7):2304-12. PMID: 17570205.
127. Segnan N, Senore C, Andreoni B, et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst 2005 Mar 2;97(5):347-57. PMID: 15741571.
128. Shaukat A, Mongin SJ, Geisser MS, et al. Long-Term Mortality after Screening for Colorectal Cancer. N Engl J Med 2013 Sep 18;369(12):1106-14. PMID: 24047060.
129. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. Lancet Oncology 2012 Jan;13(1):55-64. PMID: 22088831.
130. van Roon AH, Goede SL, van BM, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. Gut 2013 Mar;62(3):409-15. PMID: 22387523.

131. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008 Jul;135(1):82-90. PMID: 18482589.
132. Verne JECW, Roger A, Sharon BL, et al. Population based randomised study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing. BMJ 1998 Jul 18;317 PMID: 9665902.
133. Zubero MB, Arana-Arri E, Pijoan JI, et al. Population-based colorectal cancer screening: comparison of two fecal occult blood test. Front Pharmacol 2014 Jan 10;4:175. PMID: 24454288.
134. Atkin WS. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. The Lancet 2002 Apr 13;359(9314):1291-300. PMID: 11965274.
135. Atkin WS, Cuzick J, Northover JM, et al. Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 1993 Mar 20;341(8847):736-40. PMID: 8095636.
136. Bretthauer M, Gondal G, Larsen K, et al. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). Scand J Gastroenterol 2002 May;37(5):568-73. PMID: 12059059.
137. de Wijkerslooth TR, de Haan MC, Stoop EM, et al. Study protocol: population screening for colorectal cancer by colonoscopy or CT colonography: a randomized controlled trial. BMC Gastroenterology 2010;10:47. PMID: 20482825.
138. Denters MJ, Deutekom M, Bossuyt PM, et al. Lower risk of advanced neoplasia among patients with a previous negative result from a fecal test for colorectal cancer. Gastroenterology 2012 Mar;142(3):497-504. PMID: 22108194.
139. Denters MJ, Deutekom M, Fockens P, et al. Implementation of population screening for colorectal cancer by repeated fecal occult blood test in the Netherlands. BMC Gastroenterology 2009;9:28. PMID: 19393087.
140. Faivre J, Dancourt V, Manfredi S, et al. Positivity rates and performances of immunochemical faecal occult blood tests at different cut-off levels within a colorectal cancer screening programme. Digestive & Liver Disease 2012 Aug;44(8):700-4. PMID: 22542582.
141. Guittet L, Bouvier V, Guillaume E, et al. Colorectal cancer screening: why immunochemical faecal occult blood test performs as well with either one or two samples. Digestive & Liver Disease 2012 Aug;44(8):694-9. PMID: 22525156.
142. Guittet L, Bouvier V, Mariotte N, et al. Performance of immunochemical faecal occult blood test in colorectal cancer screening in average-risk population according to positivity threshold and number of samples. International Journal of Cancer 2009 Sep 1;125(5):1127-33. PMID: 19431212.
143. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996 Nov 30;348(9040):1472-7. PMID: 8942775.
144. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: A randomized clinical trial. JAMA 2014 Aug 13;312(6):606-15. PMID: 25117129.
145. Kewenter J, Brevinge H, Engaras B, et al. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult

blood testing. Results for 68,308 subjects. Scand J Gastroenterol 1994 May;29(5):468-73. PMID: 8036464.
146. Malila N, Oivanen T, Malminiemi O, et al. Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. BMJ 2008;337:a2261. PMID: 19022840.
147. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000 Nov 30;343(22):1603-7. PMID: 11096167.
148. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993 May 13;328(19):1365-71. PMID: 8474513.
149. Parra-Blanco A, Nicolas-Perez D, Gimeno-Garcia A, et al. The timing of bowel preparation before colonoscopy determines the quality of cleansing, and is a significant factor contributing to the detection of flat lesions: a randomized study. World J Gastroenterol 2006 Oct 14;12(38):6161-6. PMID: 17036388.
150. Segnan N, Senore C, Andreoni B, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. J Natl Cancer Inst 2002 Dec 4;94(23):1763-72. PMID: 12464648.
151. Thomas W, White CM, Mah J, et al. Longitudinal compliance with annual screening for fecal occult blood. Minnesota Colon Cancer Control Study. Am J Epidemiol 1995 Jul 15;142(2):176-82. PMID: 7598117.
152. UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 359(9314):1291-300, 2002 Apr 13 PMID: 12387976.
153. van Roon AH, Wilschut JA, Hol L, et al. Diagnostic yield improves with collection of 2 samples in fecal immunochemical test screening without affecting attendance. Clinical Gastroenterology & Hepatology 2011 Apr;9(4):333-9. PMID: 21185397.
154. van DL, de Wijkerslooth TR, de Haan MC, et al. Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial. Eur J Radiol 2013;45(3):182-8. PMID: 23446667.
155. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst 2005 Jul 6;97(13):989-97. PMID: 15998952.
156. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007 Oct 3;99(19):1462-70. PMID: 17895475.
157. Allison JE, Tekawa IS, Ransom LJ, et al. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996 Jan 18;334(3):155-9. PMID: 8531970.
158. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. European Journal of Cancer 2013 Sep;49(14):3049-54. PMID: 23706981.
159. Castiglione G, Visioli CB, Ciatto S, et al. Sensitivity of latex agglutination faecal occult blood test in the Florence District population-based colorectal cancer screening programme. Br J Cancer 2007 Jun 4;96(11):1750-4. PMID: 17453007.

160. Chen LS, Yen AM, Chiu SY, et al. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncology 2011 Jun;12(6):551-8. PMID: 21592859.
161. Cheng TI, Wong JM, Hong CF, et al. Colorectal cancer screening in asymptomaic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. J Formos Med Assoc 2002 Oct;101(10):685-90. PMID: 12517041.
162. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clinical Gastroenterology & Hepatology 2013 Jul;11(7):832-8. PMID: 23376002.
163. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014 Feb;63(2):317-25. PMID: 23408352.
164. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012 Oct;107(10):1570-8. PMID: 22850431.
165. Fletcher JG, Silva AC, Fidler JL, et al. Noncathartic CT colonography: Image quality assessment and performance and in a screening cohort. Am J Roentgenol 2013;201(4):787-94. PMID: 24059367.
166. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget Stool DNA Testing for Colorectal-Cancer Screening. N Engl J Med 2014 Mar 19;371(2):187-8. PMID: 25006736.
167. Itoh M, Takahashi K, Nishida H, et al. Estimation of the optimal cut off point in a new immunological faecal occult blood test in a corporate colorectal cancer screening programme. J Med Screen 1996;3(2):66-71. PMID: 8849762.
168. Johnson CD, Fletcher JG, MacCarty RL, et al. Effect of slice thickness and primary 2D versus 3D virtual dissection on colorectal lesion detection at CT colonography in 452 asymptomatic adults. AJR American journal of roentgenology 2007 Sep;189(3):672-80. PMID: 17715116.
169. Kim YS, Kim N, Kim SH, et al. The efficacy of intravenous contrast-enhanced 16-raw multidetector CT colonography for detecting patients with colorectal polyps in an asymptomatic population in Korea. Journal of Clinical Gastroenterology 2008 Aug;42(7):791-8. PMID: 18580500.
170. Launoy GD, Bertrand HJ, Berchi C, et al. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. International Journal of Cancer 2005 Jun 20;115(3):493-6. PMID: 15700317.
171. Levi Z, Birkenfeld S, Vilkin A, et al. A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study. International Journal of Cancer 2011 May 15;128(10):2415-24. PMID: 20658527.
172. Levy BT, Bay C, Xu Y, et al. Test Characteristics of Faecal Immunochemical Tests (FIT) Compared with Optical Colonoscopy. J Med Screen 2014 Jun 23;21(3):133-43. PMID: 24958730.

173. Lin, JS, Webber, EM, Beil, TL, et al. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults. 12-EHC022-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. PMID: 22457883.
174. Macari M, Bini EJ, Jacobs SL, et al. Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. Radiology 2004 Mar;230(3):629-36. PMID: 14739311.
175. Morikawa T, Kato J, Yamaji Y, et al. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005 Aug;129(2):422-8. PMID: 16083699.
176. Nakama H, Yamamoto M, Kamijo N, et al. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. Hepatogastroenterology 1999 Jan;46(25):228-31. PMID: 10228797.
177. Nakama H, Kamijo N, bdul Fattah AS, et al. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. Journal of Medical Screening 1996;3(2):63-5. PMID: 8849761.
178. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Alimentary Pharmacology & Therapeutics 2013 Oct;38(7):835-41. PMID: 23957462.
179. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010 Sep;105(9):2017-25. PMID: 20502450.
180. Sohn DK, Jeong SY, Choi HS, et al. Single immunochemical fecal occult blood test for detection of colorectal neoplasia. Cancer Res Treat 2005 Feb;37(1):20-3. PMID: 19956505.
181. Zalis ME, Blake MA, Cai W, et al. Diagnostic accuracy of laxative-free computed tomographic colonography for detection of adenomatous polyps in asymptomatic adults: a prospective evaluation. Ann Intern Med 2012 May 15;156(10):692-702. PMID: 22586008.
182. Chiang TH, Chuang SL, Chen SL, et al. Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. Gastroenterology 2014 Dec;147(6):1317-26. PMID: 25200099.
183. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World Journal of Gastroenterology 2014 Jan 28;20(4):1038-47. PMID: 24574776.
184. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2014 Aug 15 PMID: 25153599.
185. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149(7):441-50. PMID: 18838724.
186. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. International Journal of Cancer 2010 Oct 1;127(7):1643-9. PMID: 20049840.

187. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010 Nov;105(11):2457-64. PMID: 20700114.
188. Grazzini G, Castiglione G, Ciabattoni C, et al. Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results. Eur J Cancer Prev 2004 Feb;13(1):19-26. PMID: 15075784.
189. Haug U, Kuntz KM, Knudsen AB, et al. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. British Journal of Cancer 2011 May 24;104(11):1779-85. PMID: 21559011.
190. Haug U, Hillebrand T, Bendzko P, et al. Mutant-enriched PCR and allele-specific hybridization reaction to detect K-ras mutations in stool DNA: high prevalence in a large sample of older adults. Clin Chem 2007 Apr;53(4):787-90. PMID: 17317884.
191. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009 Feb 3;150(3):162-9. PMID: 19189905.
192. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004 Dec 23;351(26):2704-14. PMID: 15616205.
193. Johnson CD, Herman BA, Chen MH, et al. The National CT Colonography Trial: assessment of accuracy in participants 65 years of age and older. Radiology 2012 May;263(2):401-8. PMID: 22361006.
194. Morikawa T, Kato J, Yamaji Y, et al. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. Am J Gastroenterol 2007 Oct;102(10):2259-64. PMID: 17617203.
195. Anderson JC, Alpern Z, Messina CR, et al. Predictors of proximal neoplasia in patients without distal adenomatous pathology. Am J Gastroenterol 2004 Mar;99(3):472-7. PMID: 15056088.
196. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000 Jul 20;343(3):162-8. PMID: 10900274.
197. Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005 May;352(20):2061-8. PMID: 15901859.
198. Schoenfeld P, Lipscomb S, Crook J, et al. Accuracy of polyp detection by gastroenterologists and nurse endoscopists during flexible sigmoidoscopy: a randomized trial. Gastroenterology 1999 Aug;117(2):312-8. PMID: 10419911.
199. Schoen RE, Pinsky PF, Weissfeld JL, et al. Results of repeat sigmoidoscopy 3 years after a negative examination. JAMA 2003 Jul 2;290(1):41-8. PMID: 12837710.
200. Burke CA, Elder K, Lopez R. Screening for colorectal cancer with flexible sigmoidoscopy: is a 5-yr interval appropriate? A comparison of the detection of neoplasia 3 yr versus 5 yr after a normal examination. Am J Gastroenterol 2006 Jun;101(6):1329-32. PMID: 16771957.
201. Betes-Ibanez M., Munoz-Navas MA, Duque JM, et al. Diagnostic value of distal colonic polyps for prediction of advanced proximal neoplasia in an average-risk population undergoing screening colonoscopy. Gastrointest Endosc 2004 May;59(6):634-41. PMID: 15114305.

202. Ikeda Y, Mori M, Miyazaki M, et al. Significance of small distal adenoma for detection of proximal neoplasms in the colorectum. Gastrointest Endosc 2000 Sep;52(3):358-61. PMID: 10968850.
203. Imperiale TF, Wagner DR, Lin CY, et al. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003 Dec 16;139(12):959-65. PMID: 14678915.
204. Macari M, Milano A, Lavelle M, et al. Comparison of time-efficient CT colonography with two- and three-dimensional colonic evaluation for detecting colorectal polyps. AJR Am J Roentgenol 2000 Jun;174(6):1543-9. PMID: 10845478.
205. Rex DK, Vining D, Kopecky KK. An initial experience with screening for colon polyps using spiral CT with and without CT colography (virtual colonoscopy). Gastrointest Endosc 1999 Sep;50(3):309-13. PMID: 10462648.
206. Cologaurd summary of safety and effectiveness data (SSED). 2014.
207. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007 Feb 20;146(4):244-55. PMID: 17310056.
208. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget Stool DNA Testing for Colorectal-Cancer Screening. New England Journal of Medicine 2014 Mar 19;371(2):187-8. PMID: 25006736.
209. Johnson DA. Can Cologuard Improve Colon Cancer Screening Rates. Medscape; 2014.
210. Adeyemo A, Bannazadeh M, Riggs T, et al. Does sedation type affect colonoscopy perforation rates? Diseases of the Colon & Rectum 2014 Jan;57(1):110-4. PMID: 24316954.
211. Adler A, Wegscheider K, Lieberman D, et al. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3). Gut 2013 Feb;62(2):236-41. PMID: 22442161.
212. An S, Lee KH, Kim YH, et al. Screening CT colonography in an asymptomatic average-risk Asian population: a 2-year experience in a single institution. AJR 2008 Sep;American(3):W100-W106. PMID: 18716076.
213. Arora G, Mannalithara A, Singh G, et al. Risk of perforation from a colonoscopy in adults: a large population-based study. Gastrointest Endosc 2009 Mar;69(3:Pt 2):t-64. PMID: 19251006.
214. Bair D, Pham J, Seaton MB, et al. The quality of screening colonoscopies in an office-based endoscopy clinic. Canadian Journal of Gastroenterology 2009 Jan;23(1):41-7. PMID: 19172208.
215. Berhane C, Denning D. Incidental finding of colorectal cancer in screening colonoscopy and its cost effectiveness. American Surgeon 2009;75(8):699-703. PMID: 19725293.
216. Bielawska B, Day AG, Lieberman DA, et al. Risk factors for early colonoscopic perforation include non-gastroenterologist endoscopists: a multivariable analysis. Clinical Gastroenterology & Hepatology 2014 Jan;12(1):85-92. PMID: 23891916.
217. Blotiere PO, Weill A, Ricordeau P, et al. Perforations and haemorrhages after colonoscopy in 2010: A study based on comprehensive French health insurance data (SNIIRAM). Clin Res Hepatol Gastroenterol 2014;38(1):112-7. PMID: 24268997.
218. Bokemeyer B, Bock H, Huppe D, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. European Journal of Gastroenterology & Hepatology 2009 Jun;21(6):650-5. PMID: 19445041.

219. Cash BD, Riddle MS, Bhattacharya I, et al. CT colonography of a Medicare-aged population: outcomes observed in an analysis of more than 1400 patients. AJR 2012 Jul;American(1):W27-W34. PMID: 22733929.
220. Castro G, Azrak MF, Seeff LC, et al. Outpatient colonoscopy complications in the CDC's Colorectal Cancer Screening Demonstration Program: a prospective analysis. Cancer 2013 Aug 1;119:Suppl-54. PMID: 23868479.
221. Chin M, Mendelson R, Edwards J, et al. Computed tomographic colonography: prevalence, nature, and clinical significance of extracolonic findings in a community screening program. Am J Gastroenterol 2005 Dec;100(12):2771-6. PMID: 16393234.
222. Chukmaitov A, Bradley CJ, Dahman B, et al. Association of polypectomy techniques, endoscopist volume, and facility type with colonoscopy complications. Gastrointest Endosc 2013 Mar;77(3):436-46. PMID: 23290773.
223. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. JAMA Internal Medicine 2013 Apr 8;173(7):551-6. PMID: 23478904.
224. Cotterill M, Gasparelli R, Kirby E. Colorectal cancer detection in a rural community. Development of a colonoscopy screening program. Can Fam Physician 2005 Sep;51:1224-8. PMID: 16190175.
225. Crispin A, Birkner B, Munte A, et al. Process quality and incidence of acute complications in a series of more than 230,000 outpatient colonoscopies. Eur J Radiol 2009 Dec;41(12):1018-25. PMID: 19856246.
226. Dancourt V, Lejeune C, Lepage C, et al. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. European Journal of Cancer 2008 Oct;44(15):2254-8. PMID: 18760592.
227. Dominitz JA, Baldwin LM, Green P, et al. Regional variation in anesthesia assistance during outpatient colonoscopy is not associated with differences in polyp detection or complication rates. Gastroenterology 2013 Feb;144(2):298-306. PMID: 23103615.
228. Durbin JM, Stroup SP, Altamar HO, et al. Genitourinary abnormalities in an asymptomatic screening population: findings on virtual colonoscopy. Clinical Nephrology 2012 Mar;77(3):204-10. PMID: 22377251.
229. Edwards JT, Mendelson RM, Fritschi L, et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. Radiology 230(2):459-64, 2004 Feb PMID: 14688402.
230. Flicker MS, Tsoukas AT, Hazra A, et al. Economic impact of extracolonic findings at computed tomographic colonography. Journal of Computer Assisted Tomography 2008 Jul;32(4):497-503. PMID: 18664832.
231. Ginnerup PB, Rosenkilde M, Christiansen TE, et al. Extracolonic findings at computed tomography colonography are a challenge. Gut 2003 Dec;52(12):1744-7. PMID: 14633954.
232. Gluecker TM, Johnson CD, Wilson LA, et al. Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. Gastroenterology 2003 Apr;124(4):911-6. PMID: 12671887.
233. Hamdani U, Naeem R, Haider F, et al. Risk factors for colonoscopic perforation: a population-based study of 80118 cases. World Journal of Gastroenterology 2013 Jun 21;19(23):3596-601. PMID: 23801860.

234. Hara AK, Johnson CD, MacCarty RL, et al. Incidental Extracolonic Findings at CT Colonography. Radiology 2000 May 1;215(2):353-7. PMID: 10796907.
235. Ho JM, Gruneir A, Fischer HD, et al. Serious events in older Ontario residents receiving bowel preparations for outpatient colonoscopy with various comorbidity profiles: a descriptive, population-based study. Can J Gastroenterol 2012 Jul;26(7):436-40. PMID: 22803018.
236. Hoff G, Thiis-Evensen E, Grotmol T, et al. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? Experience from the Telemark Polyp Study 1983-1996. Eur J Cancer Prev 2001 Apr;10(2):131-7. PMID: 11330453.
237. Hsieh TK, Hung L, Kang FC, et al. Anesthesia does not increase the rate of bowel perforation during colonoscopy: a retrospective study. Acta Anaesthesiologica Taiwanica: Official Journal of the Taiwan Society of Anesthesiologists 2009 Dec;47(4):162-6. PMID: 20015815.
238. Iafrate F, Iussich G, Correale L, et al. Adverse events of computed tomography colonography: an Italian National Survey. Digestive & Liver Disease 2013 Aug;45(8):645-50. PMID: 23643567.
239. Jain A, Falzarano J, Jain A, et al. Outcome of 5,000 flexible sigmoidoscopies done by nurse endoscopists for colorectal screening in asymptomatic patients. Hawaii Med J 2002 Jun;61(6):118-20. PMID: 12148407.
240. Kamath AS, Iqbal CW, Sarr MG, et al. Colonoscopic splenic injuries: incidence and management. Journal of Gastrointestinal Surgery 2009 Dec;13(12):2136-40. PMID: 19830501.
241. Kang HY, Kang HW, Kim SG, et al. Incidence and management of colonoscopic perforations in Korea. Digestion 2008;78(4):218-23. PMID: 19142003.
242. Kao KT, Jain A, Sheinbaum A. Ischemic colitis following routine screening colonoscopy: a case report. Eur J Radiol 2009;41:Suppl. PMID: 19418419.
243. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007 Oct 4;357(14):1403-12. PMID: 17914041.
244. Kim JS, Kim BW, Kim JI, et al. Endoscopic clip closure versus surgery for the treatment of iatrogenic colon perforations developed during diagnostic colonoscopy: a review of 115,285 patients. Surgical Endoscopy 2013 Feb;27(2):501-4. PMID: 22773239.
245. Kim YS, Kim N, Kim SY, et al. Extracolonic findings in an asymptomatic screening population undergoing intravenous contrast-enhanced computed tomography colonography. Journal of Gastroenterology & Hepatology 2008 Jul;23(7:Pt 2):t-57. PMID: 17645481.
246. Ko CW, Riffle S, Michaels L, et al. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon. Clinical Gastroenterology & Hepatology 2010 Feb;8(2):166-73. PMID: 19850154.
247. Ko CW, Riffle S, Shapiro JA, et al. Incidence of minor complications and time lost from normal activities after screening or surveillance colonoscopy. Gastrointest Endosc 2007;65(4):648-56. PMID: 17173914.
248. Korman LY, Overholt BF, Box T, et al. Perforation during colonoscopy in endoscopic ambulatory surgical centers. Gastrointestinal Endoscopy 58 (4):554 -7, 2003 Oct PMID: 14520289.

249. Layton JB, Klemmer PJ, Christiansen CF, et al. Sodium Phosphate Does Not Increase Risk For Acute Kidney Injury After Routine Colonoscopy, Compared With Polyethylene Glycol. Clin Gastroenterol Hepatol 2014 Jan 29;12(9):1514-21. PMID: 24486407.
250. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Annals of Internal Medicine 145 (12):880 -6, 2006 Dec PMID: 17179057.
251. Levin TR, Conell C, Shapiro JA, et al. Complications of screening flexible sigmoidoscopy. Gastroenterology 123 (6):1786 -92, 2002 Dec PMID: 12454834.
252. Loffeld RJ, Engel A, Dekkers PE. Incidence and causes of colonoscopic perforations: a single-center case series. Eur J Radiol 2011 Mar;43(3):240-2. PMID: 21165826.
253. Lorenzo-Zuniga V, Moreno dV, V, Domenech E, et al. Endoscopist experience as a risk factor for colonoscopic complications. Colorectal Disease 2010 Oct;12(10:Online):Online-7. PMID: 19930145.
254. Macari M, Nevsky G, Bonavita J, et al. CT colonography in senior versus nonsenior patients: extracolonic findings, recommendations for additional imaging, and polyp prevalence. Radiology 2011 Jun;259(3):767-74. PMID: 21467252.
255. Mansmann U, Crispin A, Henschel V, et al. Epidemiology and quality control of 245 000 outpatient colonoscopies. Deutsches Arzteblatt International 2008 Jun;105(24):434-40. PMID: 19626186.
256. Multicentre Austrailian Colorectal-neoplasia Screening (MACS) Group. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. Med J Aust 2006 Jun 5;184(11):546-50. PMID: 16768659.
257. Nelson DB, McQuaid KR, Bond JH, et al. Procedural success and complications of large-scale screening colonoscopy. Gastrointestinal Endoscopy 55(3):307 -14, 2002 Mar PMID: 11868001.
258. O'Connor SD, Pickhardt PJ, Kim DH, et al. Incidental finding of renal masses at unenhanced CT: prevalence and analysis of features for guiding management. AJR 2011 Jul;American(1):139-45. PMID: 21701022.
259. Parente F, Boemo C, Ardizzoia A, et al. Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. Eur J Radiol 2013;45(1):27-34. PMID: 23254404.
260. Pickhardt PJ, Boyce CJ, Kim DH, et al. Should small sliding hiatal hernias be reported at CT colonography? AJR 2011 Apr;American(4):W400-W404. PMID: 21427303.
261. Pickhardt PJ, Kim DH, Meiners RJ, et al. Colorectal and extracolonic cancers detected at screening CT colonography in 10,286 asymptomatic adults. Radiology 2010 Apr;255(1):83-8. PMID: 20308446.
262. Pickhardt PJ, Kim DH, Taylor AJ, et al. Extracolonic tumors of the gastrointestinal tract detected incidentally at screening CT colonography. Dis Colon Rectum 2007 Jan;50(1):56-63. PMID: 17115333.
263. Pickhardt PJ. Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. Radiology 239 (2):313 -6, 2006 May PMID: 16641348.
264. Pox CP, Altenhofen L, Brenner H, et al. Efficacy of a nationwide screening colonoscopy program for colorectal cancer. Gastroenterology 2012 Jun;142(7):1460-7. PMID: 22446606.

265. Quallick MR, Brown WR. Rectal perforation during colonoscopic retroflexion: a large, prospective experience in an academic center. Gastrointest Endosc 2009 Apr;69(4):960-3. PMID: 19327487.
266. Rabeneck L, Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology 2008;135(6):1899-906. PMID: 18938166.
267. Rathgaber SW, Wick TM. Colonoscopy completion and complication rates in a community gastroenterology practice. Gastrointestinal Endoscopy 64 (4):556 -62, 2006 Oct PMID: 16996349.
268. Rutter CM, Johnson E, Miglioretti DL, et al. Adverse events after screening and follow-up colonoscopy. Cancer Causes & Control 2012 Feb;23(2):289-96. PMID: 22105578.
269. Sagawa T, Kakizaki S, Iizuka H, et al. Analysis of colonoscopic perforations at a local clinic and a tertiary hospital. World Journal of Gastroenterology 2012 Sep 21;18(35):4898-904. PMID: 23002362.
270. Senore C, Ederle A, Fantin A, et al. Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. Journal of Medical Screening 2011;18(3):128-34. PMID: 22045821.
271. Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists. Gastrointest Endosc 2001 May;53(6):620-7. PMID: 11323588.
272. Singh H, Penfold RB, DeCoster C, et al. Colonoscopy and its complications across a Canadian regional health authority. Gastrointest Endosc 2009 Mar;69(3:Pt 2):t-71. PMID: 19251007.
273. Sosna J, Blachar A, Amitai M, et al. Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. Radiology 2006 May;239(2):457-63. PMID: 16543590.
274. Stock C, Ihle P, Sieg A, et al. Adverse events requiring hospitalization within 30 days after outpatient screening and nonscreening colonoscopies. Gastrointest Endosc 2013 Mar;77(3):419-29. PMID: 23410698.
275. Strul H, Kariv R, Leshno M, et al. The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40-80 years. Am J Gastroenterol 2006 Feb;101(2):255-62. PMID: 16454827.
276. Suissa A, Bentur OS, Lachter J, et al. Outcome and complications of colonoscopy: a prospective multicenter study in northern Israel. Diagnostic & Therapeutic Endoscopy 2012;2012:612542. PMID: 22778539.
277. Tam MS, Abbas MA. Perforation following colorectal endoscopy: what happens beyond the endoscopy suite? Perm J 2013;17(2):17-21. PMID: 23704838.
278. Veerappan GR, Ally MR, Choi JH, et al. Extracolonic findings on CT colonography increases yield of colorectal cancer screening. AJR 2010 Sep;American(3):677-86. PMID: 20729446.
279. Viiala CH, Olynyk JK. Outcomes after 10 years of a community-based flexible sigmoidoscopy screening program for colorectal carcinoma. Med J Aust 2007 Sep 3;187(5):274-7. PMID: 17767431.
280. Wallace MB, Kemp JA, Meyer F, et al. Screening for colorectal cancer with flexible sigmoidoscopy by nonphysician endoscopists. Am J Med 1999 Sep;107(3):214-8. PMID: 10492313.

281. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150(12):849-57. PMID: 19528563.
282. Xirasagar S, Hurley TG, Sros L, et al. Screening colonoscopy vs flexible sigmoidoscopy. Medical Care 2010 Aug;48(8):703-9. PMID: 20613663.
283. Zafar HM, Harhay MO, Yang J, et al. Adverse events Following Computed Tomographic Colonography compared to Optical Colonoscopy in the Elderly. Prev Med Rep 2014;1:3-8. PMID: 25530940.
284. Gondal G, Grotmol T, Hofstad B, et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scandinavian Journal of Gastroenterology 38(6):635-42, 2003 Jun PMID: 12825872.
285. Hoff G, Grotmol T, Skovlund E, et al. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846. PMID: 19483252.
286. Kim DH, Pickhardt PJ, Hanson ME, et al. CT colonography: performance and program outcome measures in an older screening population. Radiology 2010 Feb;254(2):493-500. PMID: 20093521.
287. Miles A, Wardle J, McCaffery K, et al. The effects of colorectal cancer screening on health attitudes and practices. Cancer Epidemiol Biomarkers Prev 2003 Jul;12(7):651-5. PMID: 12869406.
288. Pickhardt PJ, Kim DH, Robbins JB. Flat (nonpolypoid) colorectal lesions identified at CT colonography in a U.S. screening population. Academic Radiology 2010 Jun;17(6):784-90. PMID: 20227304.
289. Pickhardt PJ, Hanson ME, Vanness DJ, et al. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. Radiology 2008 Oct;249(1):151-9. PMID: 18796673.
290. Regula J, Polkowski M. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2008;358(1):88-9. PMID: 18175382.
291. Atkin WS, Hart A, Edwards R, et al. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. Gut 1998 Apr;42(4):560-5. PMID: 9616321.
292. Boellaard TN, Venema HW, Streekstra GJ, et al. Effective radiation dose in CT colonography: is there a downward trend? Acad Radiol 2012 Sep;19(9):1127-33. PMID: 22750132.
293. Jensch S, van Gelder RE, Venema HW, et al. Effective radiation doses in CT colonography: results of an inventory among research institutions. European Radiology 2006 May;16(5):981-7. PMID: 16418863.
294. van Gelder RE, Venema HW, Serlie IW, et al. CT colonography at different radiation dose levels: feasibility of dose reduction. Radiology 2002 Jul;224(1):25-33. PMID: 12091658.
295. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. Radiology 2005 Jul;236(1):3-9. PMID: 15987959.
296. Lord SJ, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? Ann Intern Med 2006 Jun 6;144(11):850-5. PMID: 16754927.

297. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database of Systematic Reviews 2007(1):CD001216. PMID: 17253456.
298. California Colorectal Cancer Coalition, American Cancer Society, Operation Access. Improving Access to Colorectal Cancer Screening, Diagnosis, and Treatment in Underserved Communities. 2011.
299. Florida Department of Health. Get the FIT Facts. 2015.
300. Kaiser Permanente Division of Research. 2012 Annual Report: Cancer. 2015.
301. Debarros M, Steele SR. Colorectal cancer screening in an equal access healthcare system. Journal of Cancer 2013;4(3):270-80. PMID: 23459768.
302. Department of Veterans Affairs. Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM). 2014. https://clinicaltrials.gov/ct2/show/NCT01239082. Accessed December 15, 2014.
303. Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Preventive Medicine 2012 Aug;55(2):87-92. PMID: 22634386.
304. Mosen DM, Liles EG, Feldstein AC, et al. Participant uptake of the fecal immunochemical test decreases with the two-sample regimen compared with one-sample FIT. Eur J Cancer Prev 2014 Nov;23(6):516-23. PMID: 25203483.
305. Zheng S, Chen K, Liu X, et al. Cluster randomization trial of sequence mass screening for colorectal cancer. Dis Colon Rectum 2003 Jan;46(1):51-8. PMID: 12544522.
306. Lee JK, Liles EG, Bent S, et al. Accuracy of Fecal Immunochemical Tests for Colorectal CancerSystematic Review and Meta-analysis. Ann Intern Med 2014 Feb 4;160(3):171-81. PMID: 24658694.
307. Exact Sciences. Additional Update on CMS Reimbursement for Cologuard®. 2015.
308. Ladabaum U, Levin Z, Mannalithara A, et al. Colorectal testing utilization and payments in a large cohort of commercially insured US adults. Am J Gastroenterol 2014 Oct;109(10):1513-25. PMID: 24980877.
309. Robertson DJ, Dominitz JA. Stool DNA and colorectal-cancer screening. N Engl J Med 2014 Apr 3;370(14):1350-1. PMID: 24645801.
310. Elmunzer BJ, Hayward RA, Schoenfeld PS, et al. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Medicine / Public Library of Science 2012;9(12):e1001352. PMID: 23226108.
311. 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. PMID: 22723185.
312. Castells A, Quintero E. Programmatic Screening for Colorectal Cancer: The COLONPREV Study. Dig Dis Sci 2014:1-9.
313. Alvarez C, Andreu M, Castells A, et al. Relationship of colonoscopy-detected serrated polyps with synchronous advanced neoplasia in average-risk individuals. Gastrointest Endosc 2013 Aug;78(2):333-41. PMID: 23623039.
314. Rex DK, Bond JH, Winawer S, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002 Jun;97(6):1296-308. PMID: 12094842.

315. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015 Jan;81(1):31-53. PMID: 25480100.
316. van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006 Feb;101(2):343-50. PMID: 16454841.
317. Leufkens AM, van Oijen MG, Vleggaar FP, et al. Factors influencing the miss rate of polyps in a back-to-back colonoscopy study. Eur J Radiol 2012 May;44(5):470-5. PMID: 22441756.
318. Gralnek IM, Siersema PD, Halpern Z, et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncology 2014 Mar;15(3):353-60. PMID: 24560453.
319. Siersema PD, Rastogi A, Leufkens AM, et al. Retrograde-viewing device improves adenoma detection rate in colonoscopies for surveillance and diagnostic workup. World Journal of Gastroenterology 2012 Jul 14;18(26):3400-8. PMID: 22807609.
320. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. Am J Gastroenterol 2010 Jun;105(6):1301-7. PMID: 20179689.
321. Ikematsu H, Saito Y, Tanaka S, et al. The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy. Journal of Gastroenterology 2012 Oct;47(10):1099-107. PMID: 22441532.
322. Singla S, Keller D, Thirunavukarasu P, et al. Splenic injury during colonoscopy--a complication that warrants urgent attention. Journal of Gastrointestinal Surgery 2012 Jun;16(6):1225-34. PMID: 22450952.
323. Patselas TN, Gallagher EG. Splenic rupture: an uncommon complication after colonoscopy. American Surgeon 2009 Mar;75(3):260-1. PMID: 19350865.
324. Langer K, Kriegler S, Moser M. Colonoscopy complicated by arterial avulsion and retroperitoneal hemorrhage. Eur J Radiol 2011;43:Suppl. PMID: 21590605.
325. Tagg W, Woods S, Razdan R, et al. Hemoperitoneum after colonoscopy. Eur J Radiol 2008 Sep;40:Suppl-7. PMID: 18633865.
326. Boenicke L, Maier M, Merger M, et al. Retroperitoneal gas gangrene after colonoscopic polypectomy without bowel perforation in an otherwise healthy individual: report of a case. Langenbecks Arch Surg 2006 Apr;391(2):157-60. PMID: 16465554.
327. Gladman MA, Shami SK. Medical mystery: an unusual complication of colonoscopy--the answer. N Engl J Med 2007 Nov 29;357(22):2309-10. PMID: 18046038.
328. Lee CK, Shim JJ, Jang JY. Ceco-colic intussusception with subsequent bowel infarction as a rare complication of colonoscopic polypectomy. Eur J Radiol 2013;45:Suppl-7. PMID: 23526500.
329. Cheng YC, Wu CC, Lee CC, et al. Rare complication following screening colonoscopy: ischemic colitis. Digestive Endoscopy 2012 Sep;24(5):379. PMID: 22925295.
330. Lambert A, Nguyen SQ, Byrn JC, et al. Small-bowel perforation after colonoscopy. Gastrointest Endosc 2007 Feb;65(2):352-3. PMID: 17137862.
331. Ladas SD, Karamanolis G, Ben-Soussan E. Colonic gas explosion during therapeutic colonoscopy with electrocautery. World J Gastroenterol 2007 Oct 28;13(40):5295-8. PMID: 17879396.

332. Shaw D, Gallardo G, Basson MD. Post-colonoscopy appendicitis: A case report and systematic review. World Journal of Gastrointestinal Surgery 2013 Oct 27;5(10):259-63. PMID: 24179623.
333. Gonzalez-Candelas F, Guiral S, Carbo R, et al. Patient-to-patient transmission of hepatitis C virus (HCV) during colonoscopy diagnosis. Virology Journal 2010;7:217. PMID: 20825635.
334. Saludes V, Esteve M, Casas I, et al. Hepatitis C virus transmission during colonoscopy evidenced by phylogenetic analysis. Journal of Clinical Virology 2013 Jul;57(3):263-6. PMID: 23567025.
335. Colonoscopes may spread HCV and HPV. AIDS Patient Care STDS 2003 May;17(5):257-8.
336. Fukunaga K, Khatibi A. Glutaraldehyde colitis: a complication of screening flexible sigmoidoscopy in the primary care setting. Ann Intern Med 2000 Aug 15;133(4):315. PMID: 10929189.
337. Hookey LC, Depew WT, Vanner S. The safety profile of oral sodium phosphate for colonic cleansing before colonoscopy in adults. Gastrointest Endosc 2002 Dec;56(6):895-902. PMID: 12447305.
338. Rex DK, Schwartz H, Goldstein M, et al. Safety and colon-cleansing efficacy of a new residue-free formulation of sodium phosphate tablets. Am J Gastroenterol 2006 Nov;101(11):2594-604. PMID: 17029618.
339. Atkin WS, Hart A, Edwards R, et al. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. Gut 1998 Apr;42(4):560-5. PMID: 9616321.
340. Weir MA, Fleet JL, Vinden C, et al. Hyponatremia and sodium picosulfate bowel preparations in older adults. Am J Gastroenterol 2014 May;109(5):686-94. PMID: 24589671.
341. Tan JJ, Tjandra JJ. Which is the optimal bowel preparation for colonoscopy - a meta-analysis. Colorectal Dis 2006 May;8(4):247-58. PMID: 16630226.
342. Belsey J, Epstein O, Heresbach D. Systematic review: oral bowel preparation for colonoscopy. Aliment Pharmacol Ther 2007 Feb 15;25(4):373-84. PMID: 17269992.
343. Clark RE, Godfrey JD, Choudhary A, et al. Low-volume polyethylene glycol and bisacodyl for bowel preparation prior to colonoscopy: a meta-analysis. Ann Gastroenterol 2013;26(4):319-24. PMID: 24714413.
344. Hammadah M, Gaber L, Raghavan R. Renal cortical necrosis following a colonoscopy. Clinical Nephrology 2013 Jan;79(1):67-71. PMID: 22913920.
345. Gonlusen G, Akgun H, Ertan A, et al. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing: clinical patterns and renal biopsy findings. Arch Pathol Lab Med 2006 Jan;130(1):101-6. PMID: 16390223.
346. Carl DE, Sica DA. Acute phosphate nephropathy following colonoscopy preparation. Am J Med Sci 2007 Sep;334(3):151-4. PMID: 17873526.
347. Yu JY, Kim SK, Jang EC, et al. Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding. World Journal of Gastrointestinal Endoscopy 2013 May 16;5(5):270-2. PMID: 23678383.
348. Nagler J, Poppers D, Turetz M. Severe hyponatremia and seizure following a polyethylene glycol-based bowel preparation for colonoscopy. J Clin Gastroenterol 2006 Jul;40(6):558-9. PMID: 16825941.

349. de Haan MC, van Gelder RE, Graser A, et al. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. European Radiology 2011 Aug;21(8):1747-63. PMID: 21455818.
350. McFarland EG, Fletcher JG, Pickhardt P, et al. ACR Colon Cancer Committee white paper: status of CT colonography 2009. Journal of the American College of Radiology 2009 Nov;6(11):756-72. PMID: 19878883.
351. Burling D, Wylie P, Gupta A, et al. CT colonography: accuracy of initial interpretation by radiographers in routine clinical practice. Clinical Radiology 2010 Feb;65(2):126-32. PMID: 20103434.
352. ACR-SAR-SCBT-MR Practice Parameter for the performance of computer tomography (CT) colonography in adults. 2014. http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/CT_Colonography.pdf. Accessed December 16, 2014.
353. Poullos PD, Beaulieu CF. Current techniques in the performance, interpretation, and reporting of CT colonography. [Review] [111 refs]. Gastrointestinal Endoscopy Clinics of North America 2010 Apr;20(2):169-92. PMID: 20451809.
354. Viatronix. V3D(R)-Colon. 2011.
355. Pickhardt PJ, Hassan C, Laghi A, et al. Clinical management of small (6- to 9-mm) polyps detected at screening CT colonography: a cost-effectiveness analysis. AJR 2008 Nov;American(5):1509-16. PMID: 18941093.
356. Pickhardt PJ, Hassan C, Laghi A, et al. Small and diminutive polyps detected at screening CT colonography: a decision analysis for referral to colonoscopy. AJR 2008 Jan;American(1):136-44. PMID: 18094303.
357. Bildzukewicz NA, Weinstein MS. Appendicitis following virtual colonoscopy: a case report. Journal of Gastrointestinal Surgery 2012 Dec;16(12):2291-3. PMID: 22918862.
358. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects Research, Division on Earth and Life Studies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: National Academies Press; 2006.
359. Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ 2005 Jul 9;331(7508):77. PMID: 15987704.
360. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007 Nov 29;357(22):2277-84. PMID: 18046031.
361. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007 Jul 18;298(3):317-23. PMID: 17635892.
362. Buls N, de MJ, Covens P, et al. Health screening with CT: prospective assessment of radiation dose and associated detriment. JBR-BTR 2005 Jan;88(1):12-6. PMID: 15792162.
363. Berrington de GA, Kim KP, Knudsen AB, et al. Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis. AJR 2011 Apr;American(4):816-23. PMID: 21427330.
364. Summers RM, Baecher N, Yao J, et al. Feasibility of simultaneous computed tomographic colonography and fully automated bone mineral densitometry in a single

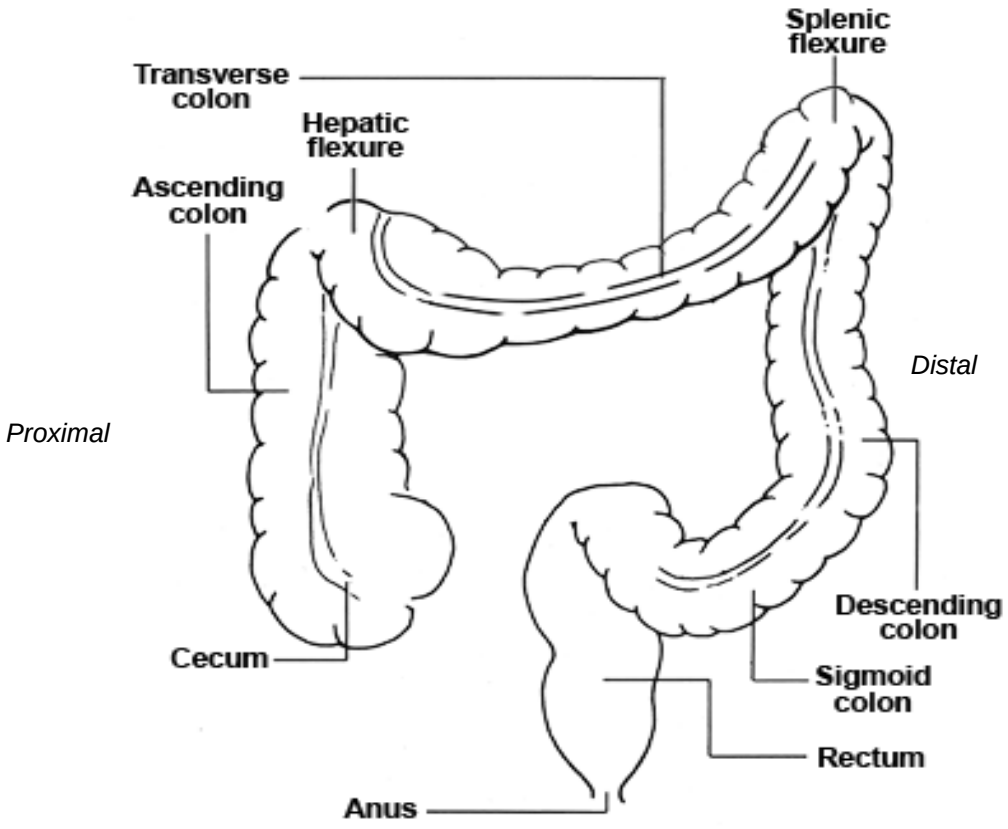
examination. Journal of Computer Assisted Tomography 2011 Mar;35(2):212-6. PMID: 21412092.
365. Pickhardt P, Bodeen G, Brett A, et al. Comparison of Femoral Neck BMD Evaluation Obtained Using Lunar DXA and QCT With Asynchronous Calibration From CT Colonography. J Clin Densitom 2014 May 28 PMID: 24880495.
366. Dolan JG, Boohaker E, Allison J, et al. Can Streamlined Multicriteria Decision Analysis Be Used to Implement Shared Decision Making for Colorectal Cancer Screening? Med Decis Making 2013 Dec 3 PMID: 24300851.
367. Holden DJ, Harris R, Porterfield DS, et al. Enhancing the use and quality of colorectal cancer screening. [Review] [220 refs]. Evidence Report/Technology Assessment 2010(190):1-195.
368. Long MD, Lance T, Robertson D, et al. Colorectal cancer testing in the national Veterans Health Administration. Dig Dis Sci 2012 Feb;57(2):288-93. PMID: 21922220.
369. Stock C, Brenner H. Utilization of lower gastrointestinal endoscopy and fecal occult blood test in 11 European countries: evidence from the Survey of Health, Aging and Retirement in Europe (SHARE). Eur J Radiol 2010 Jul;42(7):546-56. PMID: 20432204.
370. Khalid-de BC, Jonkers D, Smits K, et al. Participation in colorectal cancer screening trials after first-time invitation: a systematic review. Eur J Radiol 2011 Dec;43(12):1059-86. PMID: 22135196.
371. Hassan C, Giorgi RP, Camilloni L, et al. Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. Alimentary Pharmacology & Therapeutics 2012 Nov;36(10):929-40. PMID: 23035890.
372. Littlejohn C, Hilton S, Macfarlane GJ, et al. Systematic review and meta-analysis of the evidence for flexible sigmoidoscopy as a screening method for the prevention of colorectal cancer. British Journal of Surgery 2012 Nov;99(11):1488-500. PMID: 23001715.
373. Lo SH, Halloran S, Snowball J, et al. Colorectal cancer screening uptake over three biennial invitation rounds in the English bowel cancer screening programme. Gut 2014 May 7 PMID: 24812001.
374. Mysliwiec PA, Jensen CD, Zhao W, et al. Fecal immunochemical test performance over mulitple rounds of annual testing in an outreach screening program. Gastroenterology 2015;146(5):S-33.
375. Gellad ZF, Stechuchak KM, Fisher DA, et al. Longitudinal adherence to fecal occult blood testing impacts colorectal cancer screening quality. Am J Gastroenterol 2011 Jun;106(6):1125-34. PMID: 21304501.
376. Zauber AG, Winawer SJ, Mills GM, et al. Adherence to screening in a randomized controlled trial of a one-time screening colonoscopy versus program of annual fecal occult blood test (gFOBT): Implications of lower gFOBT adherence to screening on colorectal cancer mortality reduction. Gastroenterology 2012;142:S82-S83.
377. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007 Oct;133(4):1077-85. PMID: 17698067.
378. Carlson CM, Kirby KA, Casadei MA, et al. Lack of follow-up after fecal occult blood testing in older adults: Inappropriate screening or failure to follow up? Archives of Internal Medicine 2011 Feb 14;171(3):249-56. PMID: 20937917.

379. Crawford ND, Jones CP, Richardson LC. Understanding racial and ethnic disparities in colorectal cancer screening: Behavioral Risk Factor Surveillance System, 2002 and 2004. Ethnicity & Disease 2010;20(4):359-65. PMID: 21305822.
380. Fenton JJ, Tancredi DJ, Green P, et al. Persistent racial and ethnic disparities in up-to-date colorectal cancer testing in medicare enrollees. Journal of the American Geriatrics Society 2009 Mar;57(3):412-8. PMID: 19175435.
381. Klabunde CN, Cronin KA, Breen N, et al. Trends in colorectal cancer test use among vulnerable populations in the United States. Cancer Epidemiol Biomarkers Prev 2011 Aug;20(8):1611-21. PMID: 21653643.
382. Homayoon B, Shahidi NC, Cheung WY. Impact of asian ethnicity on colorectal cancer screening: a population-based analysis. American Journal of Clinical Oncology 2013 Apr;36(2):167-73. PMID: 22441340.
383. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Archives of Internal Medicine 2012 Apr 9;172(7):575-82. PMID: 22493463.
384. Burgess DJ, van RM, Grill J, et al. Presence and correlates of racial disparities in adherence to colorectal cancer screening guidelines. Journal of General Internal Medicine 2011 Mar;26(3):251-8. PMID: 21088920.
385. Laiyemo AO, Doubeni C, Pinsky PF, et al. Race and colorectal cancer disparities: health-care utilization vs different cancer susceptibilities. J Natl Cancer Inst 2010 Apr 21;102(8):538-46. PMID: 20357245.
386. Yager SS, Chen L, Cheung WY. Sex-based Disparities in Colorectal Cancer Screening. Am J Clin Oncol 2013 Mar 4 PMID: 23466582.
387. Gancayco J, Soulos PR, Khiani V, et al. Age-based and sex-based disparities in screening colonoscopy use among medicare beneficiaries. Journal of Clinical Gastroenterology 2013 Aug;47(7):630-6. PMID: 23619827.
388. Clarke N, Sharp L, Osborne A, et al. Comparison of Uptake of Colorectal Cancer Screening Based on Fecal Immunochemical Testing (FIT) in Males and Females: A Systematic Review and Meta-analysis. Cancer Epidemiol Biomarkers Prev 2014 Nov 6;24(1):39-47. PMID: 25378366.
389. Lieberman D. Race, gender, and colorectal cancer screening. Am J Gastroenterol 2005 Dec;100(12):2756-8. PMID: 16393231.
390. Cooper GS, Chak A, Koroukian S. The polyp detection rate of colonoscopy: a national study of Medicare beneficiaries. Am J Med 2005 Dec;118(12):1413. PMID: 16378787.
391. Yamaji Y, Mitsushima T, Yoshida H, et al. The malignant potential of freshly developed colorectal polyps according to age. Cancer Epidemiol Biomarkers Prev 2006 Dec;15(12):2418-21. PMID: 17164364.
392. Agrawal S, Bhupinderjit A, Bhutani MS, et al. Colorectal cancer in African Americans. Am J Gastroenterol 2005 Mar;100(3):515-23. PMID: 15743345.
393. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009. Am J Gastroenterol 2009 Mar;104(3):739-50. PMID: 19240699.
394. Lansdorp-Vogelaar I, van BM, Zauber AG, et al. Individualizing colonoscopy screening by sex and race. Gastrointest Endosc 2009;70(1):96-108. PMID: 19467539.
395. Cotterchio M, Manno M, Klar N, et al. Colorectal screening is associated with reduced colorectal cancer risk: a case-control study within the population-based Ontario Familial

Colorectal Cancer Registry. Cancer Causes Control 2005 Sep;16(7):865-75. PMID: 16132797.
396. Haug U, Knudsen AB, Brenner H, et al. Is fecal occult blood testing more sensitive for left- versus right-sided colorectal neoplasia? A systematic literature review. Expert Review of Molecular Diagnostics 2011 Jul;11(6):605-16. PMID: 21745014.
397. Massat NJ, Moss SM, Halloran SP, et al. Screening and primary prevention of colorectal cancer: a review of sex-specific and site-specific differences. Journal of Medical Screening 2013;20(3):125-48. PMID: 24197771.
398. Day LW, Walter LC, Velayos F. Colorectal cancer screening and surveillance in the elderly patient. Am J Gastroenterol 2012;106(7):1197-206. PMID: 21519362.
399. Zauber, AG, Lansdorp-Vogelaar, I, Knudsen, AB, et al. Evaluating Test Strategies for Colorectal Cancer Screening Age to Begin, Age to Stop, and Timing of Screening Intervals: A Decision of Colorectal Cancer Screening for the U.S. Preventive Services Task Force from the Cancer Intervention and Surveillance Modeling Network (CISNET). 2009. PMID: 20722163.
400. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. Ann Intern Med 2014 Jul 15;161(2):104-12. PMID: 25023249.
401. Lin O, Roy PK, Schembre DB, et al. Screening sigmoidoscopy and colonoscopy for reducing colorectal cancer mortality in asymtomatic persons. Cochrane Database of Systematic Reviews 2005;CD005201
402. Hol L, Wilschut JA, van BM, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. British Journal of Cancer 2009 Apr 7;100(7):1103-10. PMID: 19337257.
403. Hol L, de J, V, van Leerdam ME, et al. Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. European Journal of Cancer 2010 Jul;46(11):2059-66. PMID: 20621736.
404. Halloran SP, Launoy G, Zappa M, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Faecal occult blood testing. Eur J Radiol 2012 Sep;44:Suppl-87. PMID: 23012123.
405. Brown SR, Baraza W. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. Cochrane Database of Systematic Reviews 2010(10):CD006439. PMID: 20927746.
406. Kewenter J, Brevinge H. Endoscopic and surgical complications of work-up in screening for colorectal cancer. Dis Colon Rectum 1996 Jun;39(6):676-80. PMID: 8646956.
407. Chang CW, Chang WH, Shih SC, et al. Accidental diagnosis of Trichuris trichiura by colonoscopy. Gastrointest Endosc 2008 Jul;68(1):154. PMID: 18402953.
408. Kaiser Permanente Care Management Institute. Colorectal cancer screening clinical practice guideline. Oakland, CA: Kaiser Permanente Care Management Institute; 2008.
409. Yee J, Rosen MP, Blake MA, et al. ACR Appropriateness Criteria on colorectal cancer screening. Journal of the American College of Radiology 2010 Sep;7(9):670-8. PMID: 20816627.
410. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer: A national clinical guideline. Edinburgh: SIGN; 2011.

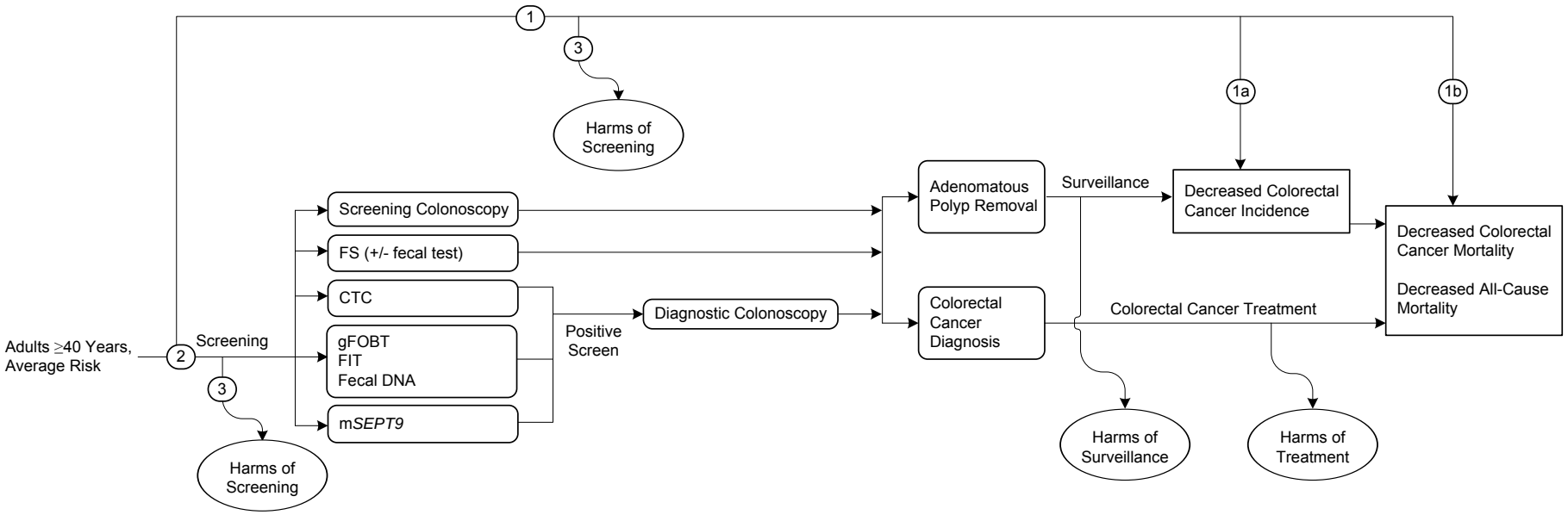
411. Brink, D, Barlow, J, Bush, K, et al. Colorectal Cancer Screening. Institute for Clinical Systems Improvement; 2012.
412. Qaseem A, Denberg TD, Hopkins RH, Jr., et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med 2012 Mar 6;156(5):378-86. PMID: 22393133.
413. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colorectal cancer screening. National Comprehensive Cancer Network; 2013.

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)



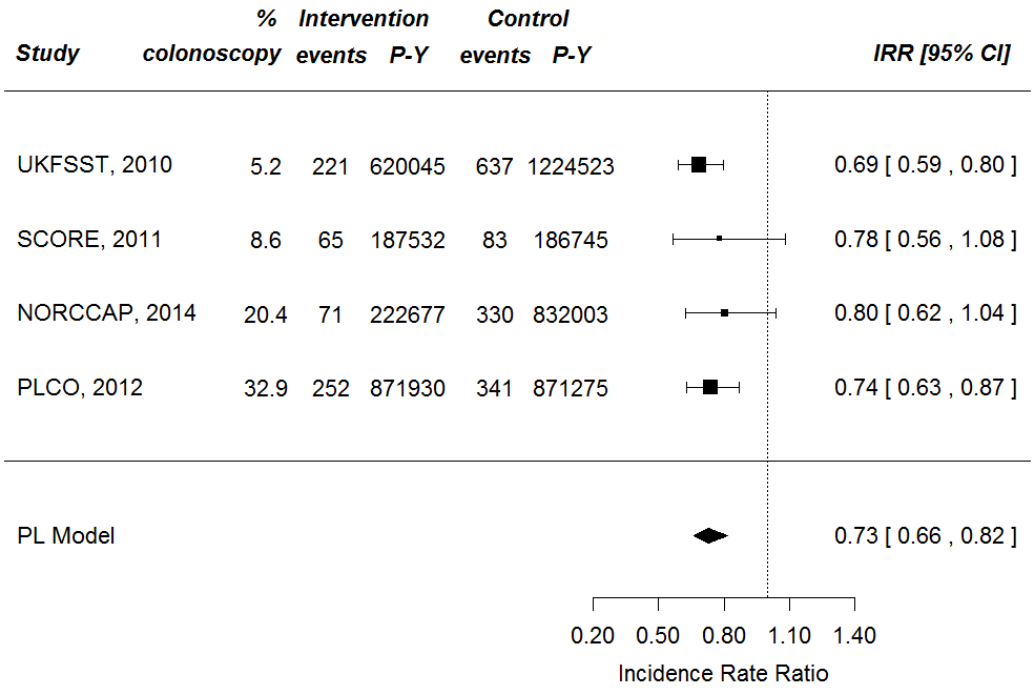
Source: http://cisnet.cancer.gov/projections/colorectal/screening.php

Figure 2. Analytic Framework



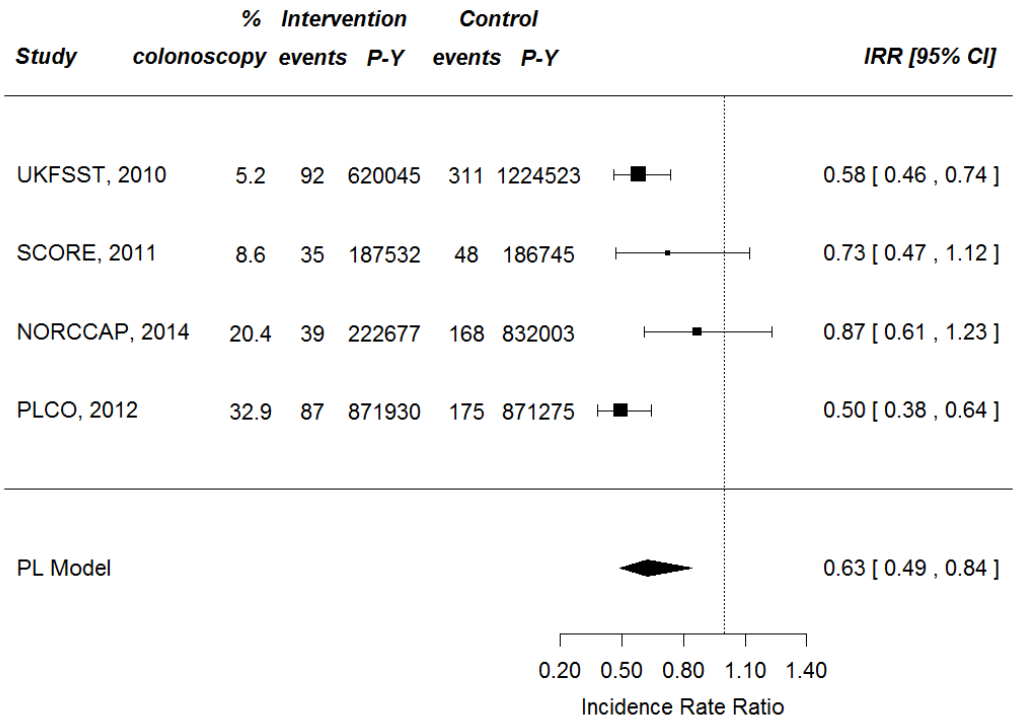
Abbreviations: CTC = computed tomographic colonography; DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood test; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid

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



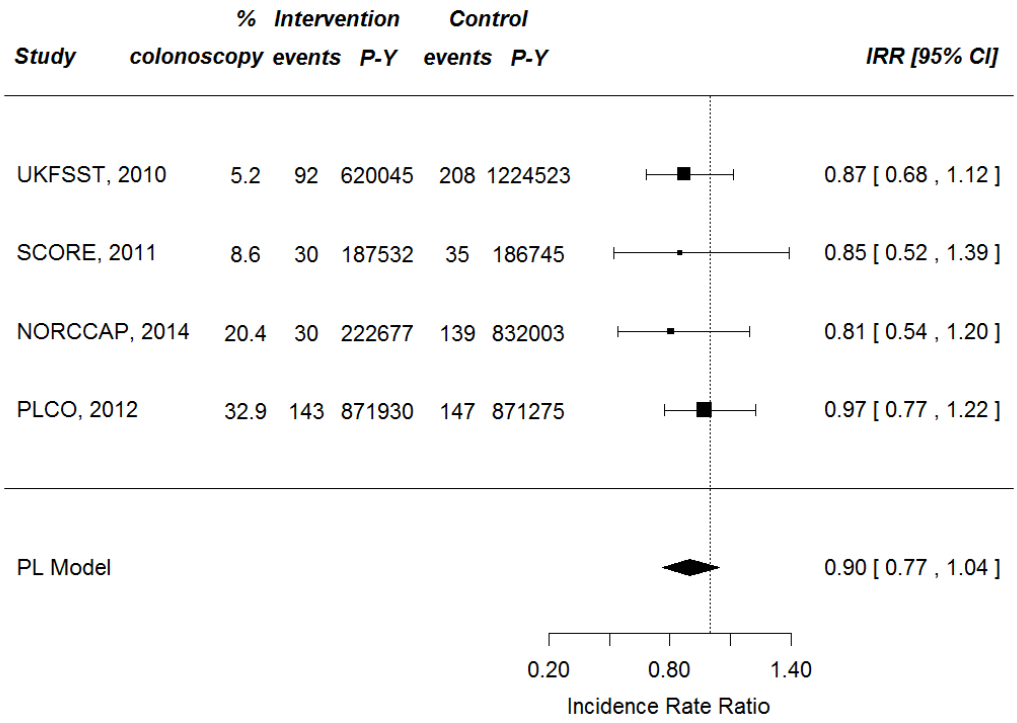
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; p-y = person-years; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I2 = 0%

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



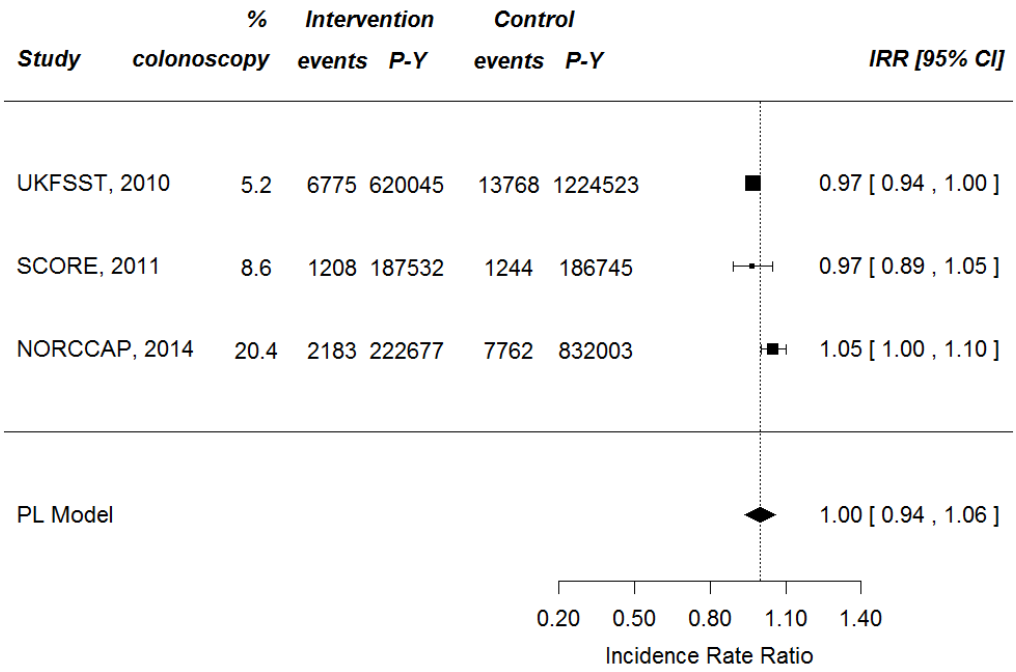
Abbreviations: CI = confidence interval; c-scopy = colonoscopy; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST =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

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



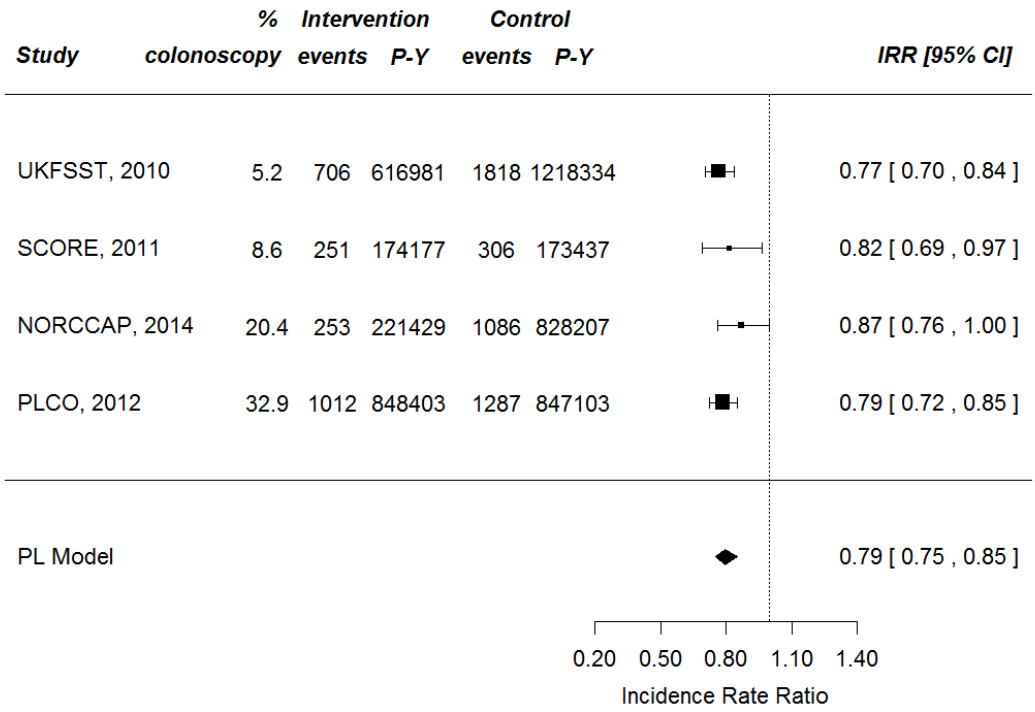
Abbreviations: CI = confidence interval; c-scopy = colonoscopy; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST =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

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



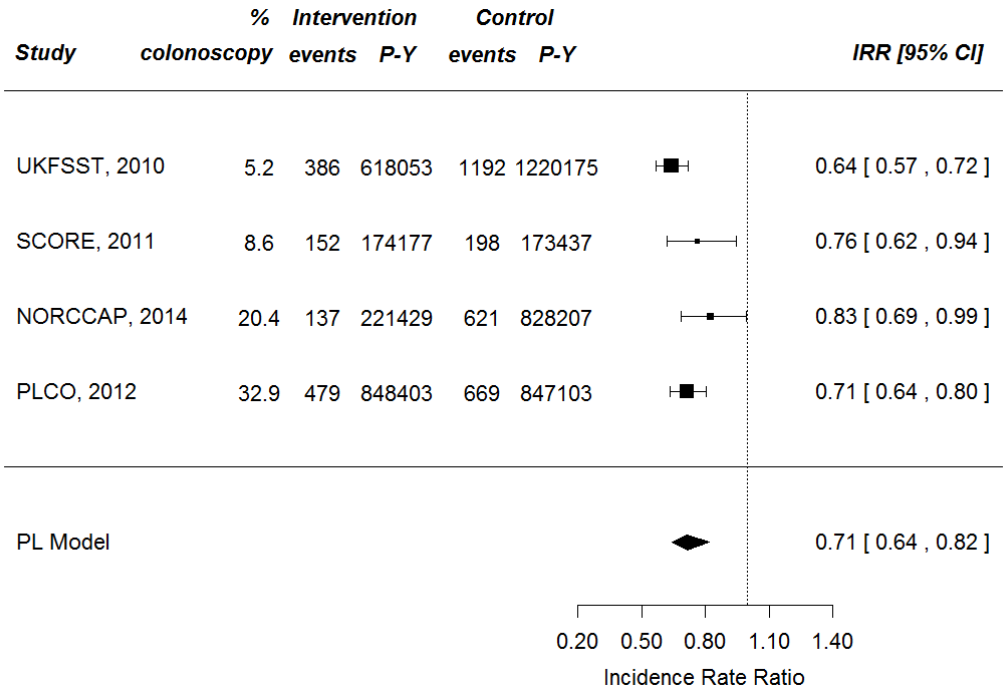
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; p-y = person-years; RE = restricted maximum likelihood; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial
* I2 = 59.8%

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



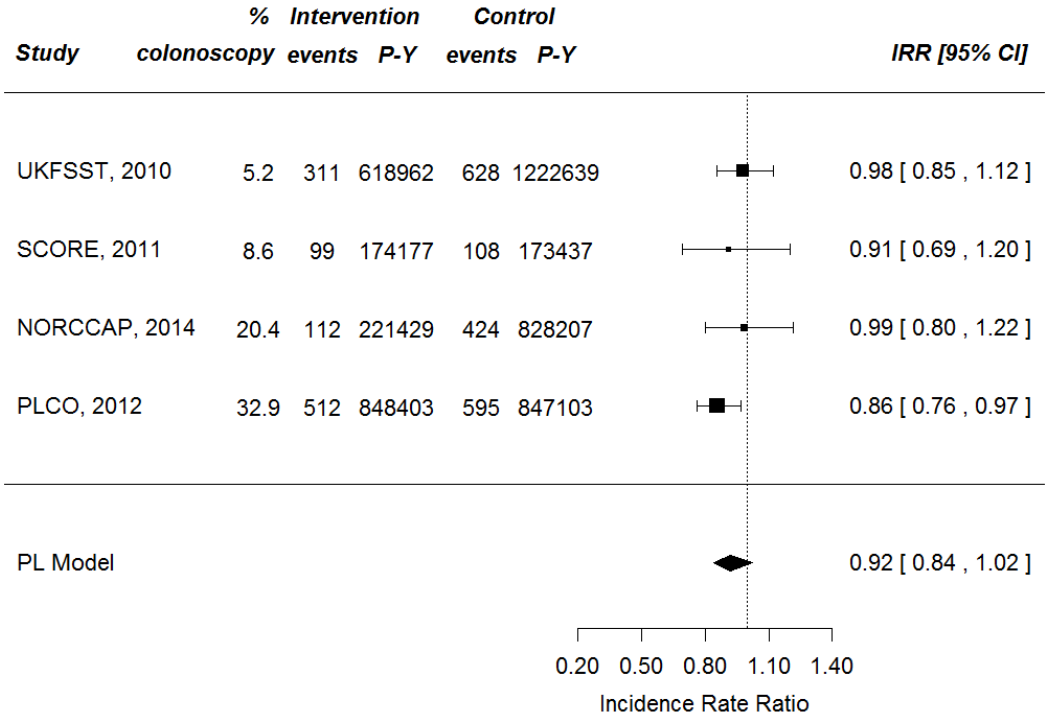
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; RE = restricted maximum likelihood; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible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

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



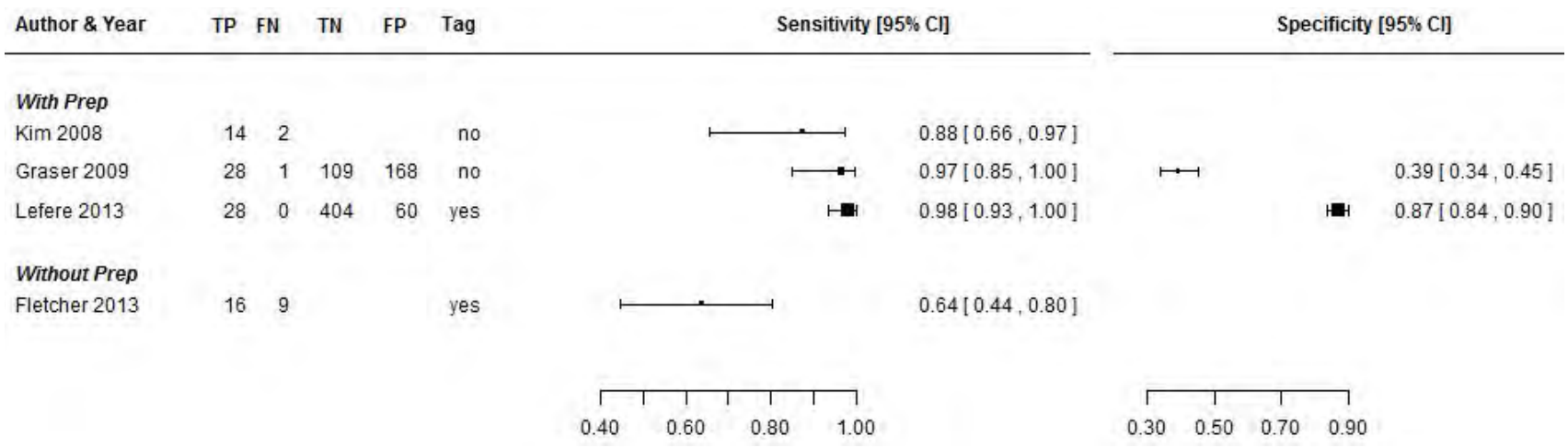
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy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

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



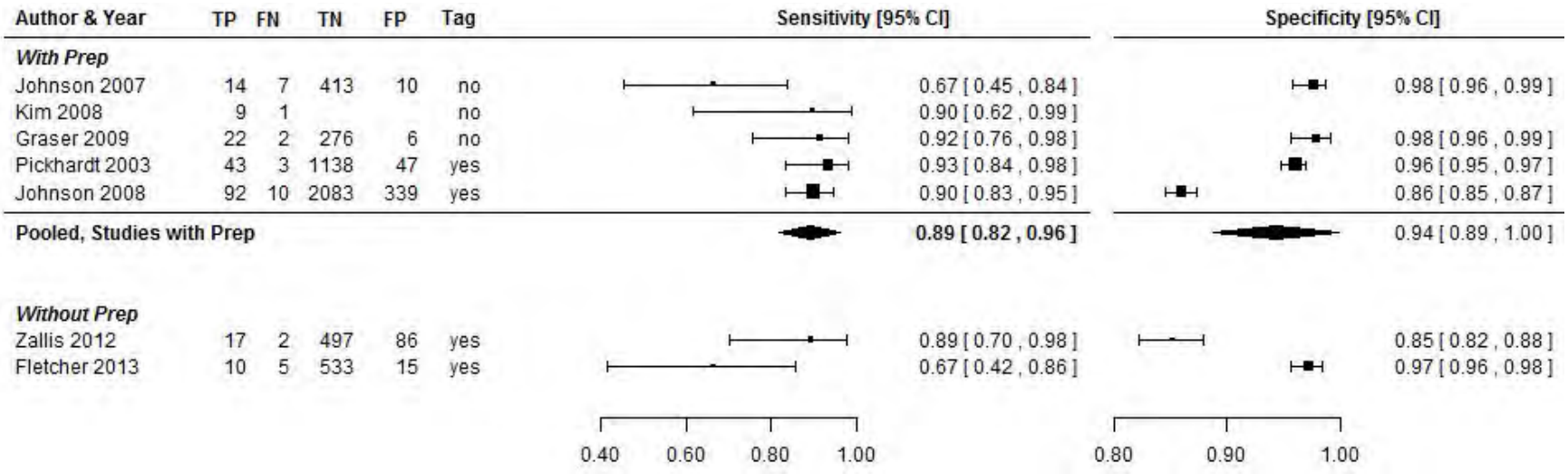
Abbreviations: CI = confidence interval; IRR = incidence rate ratio; NORCCAP = Norwegian Colorectal Cancer Prevention; PL = Profile Likelihood; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; p-y = person-years; SCORE = Screening for COlon Rectum; UKFSST = UK Flexible Sigmoidoscopy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

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



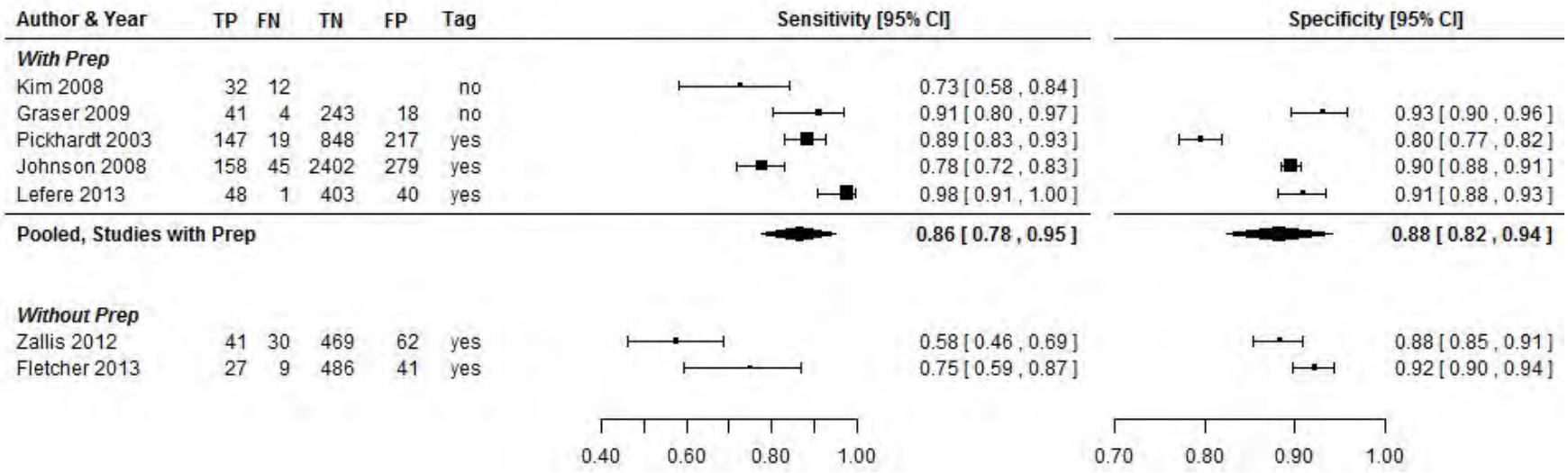
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

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



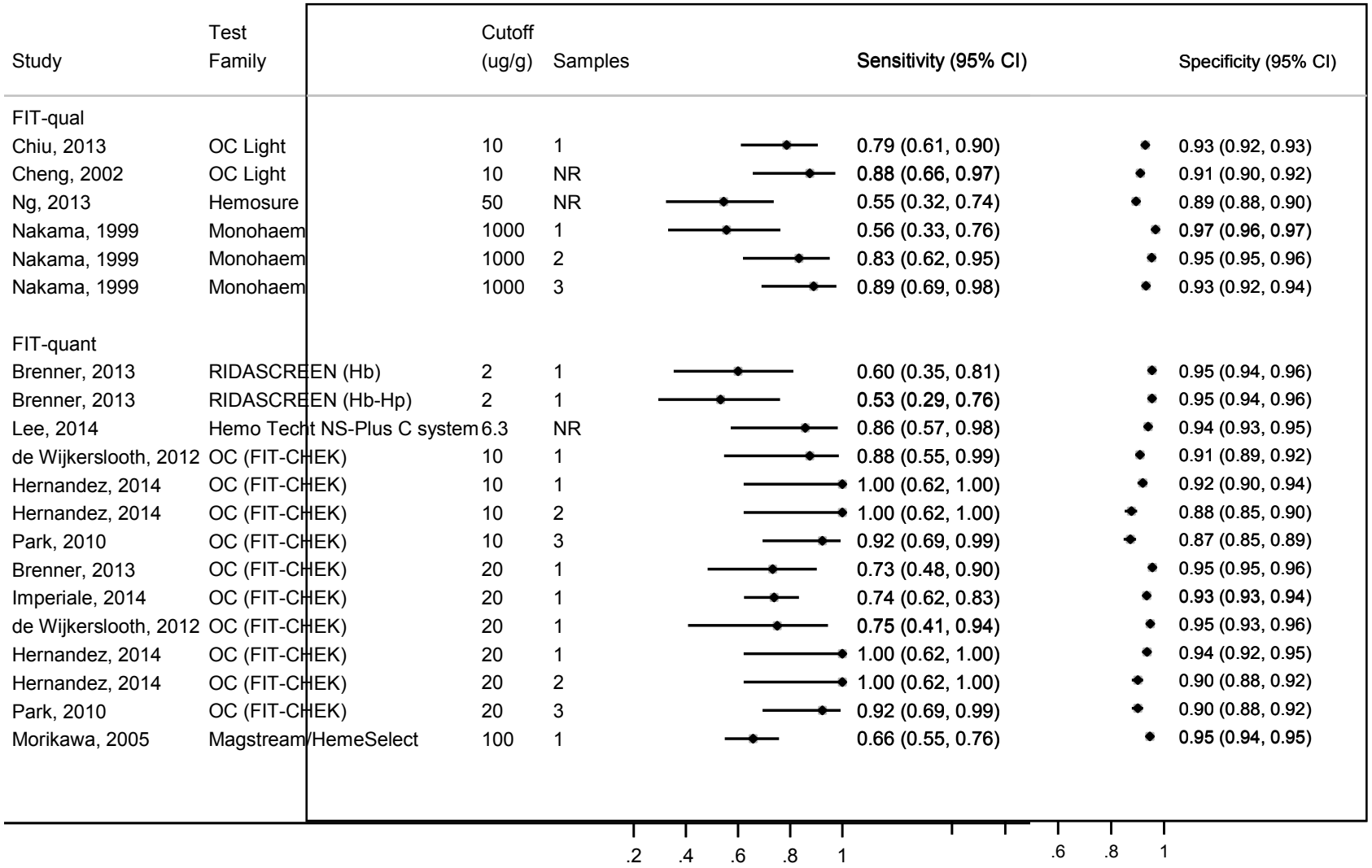
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

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



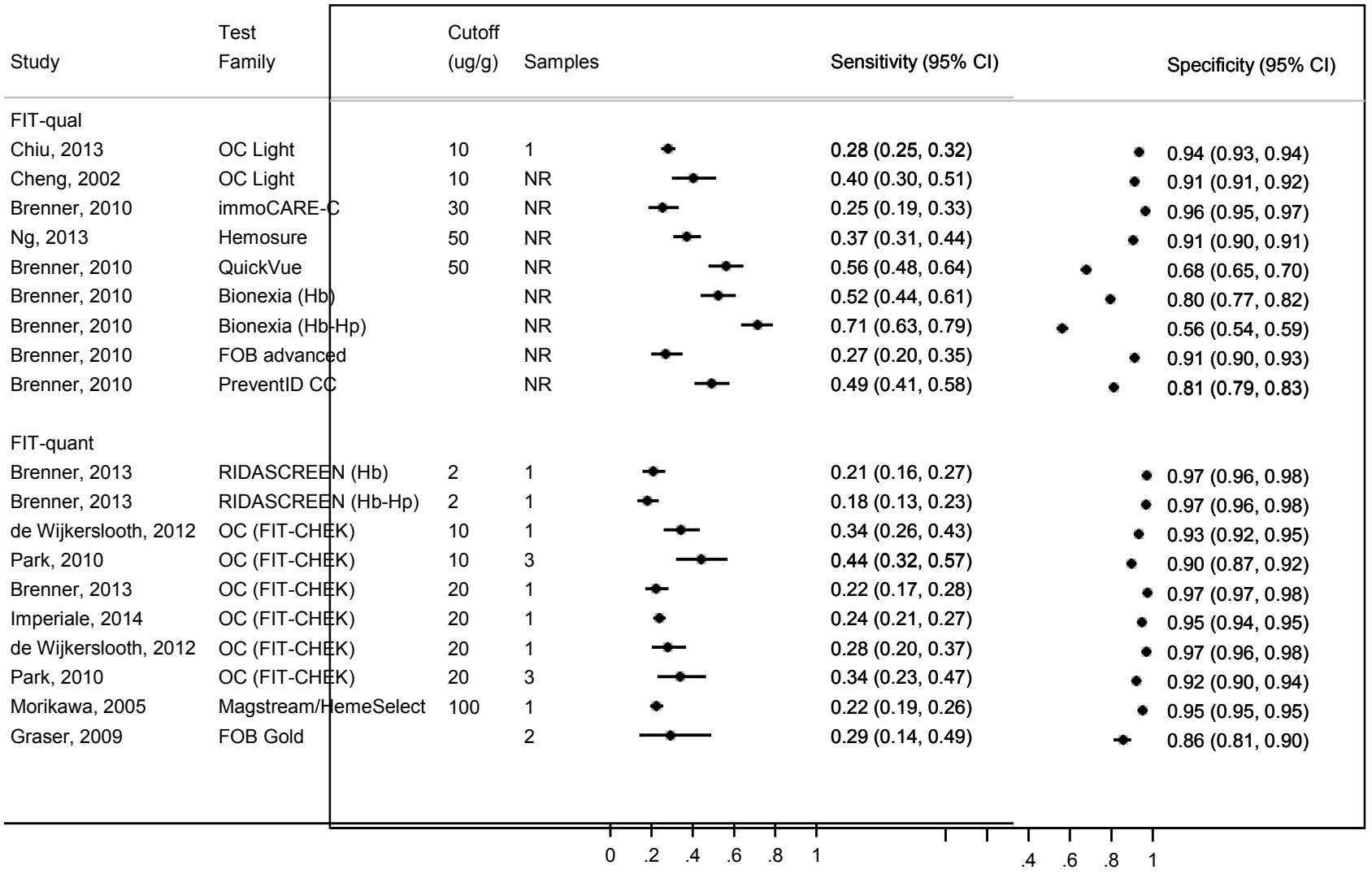
Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; prep = preparation; Tag = tagging agent; TN = true negative; TP = true positive

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



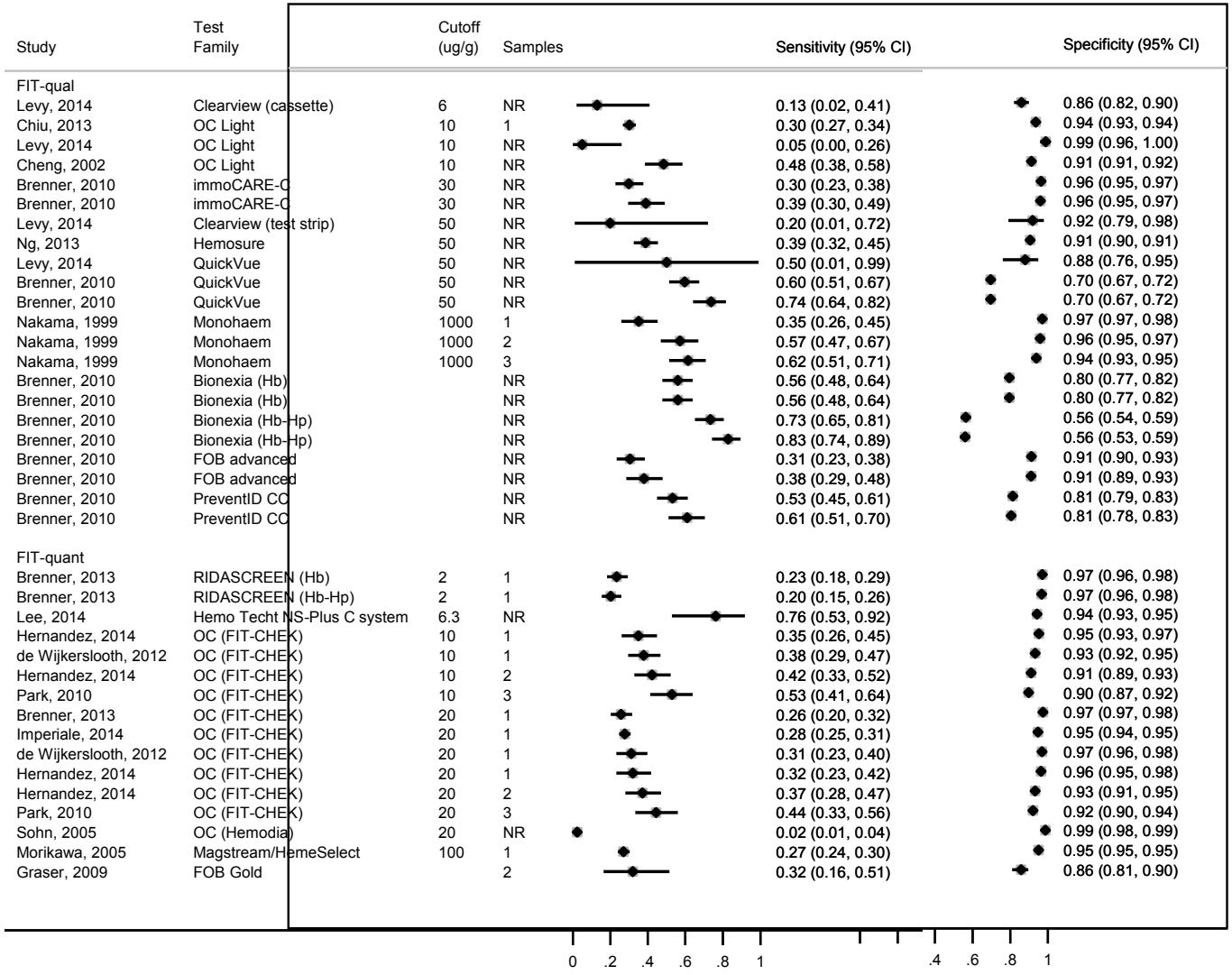
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

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



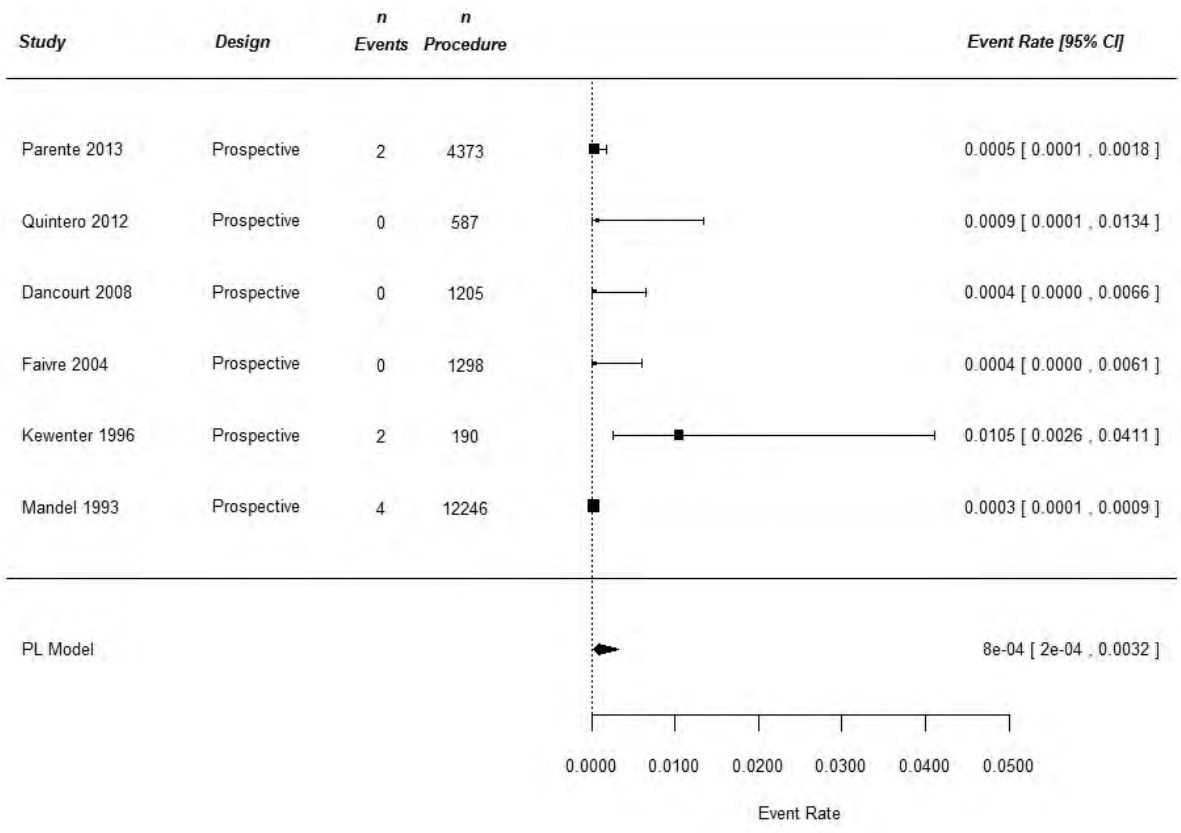
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

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



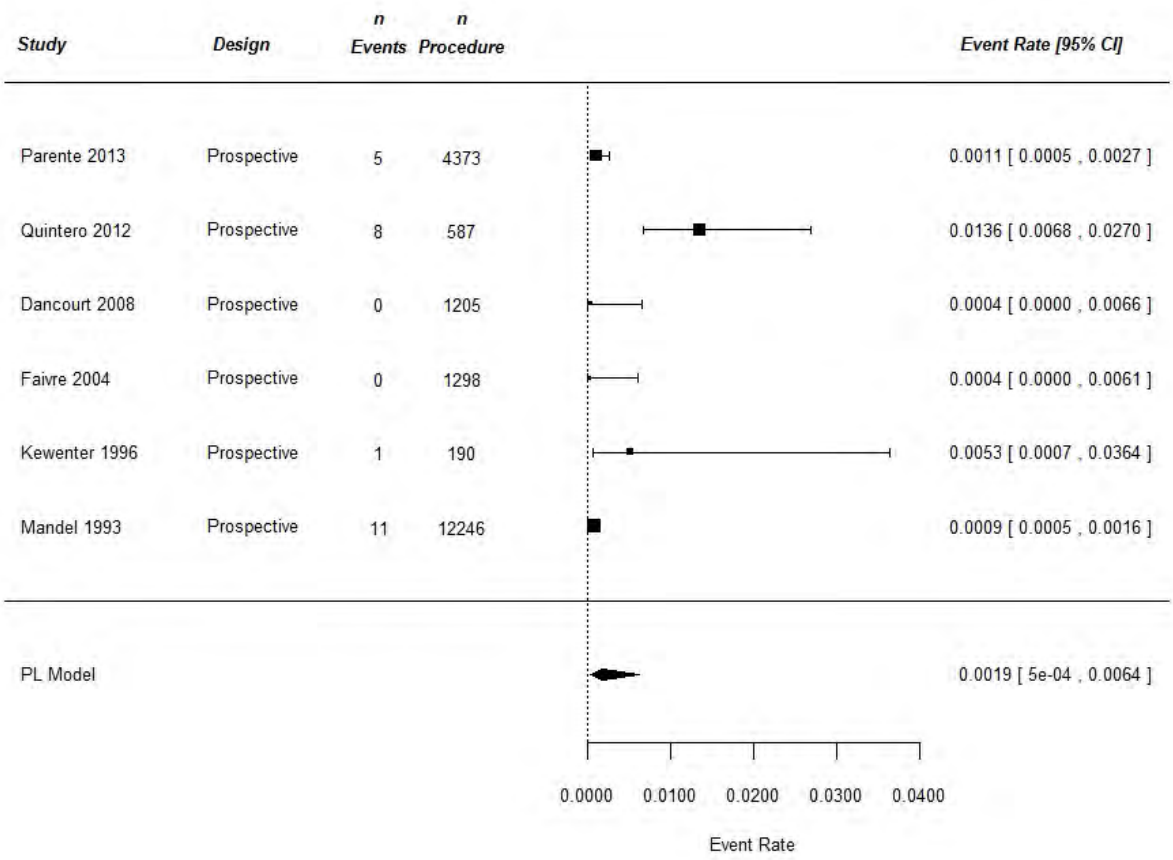
Abbreviations: CI = confidence interval; FIT = fecal immunochemical test; qual = qualitative; quant = quantitative; ug/g = micrograms per gram

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



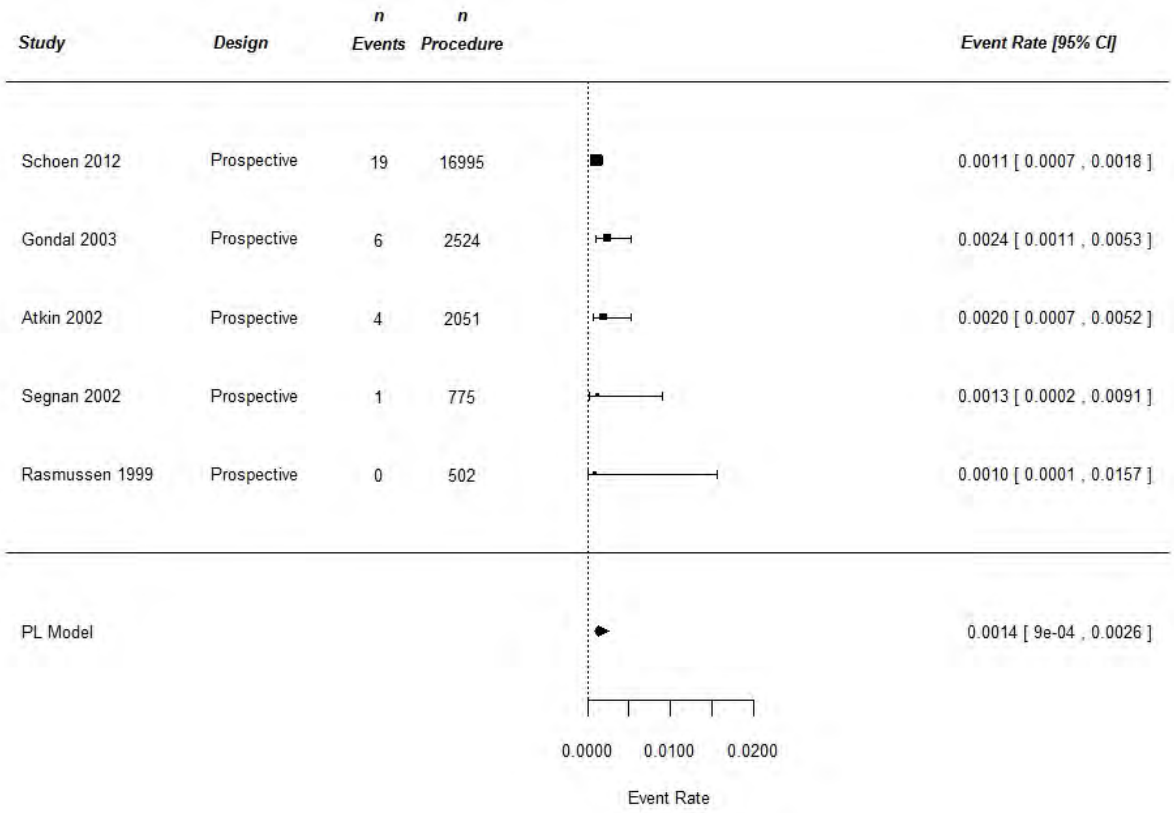
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* $I^2 = 60.04\%$

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



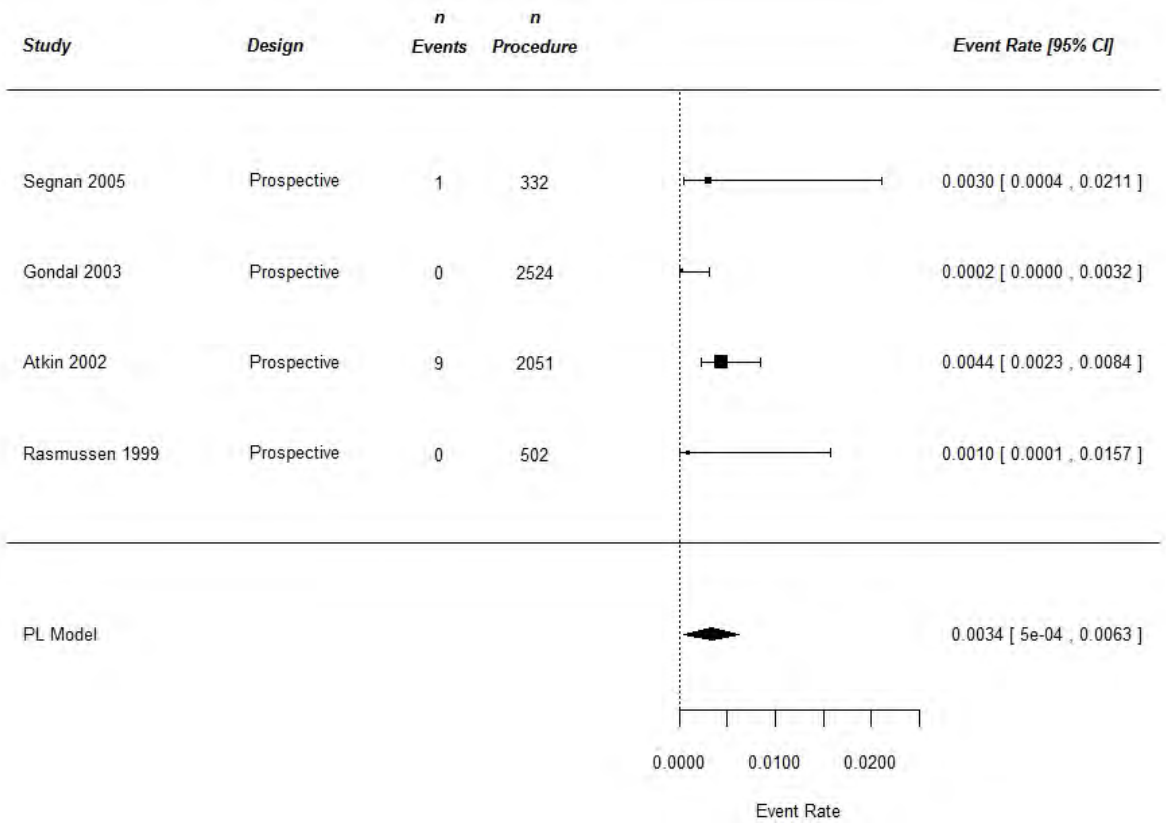
Abbreviations: CI = confidence interval; PL = Profile Likelihood
$I^2 = 83.02\%$

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



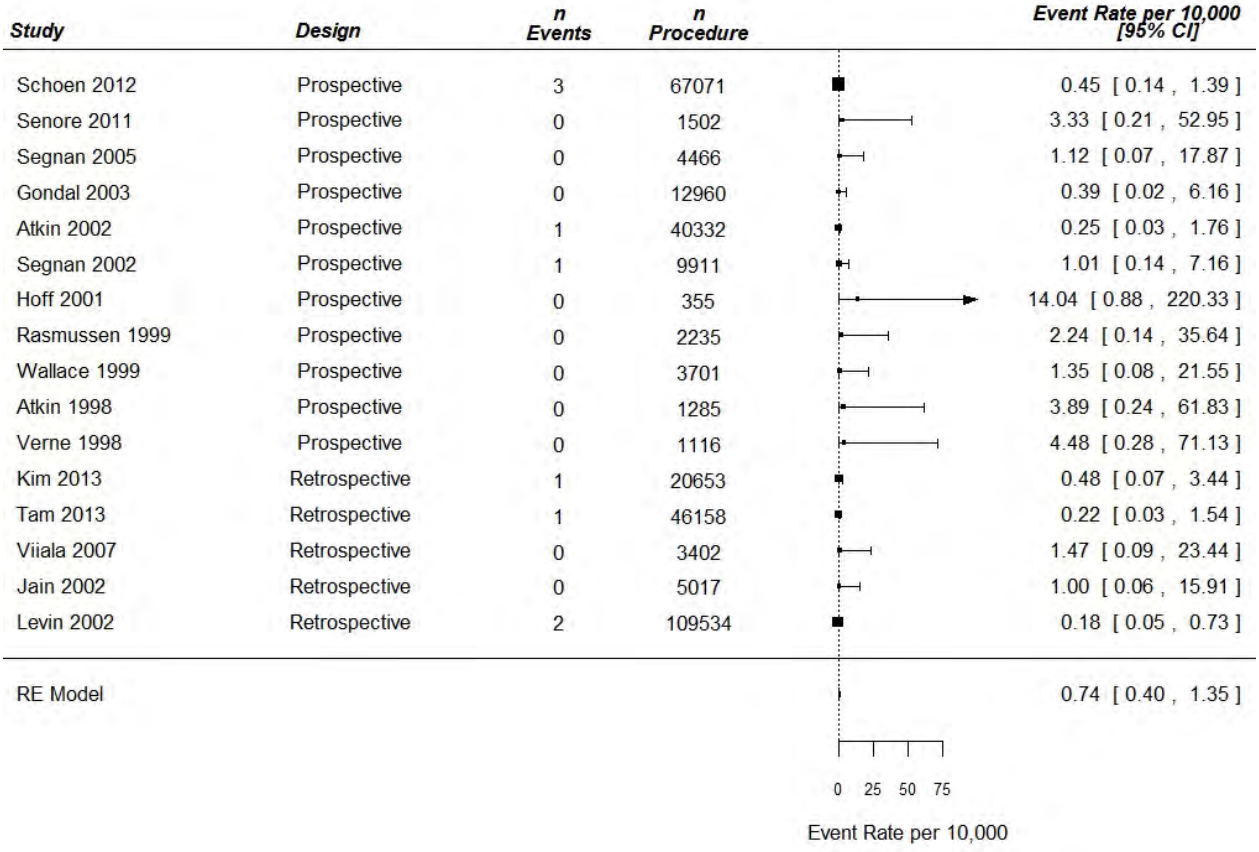
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* $I^2 = 0\%$

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



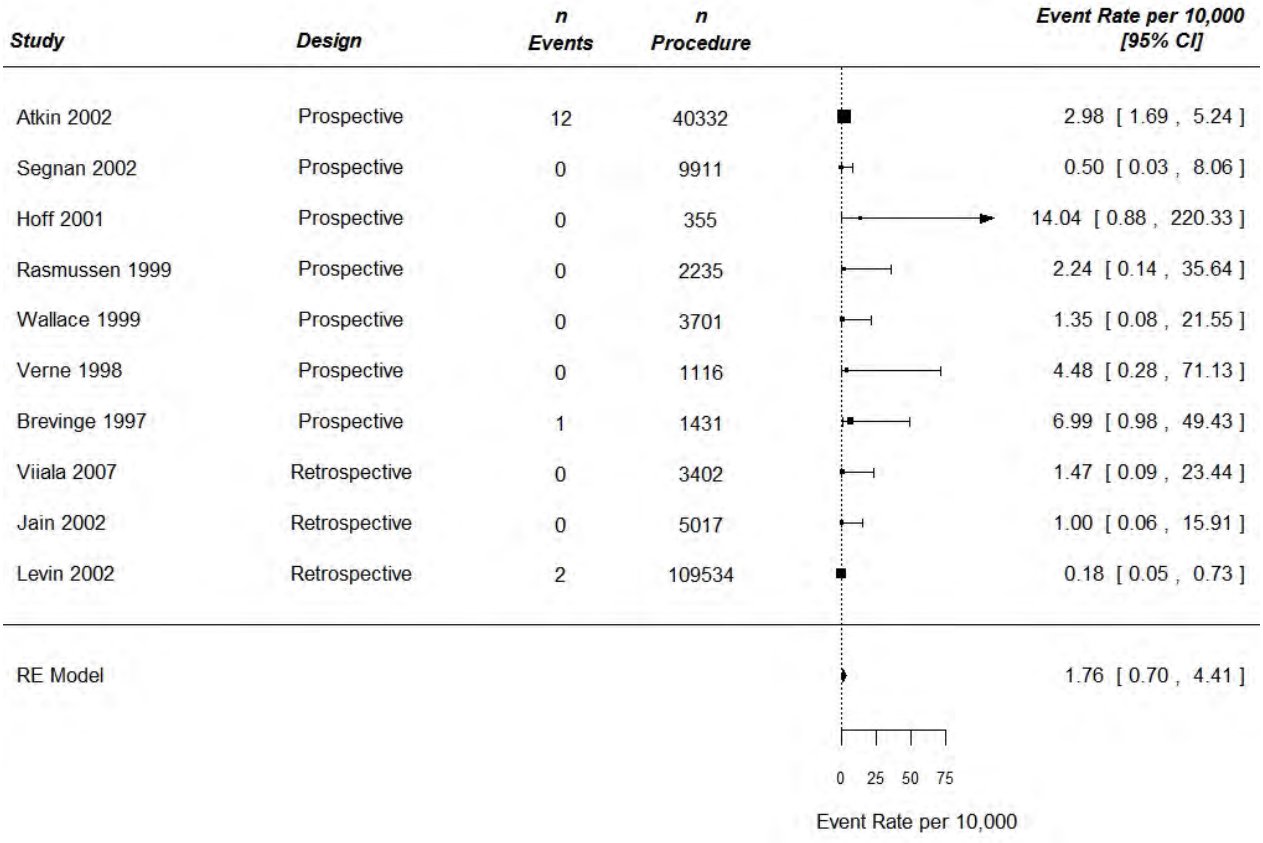
Abbreviations: CI = confidence interval; PL = Profile Likelihood
* $I^2 = 7.57\%$

Figure 20. Key Question 3: Forest Plot of Perforations From Flexible Sigmoidoscopy* **



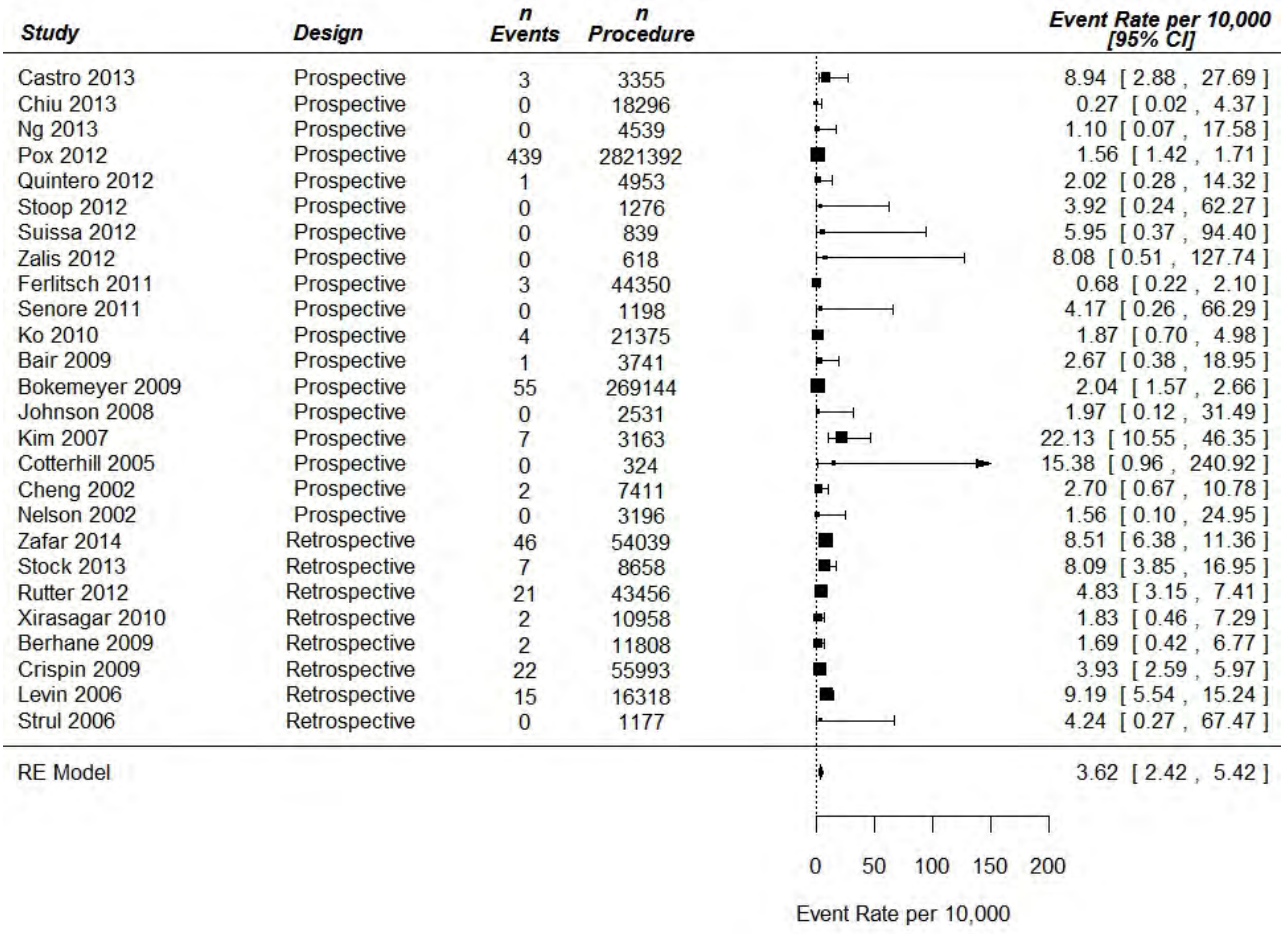
Abbreviations: CI = confidence interval; n = number; RE = restricted maximum likelihood;
* $I^2 = 18.39\%$
** One trial has been excluded from the meta-analysis due to very small n (n=52).[256] There were no episodes of serious bleeding or perforation in the study.

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



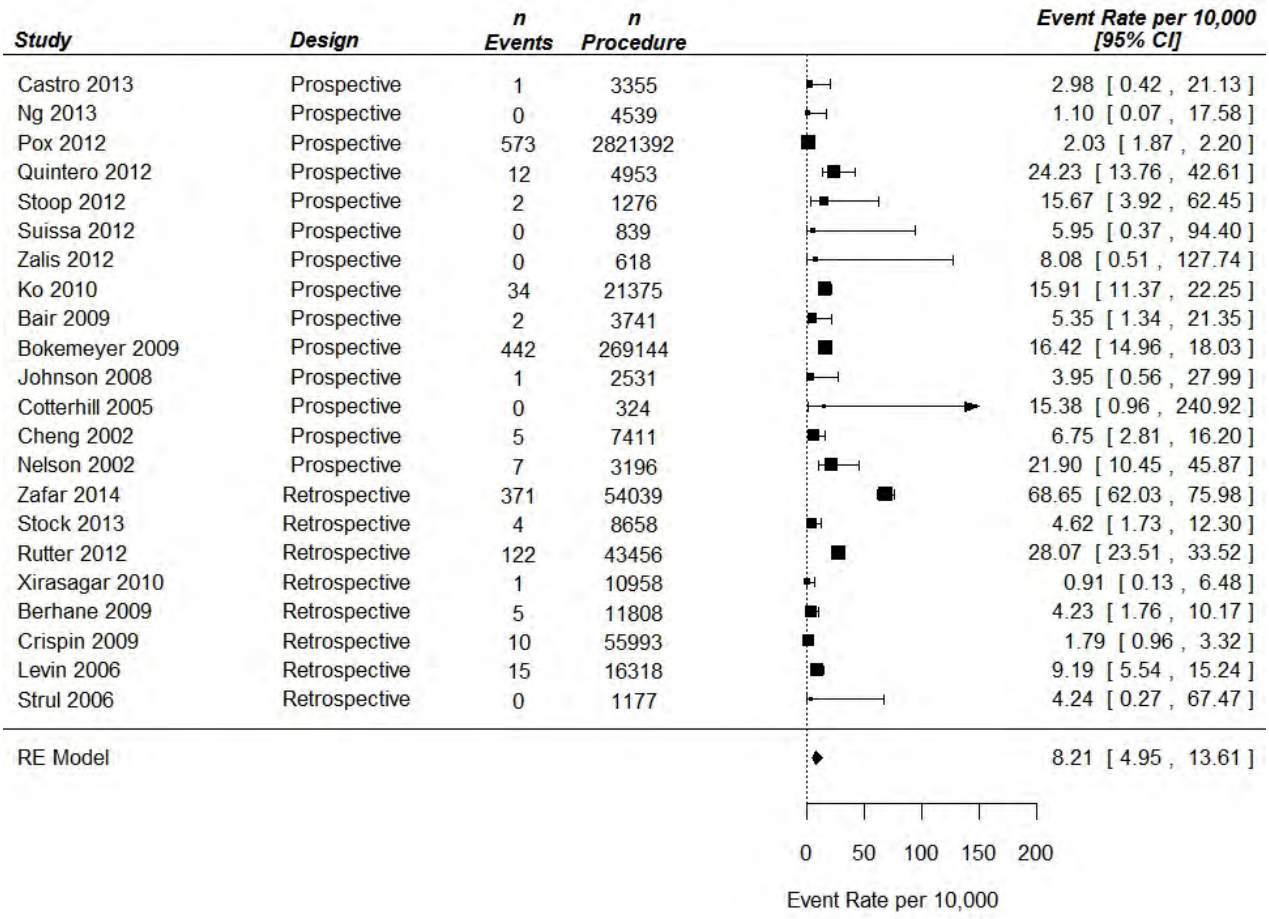
Abbreviations: CI = confidence interval; n = number; RE = restricted maximum likelihood;
* $I^2 = 52.52\%$
** One trial has been excluded from the meta-analysis due to very small n (n=52).[256] There were no episodes of serious bleeding or perforation in the study.

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).[256] 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).[256] 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 Persons 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[144] (NORCCAP)** **Schoen, 2012[123] (PLCO)** Weissfeld, 2005[155] **Segnan, 2011[125] (SCORE)** Segnan, 2002[150] **Atkin, 2010[109] (UKFSST)** Atkin, 2002[134]	None	**Shaukat, 2013[128] (Minnesota Study)** Mandel, 2000[147] Mandel, 1993†[148] Thomas, 1995[151] **Scholefield, 2012[124] (Nottingham)** Hardcastle, 1996†[143] **Malila, 2011[120]** Malila, 2008[146] **Lindholm, 2008†[119]** **Faivre, 2004[114]** **Kronborg, 2004†[118] (Hemoccult II)**	None
Comparative effectiveness trials	**Quintero, 2012[121] (COLONPREV)** Parra-Blanco, 2006[149] **Stoop, 2012[129] (COCOS)** **Segnan, 2007[126] (SCORE III)**	**Hol, 2010*[117]** Hol, 2009[402] Hol, 2010[403] **Segnan, 2007[126] (SCORE III)** **Segnan, 2005[127] (SCORE II)** **Rasmussen, 1999[122]** **Verne, 1998[132]** **Berry, 1997[110]** **Brevinge, 1997[111]**	**Stoop, 2012[129] (COCOS)**	**Hol, 2010*[117]** Hol, 2009[402] Hol, 2010[403] **van Rossum, 2008[131]** **Rasmussen, 1999[122]** **Verne, 1998[132]** **Berry, 1997[110]** **Brevinge, 1997[111]**	**Zubero, 2014[133]** **van Roon, 2013*[130]** van Roon, 2011[153] **Quintero, 2012[121] (COLONPREV)** **Hol, 2010*[117]** Hol, 2009[402] Hol, 2010[403] **van Rossum, 2008[131]** Denters, 2012[138] Denters, 2009[139] **Segnan, 2007[126] (SCORE III)** **Segnan, 2005[127] (SCORE II)**
Observational	**Nishihara, 2013[41] (HPS, NHS)**	None	None	**Hamza, 2013[116]** **Faivre, 2012[113]** Faivre, 2012[140] **Guittet, 2009[115]** Guittet, 2012[141] Guittet, 2009[142]	**Hamza, 2013[116]** **Faivre, 2012[113]** Faivre, 2012[140] **Guittet, 2009[115]** Guittet, 2012[141] Guittet, 2009[142]

* Overlapping study populations

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

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

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)*	22 y	*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)	11-12 y	*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=442,088)	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	11-28 y	*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[144]	PLCO, 2012[123,155]	SCORE, 2011[125,150]	UKFSST, 2010[109,134]
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[144]	PLCO, 2012[123,155]	SCORE, 2011[125,150]	UKFSST, 2010[109,134]
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[114]	Funen, 2004[118]	Göteborg, 2008[119]	Finland, 2011[120,146]	Nottingham, 2012[124,143]	Minnesota Colon Cancer Control Study, 2013[128,147,148,151]	
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[133]	Spain		X			
	van Roon, 2013*[130]	The Netherlands		X†			
	Quintero, 2012[121,149] (COLONPREV)	Spain		X		X	
	Stoop, 2012[129] (COCOS)	The Netherlands				X	X
	van Roon, 2011*[153]	The Netherlands		X‡			
	Hol, 2010*[117]	The Netherlands	X	X	X		
	van Rossum, 2008[131,138,139]	The Netherlands	X	X			
	Segnan, 2007[126] (SCORE III)	Italy		X	X	X	
	Segnan, 2005[127] (SCORE II)	Italy		X	X**		
	Rasmussen, 1999[122]	Denmark	X		X**		
	Verne, 1998[132]	UK	X		X**		
	Berry, 1997[110]	UK	X		X**		
	Brevinge, 1997[111]	Sweden	X		X		
Observational	Hamza, 2013[116]	France	X	X			
	Faivre, 2012[113,140]	France	X	X‡			
	Guittet, 2009[115,141,142]	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[181]** **Johnson, 2008 (ACRIN)[50]** Johnson,2012[193] **Johnson, 2007*[168]** **Pickhardt, 2003*[52]**	None	**Lefere, 2013[51]** **Fletcher, 2013[165]** **Zalis, 2012[181]** **Graser, 2009[49]** **Johnson, 2008[50] (ACRIN)** Johnson, 2012[193] **Kim, 2008[169]** **Johnson, 2007*[168]** **Macari, 2004*[174]** **Pickhardt, 2003*[52]**	None	**Hernandez, 2014[183]** **Imperiale, 2014[166]** SSED[206] **Lee, 2014[184]** **Levy, 2014[172]** **Brenner, 2013[158] (BliTz)** Haug, 2011[189] Brenner, 2010[187] Brenner, 2010[186] Hundt, 2009[191] **Chiu, 2013[162]** **Ng, 2013[178]** **de Wijkerslooth, 2012[164] (COCOS)** **Park, 2010[179]** **Graser, 2009[49]** **Morikawa, 2005*[175]** Morikawa, 2007*[194] **Sohn, 2005[180]** **Cheng, 2002*[161]** **Nakama, 1999*[176]**	**Imperiale, 2014[166]** SSED[206] **Lin, 2012[173]** 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*[156]** **Allison, 1996*[157]** **Levi, 2011[171]**	**Chiang, 2014[182]** **Chen, 2011[160]** **Levi, 2011[171]** **Allison, 2007*[156]** **Castiglione, 2007[159]** Grazzini, 2004[188] **Launoy, 2005*[170]** **Allison, 1996*[157]** **Nakama, 1996*[177]** **Itoh, 1996*[167]**	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 Visual-ization†	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[160] for study design differences that likely affected diagnostic accuracy calculations; excluding Levi and colleagues[171] 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[183] 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[181] 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[168] 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: CT 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	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	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[169] 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

Table 12. Key Question 2: CT 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)
Johnson, 2007[168] 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
Macari, 2004[174] 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* 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

Table 12. Key Question 2: CT 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)
Zalis, 2012[181] 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[171] 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[157] 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†	--	Ultimed, Ahrensburg, 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?
PreventID CC	PreventID CC	Qualitative	Immunochromatographic	10**	--	Preventis, Bensheim, Germany	--	No
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 agglutination	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[172]
* 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;[404] different cutoff of 0.2 mg/g feces (200 µg/g feces) reported by Nakama and colleagues[176]
‡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[183] 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[166] 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[184] 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[172] 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	clearview ULTRA iFOB (test strip) (Clearview (test strip))
						308	Clearview iFOB complete (cassette) (Clearview (cassette))
						217	OC-Light (OC Light)
						52	QuickVue (QuickVue)

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, 2013[158] (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))
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

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)
Ng, 2013[178] 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[179] 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)
Morikawa, 2005[175] 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/Heme Select)
Sohn, 2005[180] 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[405] 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)

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)
Nakama, 1999[176] 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. Key Question 2: 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[172] 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[162,178] 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)
	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)

Table 16. Key Question 2: 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[161] Fair Taiwan	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[176] Fair Japan	Monohaem	1	NR	~1,000*	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	~1,000*	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	~1,000*	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. Key Question 2: 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[183] 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[166] 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[184] 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[158] (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. Key Question 2: 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[179] 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 cut-offs 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[175] 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[180] 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. Key Question 2: Fecal Immunochemical Tests 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[182] 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[160] 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[171] 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*[156] 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[159] 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[170] 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. Key Question 2: Fecal Immunochemical Tests 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[157] 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[167] 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[177] 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[156] 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. Key Question 2: 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[159] 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[157] 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[177] 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. Key Question 2: 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[160] 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[171] 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[170] 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[167] 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. Key Question 2: 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 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
		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	
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

Table 21. Key Question 2: 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
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 IITM	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[210]	**Sagawa, 2012**[269]	**Warren, 2009**[281]	**Kim, 2013**[244]	**Wallace, 1999**[280]	**Zafar, 2014**[283]	**Flicker, 2008**[230]	**Parente, 2013**[259]	**Schoen, 2012**[123] **(PLCO)**
Bielawska, 2014[216]	**Stoop, 2012**[129] **(COCOS)**	**Kang, 2008**[241]	**Tam, 2013**[277]	**Atkin, 1998**[291]	**Fletcher, 2013**[165]	**Johnson, 2008**[50] **(ACRIN)** Johnson, 2012[193]	**Quintero, 2012**[121] **(COLONPREV)**	**Segnan, 2005**[127] **(SCORE III)**
Blotiere, 2014[217]	**Suissa, 2012**[276]	**Johnson, 2008**[50] **(ACRIN)** Johnson,2012[193]	**Schoen, 2012**[123] **(PLCO)**	**Verne, 1998**[132]	**Iafrate, 2013**[238]	**Kim, 2008**[245]	**Dancourt, 2008**[226]	**Gondal, 2003**[284] **(NORCCAP)** Hoff, 2009[285]
Layton, 2014[249]	**Zalis, 2012**[181]	**Mansmann, 2008**[255]	**Senore, 2011**[270] **(SCORE III)**	**Brevinge, 1997**[111]	**Lefere, 2013**[51]	**Kim, 2008**[169]	**MACS group, 2006**[256]	**Atkin, 2002**[134] **(UKFSST)**
Zafar, 2014[283]	**Ferlitsch, 2011**[48]	**Rabeneck, 2008**[266]	**Viiala, 2007**[279]		**Cash, 2012**[219]	**Pickhardt, 2008**[289]	**Faivre, 2004**[114]	**Segnan, 2002**[150] **(SCORE)**
Adler, 2013[211]	**Loffeld, 2011**[252]	**Kim 2007**[243]	**MACS group, 2006**[256]		**Durbin, 2012**[228]	**Kim, 2007**[243]	**Kewenter, 1996**[406] **(Göteborg)** Lindholm, 2008[119]	**Rasmussen, 1999**[122]
Castro, 2013[220]	**Senore, 2011**[270] **(SCORE III)**	**Ko, 2007**[247]	**Segnan, 2005**[127] **(SCORE II)**		**Stoop, 2012**[129] **(COCOS)**	**Pickhardt, 2007**[262]	**Mandel, 1993**[148] **(Minnesota)** Shaukat, 2013[128]	
Chiu, 2013[162]	**Ko, 2010**[246]	**Levin, 2006**[250]	**Gondal, 2003**[284] Hoff, 2009[285]		**Zalis, 2012**[181]	**MACS group, 2006**[256]		
Chukmaitov, 2013[222]	**Lorenzo-Zungia, 2010**[253]	**MACS group, 2006**[256]	**Atkin, 2002**[134] **(UKFSST)**		**Macari, 2011**[254]	**Pickhardt, 2006**[263]		
Cooper, 2013[223]	**Xirasagar, 2010**[282]	**Rathgaber, 2006**[267]	**Jain, 2002**[239]		**O'Connor, 2011**[258]	**Sosna, 2006**[273]		
Dominitz, 2013[227]	**Arora, 2009**[213]	**Strul, 2006**[275]	**Levin, 2002**[251]		**Pickhardt, 2011**[260]	**Chin, 2005**[221]		
Hamdani, 2013[233]	**Bair, 2009**[214]	**Cotterhill, 2005**[224]	**Segnan, 2002**[150] **(SCORE)**		**Kim, 2010**[286]	**Edwards, 2004**[229]		
Kim, 2013[244]	**Berhane, 2009**[215]	**Korman, 2003**[248]	**Hoff, 2001**[236] **(Telemark Polyp Study I)** Thiis-Evensen, 1999[17] Hoff, 1996[33]		**Pickhardt, 2010**[261]	**Ginnerup, 2003**[231]		
Ng, 2013[178]	**Bokemeyer, 2009**[218]	**Cheng, 2002**[161]			**Veerappan, 2010**[278]	**Gluecker, 2003**[232]		
Stock, 2013[274]	**Crispin, 2009**[225]	**Nelson, 2002**[257]			**Graser, 2009**[49]	**Hara, 2000**[234]		
Tam, 2013[277]	**Hsieh, 2009**[237]	**Sieg, 2001**[271]			**An, 2008**[212]			
Ho, 2012[235]	**Kamath, 2009**[240]		**Rasmussen, 1999**[122]					
Pox, 2012[264]	**Quallick, 2009**[265]							
Quintero, 2012[121] **(COLONPREV)**	**Singh, 2009**[272]							
Rutter, 2012[268]								

* 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[259] 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[121] Fair	FIT positives Spain	Prospective NR	7.2 587	0 (0)	8 (1.4)	NR	Hypotension or bradycardia: 2 (0.3)
	Dancourt, 2008[226] Fair	FOBT or FIT positives France	Prospective NR	9.0 1205	0 (0)	0 (0)	NR	NR
	MACS group, 2006[256] Fair	FIT positives Australia	Prospective 4 weeks	3.2 4	0 (0)	0 (0)	0 (0)	0 (0)
	Faivre, 2004[114] Fair	FOBT positives France	Prospective NR	1.5 1298	0 (0)	0 (0)	NR	NR
	Kewenter, 1996[119,406] 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[128,148] Good	FOBT positives US	Prospective NR	2.4 (unhydrated slides) 9.8 (hydrated slides) 12246	4 (0.03)	11 (0.09)	NR	NR

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 (%)
FS†	Schoen, 2012[123] PLCO Fair	FS positives€ US	Prospective NR	28 17,672¥	19 (0.1)	NR	NR	NR
	Segnan, 2005[127]† SCORE II Fair	FS positives[θ] Italy	Prospective NR	7.6 332	NR	1 (0.3)	NR	Hospitalization††: 1
	Gondal, 2003[284,285] 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[134] 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[150] SCORE Fair	FS positivesδ Italy	Prospective 30 days	8.4 775	1 (0.1)	1 (0.1)	NR	0 (0)
	Rasmussen, 1999[122] 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

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

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	Sigmoidoscopies, n	Perforation, n (%)	Bleeding, n (%)	Mortality, n (%)	Other serious events, n (%)
Prospective	Schoen, 2012[123] Fair	Screening US	NR NR	NR 50	NR	67,071	3 (0.004)	NR	NR	NR
	Senore, 2011[270] Fair	Screening Italy	NR NR	NR 49	30 days	1502	0 (0)	12 (0.8)δ	NR	Hospitalization: 16 ED: 2 Other: 18 (CVD, hernia, severe pain, hypotension)
	MACS group, 2006[256] Fair	Screening Australia	NR NR	NR 49	4 weeks	52	0 (0)	0 (0)	NR	0 (0)
	Segnan, 2005[127] Fair	Screening Italy	NR 87 (to distal)	NR 52‡	NR	4466	NR	0 (0)	NR	Syncope: 1
	Gondal, 2003[284,285] Fair	Screening Norway	NR NR	NR 66	NR	12,960	0 (0)	0 (0)	NR	Syncope: 26 Other: 1 (PE)
	Atkin, 2002[134] Fair	Screening UK	NR NR	NR 50	30 days	40,332	1 (0.002)	12 (0.03)	6 (0.01)	Hospitalization: 12 MI: 2 Syncope: 95 Other: 1 (PE)
	Segnan, 2002[150] Fair	Screening Italy	NR 84 (to distal)	NR 50	30 days	9911	1 (0.01)	0 (0)	NR	Other: 4 (colitis, seizure)
	Hoff, 2001[17,33,236] Fair	Screening Norway	NR NR	NR NR	NR	355	0 (0)	0 (0)	0 (0)	Hospitalization: 1** Other: 0
	Rasmussen, 1999[122] Fair	Screening Denmark	15 85 (60 cm)	NR NR	NR	2235	0 (0)	0 (0)	0 (0)	Other: 0 (0)

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 (%)
	Wallace, 1999[280] Fair	US Screening	18 77 (50 cm)	59 50	NR	3701	0 (0)	0 (0)	0 (0)	NR
	Atkin, 1998[291] Fair	Screening UK	NR NR	NR NR	NR	1285	NR	40 (3.1)δ	1 (0.08)	Hospitalization: 1 MI: 1 Syncope: 1 Other†: 1 (severe diarrhea)
	Verne, 1998[132] Fair	Screening UK	1 NR	NR 49	NR	1116	0 (0)	0 (0)	NR	Other: 0 (0)
	Brevinge, 1997[111] Fair	Screening Sweden	NR NR	NR 49	NR	1431	NR	1 (0.07)	NR	Other: 1 (diverticulitis)
Retrospective	Kim, 2013[244] Fair	Mixed (including symptomatic) South Korea	NR NR	NR 63	NR	20,653	1 (0.005)	NR	NR	NR
	Tam, 2013[277] Fair	Screening US	NR NR	NR NR	NR	46,158	1 (0.002)	NR	5 (0.004)β	Other: 4 (0.003) ("long-term complications")β
	Viiala, 2007[279] Fair	Screening Australia	NR 73 (50 cm)	60 41	NR	3402	0 (0)	0 (0)	NR	NR
	Jain, 2002[239] Fair	Screening US	NR NR	NR NR	NR	5017	0 (0)	0 (0)	0 (0)	NR
	Levin, 2002[251] Fair	Screening US	NR NR	61 49	4 weeks	109,534	2 (0.002)	2 (0.002)	10 (0.009)	MI: 33 Other†: 3 (GI serious adverse events)

* 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

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

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[211] Fair	Screening Germany	21 98	64 53	NR	12,134	NR	NR	NR	NR***
	Castro, 2013[220] 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[178] Fair	Screening Hong Kong	NR NR	58 55	NR	4539	0 (0)	0 (0)	NR	NR
	Pox, 2012[264] 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[121] COLONPREV Fair	Screening Spain	NR NR	NR NR	NR	4953	1 (0.02)	12 (0.2)	NR	Other: 11 (cardiopulmonary event)
	Stoop, 2012[129] 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[276] Fair	Screening Israel	NR NR	58 NR	NR	839	0 (0)	0 (0)	NR	NR
	Zalis, 2012[181] 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[252] Fair	Mixed (including symptomatic) The Netherlands	NR NR	NR NR	NR	19,135	26 (0.1)	NR	NR	NR
	Senore, 2011[270] 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[246] 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[214] Fair	Screening Canada	9 99	57 52	NR	3741	1 (0.03)	2 (0.05)	NR	NR
	Bokemeyer, 2009[218] Fair	Screening Germany	280 NR	NR 56	NR	269,144	55 (0.02)	442 (0.16)	NR	Other: 222 (cardiopulmonary event)
	Quallick, 2009[265] 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*[243] 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[247] Fair	Mixed (including symptomatic) US	8 99	NR 51	30 days	502	0 (0)	3 (0.6)	NR	Hospitalization: 2 ED: 2 Other: NR
	MACS group, 2006[256] Fair	Screening Australia	NR NR	NR 49	4 weeks	63	0 (0)	0 (0)	NR	0 (0)
	Cotterhill, 2005[224] Fair	Screening Canada	NR 94	NR 44	NR	324	0 (0)	0 (0)	NR	NR
	Cheng, 2002[161] Fair	Screening Taiwan	NR 99	47 45	NR	7411	2 (0.03)	5 (0.07)	0 (0)	Hospitalization: 0 (0)
	Nelson, 2002[257] Fair	Screening US	NR 97	63 3	30 days	3196	0 (0)	7 (0.2)§	3 (0.09)	MI: 4 (includes CVA) Other: 19 (infection, CV event, syncope)
	Sieg, 2001[271] Fair	Mixed (including symptomatic) Germany	94 95	NR NR	NR	96,665	13 (0.01)	17 (0.02)	2 (0.002)	Other: 12 (cardiopulmonary events)
Retrospective	Adeyemo, 2014[210] Fair	Mixed (including symptomatic) US	NR NR	61 54	NR	118,004	48 (0.04)	NR	NR	NR
	Bielawska, 2014[216] Fair	Mixed (including symptomatic) US	NR NR	NR 48	NR	1,144,900	192 (0.02)	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 (%)
	Blotiere, 2014[217] Fair	Mixed (including symptomatic) France	NR NR	NR 56	3 days	947,061	424 (0.04)	182 (0.02)	NR	NR
	Layton, 2014[407] Fair	Screening US	NR NR	59 40	6 months	550,696	NR	NR	NR	AKI††: 1595
	Zafar, 2014[283] Fair	Screening US	NR NR	74 55	30 days	54,039	46 (0.08)	371 (0.7)	NR	Other: 921 (CVD or other GI events)
	Chukmaitov, 2013[222] Fair	Mixed (including symptomatic) US	NR NR	NR 54	30 days	2,315,126	773 (0.03)	3822 (0.2)	NR	NR
	Cooper, 2013[223] Fair	Mixed (including symptomatic) US	NR NR	76 55	30 days	100,359	101 (0.1)	NR	291 (0.2)	Other: 185 (splenic injury, aspiration)
	Dominitz, 2013[227] Fair	Mixed (including symptomatic) US	18,578 NR	NR 58	30 days	328,167	374 (0.1)	2299 (0.7)€	NR	Hospitalization: 10,478 ED: 14,278
	Hamdani, 2013[233] Fair	Mixed (including symptomatic) US	NR NR	NR 51	7 days	80,118	50 (0.06)	NR	NR	NR
	Kim, 2013[244] Fair	Mixed (including symptomatic) South Korea	NR NR	NR NR	NR	94,632	26 (0.03)	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 (%)
	Stock, 2013*[274] Good	Screening Germany	NR 100	66 55	30 days	8658	7 (0.08)	4 (0.05)	5 (0.06)	MI: 2 Other: 8 (CV, splenic injury, syncope)
	Tam, 2013[277] Fair	Mixed (including symptomatic) US	NR NR	NR NR	NR	86,101	25 (0.03)	NR	NR	Other: 4 ("long-term complications") £
	Ho, 2012[235] Fair	Mixed (including symptomatic) Canada	NR NR	NR 52	7 days	50,660	NR	NR	≤13	Hospitalization: 534 ED: 682 Other: 1218 (not specified)
	Rutter, 2012[268] Fair	Mixed (excluding symptomatic) US	NR NR	NR 51	30 days	43,456	21 (0.05)	122 (0.3)	15 (0.03)	Hospitalization: 508 ED: 1019
	Sagawa, 2012[269] Fair	Mixed (including symptomatic) Japan	NR NR	67 38	NR	10,826	8 (0.07)	NR	NR	NR
	Lorenzo-Zuniga, 2010[253] Fair	Mixed (including symptomatic) Spain	NR NR	57 NR	NR	25,214	13 (0.05)	59 (0.2)	NR	NR
	Xirasagar, 2010[282] Fair	Mixed (including symptomatic) US	51 98	58 52	NR	10,958	2 (0.02)	1 (0.009)	NR	Other: 3 (severe pain, aspiration, AKI)
	Arora, 2009[213] Fair	Screening US	NR NR	NR NR	7 days	58,457	39 (0.07)	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 (%)
	Berhane, 2009[215] Fair	Screening US	NR 98	NR NR	NR	11,808	2 (0.02)	5 (0.04)	0 (0)	MI: 1 Other: 8 (CV event other than MI)
	Crispin, 2009[225] Fair	Screening Germany	NR 98	NR 56	NR	55,993	22 (0.04)	10 (0.02)	NR	Other: 39 (cardiopulmonary events)
	Hsieh, 2009[237] Fair	Mixed (including symptomatic) Taiwan	NR NR	51 42	NR	9501	3 (0.03)	NR	NR	NR
	Kamath, 2009[240] Fair	Mixed (including symptomatic) US	NR NR	NR NR	22 months (median)	296,248	NR	NR	NR	Splenic injury‡: 7
	Singh, 2009[272] 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*[281] 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[241] Fair	Mixed (including symptomatic) South Korea	NR NR	60 36	NR	44,534£	53 (0.1)	NR	NR	NR
	Mansmann, 2008[255] Fair	Mixed (including symptomatic) Germany	NR 97	59 57	NR	236,087	69 (0.03)	10 (0.004)	NR	Other: 152 (cardiopulmonary events)

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 (%)
	Rabeneck, 2008[266] 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
	Levin, 2006[250] Fair	Mixed (excluding symptomatic) US	NR 70	62 40	30 days	16,318	15 (0.09)	15 (0.09)	10 (0.06)θ	MI: 9 Other: 82 (not specified, unclear if bleeding and perf are included)‡‡
	Rathgaber, 2006[267] Fair	Mixed (including symptomatic) US	8 98	60 52	30 days	12,407	2 (0.02)	11 (0.09)	0 (0)	Other: 1 (CV)
	Strul, 2006†[275] Fair	Screening Israel	NR NR	60 53	NR	1177	0 (0)	0 (0)	0 (0)	Other: 1 (severe pain)
	Korman, 2003[248] Fair	Mixed (including symptomatic) US	265 NR	NR NR	NR	116,000	37 (0.03)	NR	NR	NR

*** 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

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

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[129] 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[181] 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[212] 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[169] Fair	Screening South Korea	NR	2	58 49	241	0 (0)	No serious adverse events
	Kim, 2007[243] Fair	Screening US	NR	5	57 56	3120	0 (0)	NR
	MACS group, 2006[256] Fair	Screening Australia	4 weeks	NR	NR 49	38	0 (0)	No serious adverse events

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
	Edwards, 2004[229] Fair	Screening Australia	NR	2	NR 46	340	0 (0)	No serious adverse events
Retrospective	Zafar, 2014[283] 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[238] 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)
	Sosna, 2006[273] Fair	Mixed (including symptomatic) Israel	NR	16	60 42	11,870	7 (0.06) (only 1 was in a screening patient)	Mortality: 0 (0)
	Pickhardt, 2006[263] Fair	Screening US, Belgium, Ireland, Italy, The Netherlands	NR	NR	NR NR	11,707	0 (0)	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[181]	5.3mSv	NR	NR
Graser, 2009[49]	4.5 mSv	3.2 mSv	1.3 mSv
An, 2008[212]	0.8–1.0 mSv	NR	NR
Johnson, 2008[50]	50 mAs*	NR	NR
Kim, 2008[169]	NR	120 mAs*	50 mAs*
Johnson, 2007[168]	70 mAs*	NR	NR
MACS group, 2006[256]	<5 mSv	NR	NR
Edwards, 2004[229]	5 mSv	NR	NR
Macari, 2004[174]	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[228] Prospective	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[129] Prospective	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%) extra-colonic cancer (four renal-cell carcinoma, one duodenal carcinoma). 7 (0.7%) abdominal aortic aneurysms (three 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[181] Prospective	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*[261] Prospective	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*[258] Retrospective	N= 3001 Asymptomatic, mean 57 years Followup: chart review, 3 years	Benign renal mass (masses containing fat or with attenuation less than 20 HU or greater than 70 HU without thickened walls or septations, three or more septations, mural nodules, or thick clacifications. Indeterminate renal mass (attenuation between 20 and 70 HU or any with without thickened walls or septations, three or more 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*[260] Retrospective	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*[243] Prospective	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%) persons with extra-colonic cancers, (treatment NR) (3 renal cancers, 2 bronchogenic cancers, 1 non-Hodgkin's lymphoma, 1 endometrial cancer, 1 GI stromal tumor)
	Kim, 2010*[286] Retrospective	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*[289] Prospective	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*[262] Prospective	N=2014 Presumed asymptomatic, mean 57 years Followup: chart review, unclear duration	NR Only evaluated extra-colonic GI tumors	10 (0.5%) focal extra-colonic 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[278] Retrospective	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	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[230] Retrospective	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[245] Prospective	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) extra-colonic 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 [221] Prospective	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	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%) extra-colonic 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 [219] Prospective	N= 1410 Asymptomatic, mean 75 years Followup: None	C-RADS	E3: 196 (13.9%) E4: 41 (2.9%)	Subsequent evaluation NR
	Macari, 2011[254] Retrospective	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 [231] Prospective	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 eventsof 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 [232] Prospective	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)

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
	Hara, 2000 [234] Prospective	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 non-malignant 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.
† 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 colonoscopies, multivariate adjusted HR 0.32 (95% CI 0.24, 0.45), compared with 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 follow-up, 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 follow-up colonoscopy. No reporting bias.	Fair to good	Fair to poor- no longer widely used in US
	gFOBT	k=5 n=442,088 RCT‡	Biennial screening with Hemoccult II compared to no screening consistently resulted in reduction of CRC specific mortality, ranging from 9 to 22 percentage points after 2-9 rounds of screening with 11 to 30 years of follow-up; 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 follow-up. 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 on 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
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 percent, and the per-person sensitivity for adenomas ≥6 mm ranged from 74.6 to 92.8 percent.	Studies are not designed to assess diagnostic accuracy to detect cancers. 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

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	k=9 n=6497 Prospective diagnostic accuracy	In 1 study (n=2531), CTC missed 1 of 7 cancer. 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 percent, 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 percent, respectively. Only 3 studies (n=1044) reported sensitivity to detect advanced adenomas, ranging from 87.5 to 100 percent. 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 it.	Studies are not designed to assess diagnostic accuracy to detect cancers. 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 percent and from 86.7 to 96.4 percent, 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 one study, and best results from small studies using more than one 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 one study, and 78.6% and 92.8% in another). For advanced adenoma, sensitivity and specificity were lower (40.3% and 92.3%, respectively, in one 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 percent (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 percent (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 percent (95% CI, 32.4 to 63.6) and 91.5 percent (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 the 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 per 10,000). Likewise rates of serious adverse events from follow-up diagnostic/therapeutic colonoscopy post FS (k=6) is estimated at 14 perforations per 10,000 (95% CI, 9 to 26 per 10,000), and 34 major bleeds per 10,000 (95% CI, 5 to 63 per 10,000).	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 per 10,000), and 8 major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14 per 10,000). 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 per 10,000), and 2 major bleeds (k=10) per 10,000 procedures (95% CI, 1 to 4 per 10,000).	No studies reported serious adverse events in persons without FS. Likely reporting bias of serious harms other than perforation and bleeding. Only one 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	Extra-colonic findings, which could be a benefit or harm, are estimated to occur in 41 to 69 percent of examinations. Similarly, the estimated proportion of these findings that necessitate actual diagnostic followup varies widely from 5 to 37 percent), with a very small proportion that require any type of definitive treatment (up to 3 percent). Higher prevalence of ECF with increasing age.	No studies able to quantify net benefit/harms of ECF findings. Varying levels of follow-up, 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 Organizations 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[408]	Y	Y	Y	Y	N	N	N	--
ACG, 2008[393]	Y	M	Y	Y	Y	M	--	--
ACR, 2010[409]	--	--	--	--	Y	--	Y	M
SIGN, 2011[410]	--	--	Y	--	--	--	--	--
ICSI, 2012[411]	Y	Y	Y	Y	Y	--	--	--
ACP, 2012[412]	Y	Y	Y	Y	I	Y	Y	--
NCCN, 2013[413]	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 Clinical 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/ (14005)
2 colonoscop$.ti,ab. (14630)
3 Sigmoidoscopy/ (1906)
4 sigmoidoscop$.ti,ab. (2250)
5 Colonography, Computed Tomographic/ (1556)
6 colonograph$.ti,ab. (1517)

7 Occult Blood/ (2422)
8 occult blood.ti,ab. (2718)
9 ((fecal or faecal or stool) adj occult).ti,ab. (2300)
10 (fobt or ifobt or gfobt).ti,ab. (934)
11 guaiac.ti,ab. (344)
12 ((fecal or faecal or stool) adj5 test$).ti,ab. (5347)
13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab. (1265)
14 DNA/ (110045)
15 DNA Methylation/ (24664)
16 DNA Mutational Analysis/ (38253)
17 DNA, neoplasm/ (19836)
18 14 or 15 or 16 or 17 (183020)
19 Feces/ (32446)
20 18 and 19 (379)
21 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab. (984)
22 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab. (185)
23 ((fecal or faecal or stool) adj5 molecular).ti,ab. (186)
24 (f-dna or fdna or s-dna or sdna).ti,ab. (296)
25 "SEPT9 protein, human".nm. (81)
26 Septins/ (405)
27 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab. (118)
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (30152)
29 Mass screening/ or "Early Detection of Cancer"/ (58851)
30 (screen$ or detect$).ti,ab. (1394000)
31 29 or 30 (1407263)
32 28 and 31 (12253)
33 Colorectal Neoplasms/ (46318)
34 Adenomatous Polyposis Coli/ (3299)
35 Colonic Neoplasms/ (28718)
36 Sigmoid Neoplasms/ (1359)
37 Colorectal Neoplasms, Hereditary Nonpolyposis/ (2917)
38 Rectal Neoplasms/ (13801)
39 Anus Neoplasms/ (2386)
40 Anal Gland Neoplasms/ (58)
41 Colonic Polyps/ (4139)
42 Adenomatous Polyps/ (913)
43 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (94445)
44 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab. (106314)
45 limit 44 to ("in data review" or in process or "pubmed not medline") (9032)
46 43 or 45 (103476)
47 (screen$ or detect$).ti. (239652)
48 46 and (29 or 47) (9002)
49 32 or 48 (16145)

50 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (165918)
51 meta-analysis as topic/ (11160)
52 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (482998)
53 control groups/ or double-blind method/ or single-blind method/ (94116)
54 Random$.ti,ab. (554141)
55 clinical trial$.ti,ab. (170772)
56 controlled trial$.ti,ab. (99181)
57 meta analy$.ti,ab. (55010)
58 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 (1022083)
59 49 and 58 (2383)
60 Mortality/ (15291)
61 mortality.fs. (261644)
62 Survival rate/ (98370)
63 Survival analysis/ (86313)
64 Life Expectancy/ (8156)
65 "Cause of Death"/ (25766)
66 mortality.ti,ab. (338625)
67 (death or deaths).ti,ab. (390123)
68 survival.ti,ab. (437227)
69 (registry or registries).ti,ab. (50430)
70 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (1097071)
71 49 and 70 (2855)
72 59 or 71 (4660)
73 limit 72 to humans (4194)
74 limit 72 to animals (193)
75 74 not 73 (98)
76 72 not 75 (4562)
77 limit 76 to english language (4188)
78 limit 77 to yr="2008 -Current" (2199)
79 remove duplicates from 78 (2190)

KQ2

1 Colonoscopy/ (14005)
2 colonoscop$.ti,ab. (14630)
3 Sigmoidoscopy/ (1906)
4 sigmoidoscop$.ti,ab. (2250)
5 Colonography, Computed Tomographic/ (1556)
6 colonograph$.ti,ab. (1517)
7 Occult Blood/ (2422)
8 occult blood.ti,ab. (2718)
9 ((fecal or faecal or stool) adj occult).ti,ab. (2300)
10 (fobt or ifobt or gfobt).ti,ab. (934)
11 guaiac.ti,ab. (344)
12 ((fecal or faecal or stool) adj5 test$).ti,ab. (5347)
13 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab. (1265)

14 DNA/ (110045)
15 DNA Methylation/ (24664)
16 DNA Mutational Analysis/ (38253)
17 DNA, neoplasm/ (19836)
18 14 or 15 or 16 or 17 (183020)
19 Feces/ (32446)
20 18 and 19 (379)
21 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab. (984)
22 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab. (185)
23 ((fecal or faecal or stool) adj5 molecular).ti,ab. (186)
24 (f-dna or fdna or s-dna or sdna).ti,ab. (296)
25 "SEPT9 protein, human".nm. (81)
26 Septins/ (405)
27 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab. (118)
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (30152)
29 "Sensitivity and Specificity"/ (243253)
30 "Predictive Value of Tests"/ (118624)
31 ROC Curve/ (26200)
32 False Negative Reactions/ (7539)
33 False Positive Reactions/ (12436)
34 Diagnostic Errors/ (14891)
35 "Reproducibility of Results"/ (239269)
36 Reference Values/ (88728)
37 Reference Standards/ (23651)
38 Observer Variation/ (26441)
39 Receiver operat$.ti,ab. (30373)
40 ROC curve$.ti,ab. (12666)
41 sensitivit$.ti,ab. (378638)
42 specificit$.ti,ab. (228424)
43 predictive value.ti,ab. (44345)
44 accuracy.ti,ab. (176991)
45 false positive$.ti,ab. (27679)
46 false negative$.ti,ab. (15703)
47 miss rate$.ti,ab. (210)
48 error rate$.ti,ab. (7077)
49 detection rate$.ti,ab. (11033)
50 diagnostic yield$.ti,ab. (4074)
51 likelihood ratio$.ti,ab. (7718)
52 diagnostic odds ratio$.ti,ab. (584)
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 (1130157)
54 28 and 53 (6855)
55 Colonoscopy/st (601)
56 Sigmoidoscopy/st (67)
57 Colonography, Computed Tomographic/st (78)

58 55 or 56 or 57 (720)
59 54 or 58 (7299)
60 Mass screening/ or "Early Detection of Cancer"/ (58851)
61 (screen$ or detect$).ti,ab. (1394000)
62 60 or 61 (1407263)
63 59 and 62 (4853)
64 limit 63 to english language (4453)
65 limit 64 to yr="2008 -Current" (2293)
66 remove duplicates from 65 (2289)

KQ3

1 Colonoscopy/ae, mo [Adverse Effects, Mortality] (1200)
2 Sigmoidoscopy/ae, mo (101)
3 Colonography, Computed Tomographic/ae, mo (69)
4 1 or 2 or 3 (1324)
5 Colonoscopy/ (14005)
6 Sigmoidoscopy/ (1906)
7 Colonography, Computed Tomographic/ (1556)
8 Occult Blood/ (2422)
9 DNA/ (110045)
10 DNA Methylation/ (24664)
11 DNA Mutational Analysis/ (38253)
12 DNA, neoplasm/ (19836)
13 9 or 10 or 11 or 12 (183020)
14 Feces/ (32446)
15 13 and 14 (379)
16 "SEPT9 protein, human".nm. (81)
17 Septins/ (405)
18 5 or 6 or 7 or 8 or 15 or 16 or 17 (18074)
19 Colorectal Neoplasms/ (46318)
20 Adenomatous Polyposis Coli/ (3299)
21 Colonic Neoplasms/ (28718)
22 Sigmoid Neoplasms/ (1359)
23 Colorectal Neoplasms, Hereditary Nonpolyposis/ (2917)
24 Rectal Neoplasms/ (13801)
25 Anus Neoplasms/ (2386)
26 Anal Gland Neoplasms/ (58)
27 Colonic Polyps/ (4139)
28 Adenomatous Polyps/ (913)
29 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (94445)
30 Mass screening/ or "Early Detection of Cancer"/ (58851)
31 (screen$ or detect$).ti. (239652)
32 29 and (30 or 31) (8390)
33 Mortality/ (15291)
34 Morbidity/ (12534)
35 Death/ (4271)
36 Hemorrhage/ (21132)

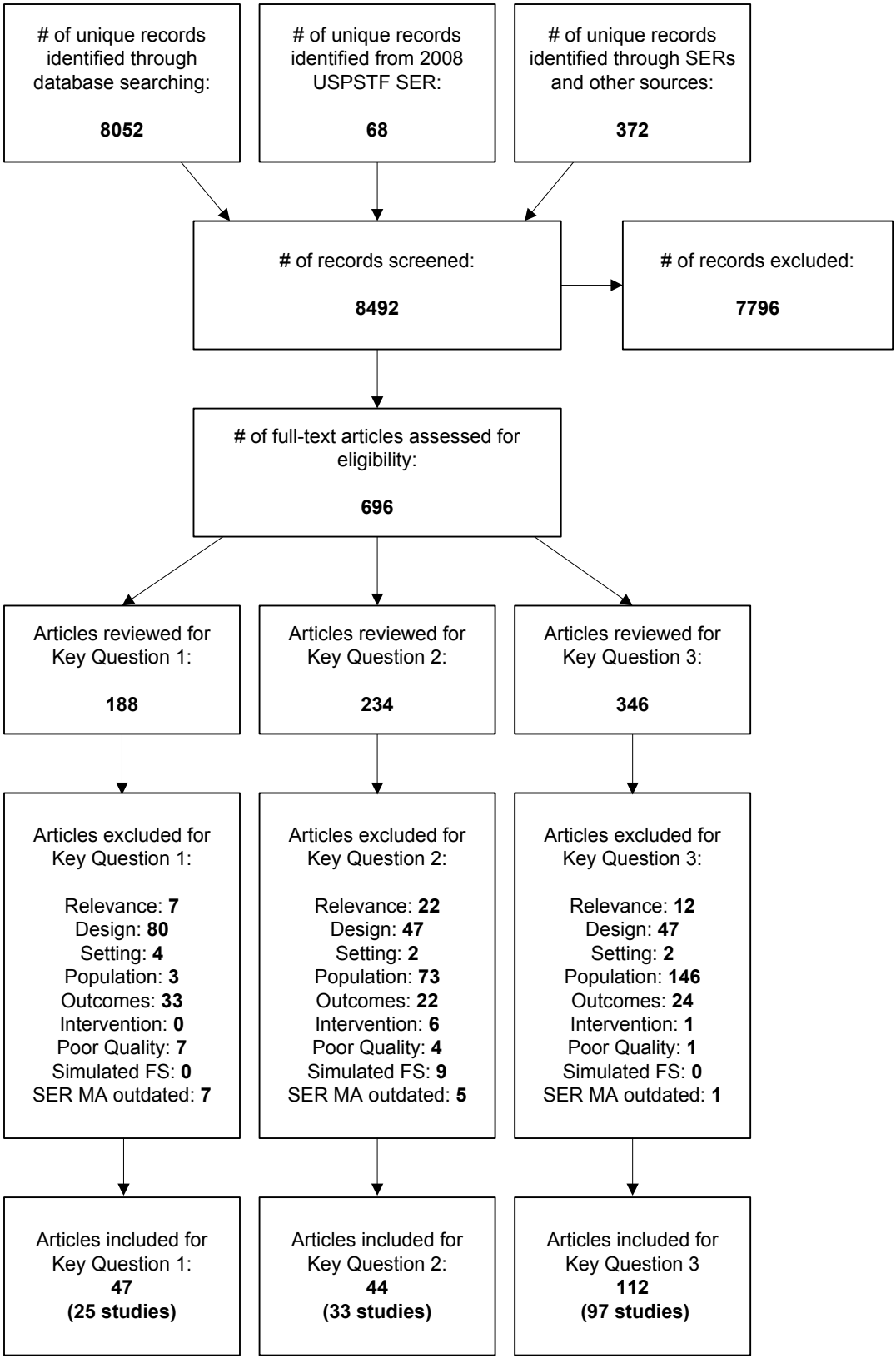
37 Gastrointestinal hemorrhage/ (13674)
38 Postoperative hemorrhage/ (5615)
39 Intraoperative complications/ (17061)
40 Postoperative complications/ (136556)
41 incidental findings/ (5408)
42 (harm or harms or harmful or harmed).ti. (6273)
43 (adverse adj (effect$ or event$ or outcome$)).ti. (9388)
44 safety.ti. (54415)
45 complication$.ti. (48206)
46 (death or deaths).ti. (58420)
47 (hemorrhag$ or haemorrhag$).ti. (33678)
48 bleed$.ti. (16472)
49 (death or deaths).ti. (58420)
50 ((incidental or extracolonic) adj finding$).ti. (925)
51 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (407041)
52 (18 or 32) and 51 (2213)
53 4 or 52 (3159)
54 limit 53 to humans (3122)
55 limit 53 to animals (63)
56 55 not 54 (32)
57 53 not 56 (3127)
58 limit 57 to (english language and yr="2008 -Current") (1353)
59 colonoscop$.ti,ab. (14630)
60 sigmoidoscop$.ti,ab. (2250)
61 colonograph$.ti,ab. (1517)
62 occult blood.ti,ab. (2718)
63 ((fecal or faecal) adj occult).ti,ab. (2256)
64 (fobt or ifobt or gfobt).ti,ab. (934)
65 guaiac.ti,ab. (344)
66 ((fecal or faecal or stool) adj5 test$).ti,ab. (5347)
67 ((fecal or faecal or stool) and (immunochemical or immunoassay)).ti,ab. (1265)
68 ((fecal or faecal or stool) adj5 (DNA or deoxyribonucleic acid)).ti,ab. (984)
69 ((fecal or faecal or stool) adj5 (genetic$ or genomic$)).ti,ab. (185)
70 ((fecal or faecal or stool) adj5 molecular).ti,ab. (186)
71 (f-dna or fdna or s-dna or sdna).ti,ab. (296)
72 (SEPTIN9 or SEPTIN 9 or SEPT9 or mSEPT9).ti,ab. (118)
73 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 (22886)
74 ((colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$)).ti,ab. (106314)
75 (screen$ or detect$).ti. (239652)
76 74 and 75 (7062)
77 73 or 76 (26827)
78 (harm or harms or harmful or harmed).ti,ab. (49263)
79 (adverse adj (effect$ or event$ or outcome$)).ti,ab. (152656)

80 safety.ti,ab. (227560)
81 complication$.ti,ab. (412327)
82 (death or deaths).ti,ab. (390123)
83 (hemorrhag$ or haemorrhag$).ti,ab. (103659)
84 bleed$.ti,ab. (93361)
85 perforat$.ti,ab. (37965)
86 ((incidental or extracolonic) adj finding$).ti,ab. (3929)
87 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 (1230463)
88 77 and 87 (5626)
89 limit 88 to ("in data review" or in process or "pubmed not medline") (624)
90 limit 89 to (english language and yr="2008 -Current") (519)
91 58 or 90 (1872)
92 remove duplicates from 91 (1869)

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, ≥0 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. 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.**
53. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. Ann Intern Med 2013 Mar 5;158(5 Pt 1):312-20. PMID: 23460054. **KQ1E2.**
54. Tan WS, Tang CL, Koo WH. Opportunistic screening for colorectal neoplasia in Singapore using faecal immunochemical occult blood test. Singapore Medical Journal 2013 Apr;54(4):220-3. PMID: 23624450. **KQ1E2.**
55. Ferrante JM, Lee JH, McCarthy EP, et al. Primary care utilization and colorectal cancer incidence and mortality among Medicare beneficiaries: a population-based, case-control study.[Summary for patients in Ann Intern Med. 2013 Oct 1;159(7):I-24; PMID: 24081298]. Ann Intern Med 2013 Oct 1;159(7):437-46. PMID: 24081284. **KQ1E2.**
56. Amri R, Bordeianou LG, Sylla P, et al. Impact of screening colonoscopy on outcomes in colon cancer surgery. JAMA Surgery 2013 Aug;148(8):747-54. PMID: 23784448. **KQ1E2.**
57. Wang YR, Cangemi JR, Loftus EV, Jr., et al. Risk of colorectal cancer after colonoscopy compared with flexible sigmoidoscopy or no lower endoscopy among older patients in the United States, 1998-2005. Mayo Clinic

Proceedings 2013 May;88(5):464-70. PMID: 23522751. **KQ1E2.**
58. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. Med J Aust 2013 Apr 1;198(6):327-30. PMID: 23545032. **KQ1E2.**
59. Riboe DG, Dogan TS, Brodersen J. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. Journal of Evaluation in Clinical Practice 2013 Apr;19(2):311-6. PMID: 22332801. **KQ1E2.**
60. Roxburgh CS, McTaggart F, Balsitis M, et al. Impact of the bowel-screening programme on the diagnosis of colorectal cancer in Ayrshire and Arran. Colorectal Disease 2013 Jan;15(1):34-41. PMID: 22632378. **KQ1E2.**
61. Rees CJ, Bevan R. The National Health Service Bowel Cancer Screening Program: the early years. Expert review of gastroenterology & hepatology 2013 Jul;7(5):421-37. PMID: 23899282. **KQ1E2.**
62. Cha JM, Lee JI, Joo KR, et al. Use of a low cut-off value for the fecal immunochemical test enables better detection of proximal neoplasia. Digestive Diseases & Sciences 2013 Nov;58(11):3256-62. PMID: 23912251. **KQ1E2.**
63. Kershenbaum A, Flugelman A, Lejbkowicz F, et al. Excellent performance of Hemoccult Sensa in organised colorectal cancer screening. European Journal of Cancer 2013 Mar;49(4):923-30. PMID: 23099005. **KQ1E2.**
64. Shin A, Choi KS, Jun JK, et al. Validity of fecal occult blood test in the national cancer screening program, Korea. PLoS ONE [Electronic Resource] 2013;8(11):e79292. PMID: 24260189. **KQ1E2.**
65. Leuraud K, Jezewski-Serra D, Viguier J, et al. Colorectal cancer screening by guaiac faecal occult blood test in France: Evaluation of the programme two years after launching. Cancer Epidemiology 2013 Dec;37(6):959-67. PMID: 24035240. **KQ1E2.**
66. Kelley L, Swan N, Hughes DJ. An analysis of the duplicate testing strategy of an Irish immunochemical faecal occult blood test colorectal cancer screening programme. Colorectal Disease 2013 Sep;15(9):e512-e521. PMID: 23746062. **KQ1E2.**
67. Major D, Bryant H, Delaney M, et al. Colorectal cancer screening in Canada: results from the first round of screening for five provincial programs. Current Oncology 2013 Oct;20(5):252-7. PMID: 24155629. **KQ1E2.**
68. Bretthauer M, Holme O, Garborg K. Computed tomography colonography vs. colonoscopy for colorectal cancer screening: close call, but not closed case. Eur J Radiol 2013;45(3):159-60. PMID: 23446666. **KQ1E2.**
69. Ladabaum U, Allen J, Wandell M, et al. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiology, Biomarkers & Prevention 2013 Sep;22(9):1567-76. PMID: 23796793. **KQ1E2.**
70. Suchanek S, Majek O, Vojtechova G, et al. Colorectal cancer prevention in the Czech Republic: time trends in performance indicators and current situation after 10 years of screening. Eur J Cancer Prev 2014 Jan;23(1):18-26. PMID: 24129196. **KQ1E2.**
71. Rabeneck L, Tinmouth JM, Paszat LF, et al. Ontario's ColonCancerCheck: Results from Canada's first province-wide colorectal cancer screening program. Cancer Epidemiol Biomarkers Prev 2014 Jan 17;23(3):508-15. PMID: 24443406. **KQ1E2.**
72. Brenner H, Chang-Claude J, Jansen L, et al. Reduced Risk of Colorectal Cancer Up to 10 Years After Screening, Surveillance, or Diagnostic Colonoscopy. Gastroenterology 2014 PMID: 24012982. **KQ1E2.**
73. Hermann B, Christian S, Michael H. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014 Apr 9;348 PMID: 24922745. **KQ1E2.**
74. Wu BU, Longstreth GF, Ngor EW. Screening colonoscopy versus sigmoidoscopy: implications of a negative examination for cancer prevention and racial disparities in average-risk patients. Gastrointest Endosc 2014 Nov;80(5):852-61. PMID: 24814774. **KQ1E2.**
75. Wolf HJ, Dwyer A, Ahnen DJ, et al. Colon Cancer Screening for Colorado's Underserved: A Community Clinic/Academic Partnership. Am J Prev Med 2014 Dec 26 PMID: 25547926. **KQ1E2.**
76. Xirasagar S, Li YJ, Hurley TG, et al. Colorectal cancer prevention by an optimized colonoscopy protocol in routine practice. Int J Cancer 2014 Sep 20 PMID: 25242510. **KQ1E2.**
77. Zorzi M, Fedeli U, Schievano E, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2014 Sep 1 PMID: 25179811. **KQ1E2.**
78. Kahi CJ, Rex DK, Imperiale TF. Screening, surveillance, and primary prevention for colorectal cancer: a review of the recent

literature. Gastroenterology 2008 Aug;135(2):380-99. PMID: 18582467. **KQ1E2, KQ2E2.**

79. Faivre J, Dancourt V, Lejeune C. Screening for colorectal cancer with immunochemical faecal occult blood tests. [Review]. Digestive & Liver Disease 2012 Dec;44(12):967-73. PMID: 22898146. **KQ1E2, KQ2E2.**
80. Kim DH, Pooler BD, Weiss JM, et al. Five year colorectal cancer outcomes in a large negative CT colonography screening cohort. European Radiology 2012 Jul;22(7):1488-94. PMID: 22210409. **KQ1E2, KQ2E2.**
81. Crotta S, Segnan N, Paganin S, et al. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin Gastroenterol Hepatol 2012 Jun;10(6):633-8. PMID: 22426085. **KQ1E2, KQ2E2.**
82. Seeff LC, Royalty J, Helsel WE, et al. Clinical outcomes from the CDC's Colorectal Cancer Screening Demonstration Program. Cancer 2013 Aug 1;119:Suppl-33. PMID: 23868476. **KQ1E2, KQ2E2.**
83. McNamara D, Leen R, Seng-Lee C, et al. Sustained participation, colonoscopy uptake and adenoma detection rates over two rounds of the Tallaght-Trinity College colorectal cancer screening programme with the faecal immunological test. European Journal of Gastroenterology & Hepatology 2014 Dec;26(12):1415-21. PMID: 25244415. **KQ1E2, KQ2E2b.**
84. Parente F, Vailati C, Boemo C, et al. Improved 5-year survival of patients with immunochemical faecal blood test-screen-detected colorectal cancer versus non-screening cancers in northern Italy. Digestive & Liver Disease 2015 Jan;47(1):68-72. PMID: 25306524. **KQ1E2, KQ2E5.**
85. Dancourt V, Lejeune C, Lepage C, et al. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. European Journal of Cancer 2008 Oct;44(15):2254-8. PMID: 18760592. **KQ1E2, KQ2E7.**
86. Elwood JM, Ali G, Schlup MM, et al. Flexible sigmoidoscopy or colonoscopy for colorectal screening: a randomized trial of performance and acceptability. Cancer Detect Prev 1995;19(4):337-47. PMID: 7553676. **KQ1E2, KQ3E5.**
87. Jin P, Wu ZT, Li SR, et al. Colorectal cancer screening with fecal occult blood test: A 22-year cohort study. Oncol Lett 2013 Aug;6(2):576-82. PMID: 24137374. **KQ1E3a.**
88. Huang Y, Li Q, Ge W, et al. Predictive power of quantitative and qualitative fecal immunochemical tests for hemoglobin in population screening for colorectal neoplasm. Eur J Cancer Prev 2014 Jan;23(1):27-34. PMID: 23942476. **KQ1E3a.**
89. Alatise OI, Arigbabu AO, Agbakwuru AE, et al. Polyp prevalence at colonoscopy among Nigerians: A prospective observational study. Nigerian Journal of Clinical Practice 2014 Nov;17(6):756-62. PMID: 25385915. **KQ1E3a.**
90. Sudoyo AW, Lesmana CR, Krisnuhoni E, et al. Detection rate of colorectal adenoma or cancer in unselected colonoscopy patients: indonesian experience in a private hospital. Asian Pacific Journal of Cancer Prevention: Apjcp 2014;15(22):9801-4. PMID: 25520108. **KQ1E3a.**
91. Cotterchio M, Manno M, Klar N, et al. Colorectal screening is associated with reduced colorectal cancer risk: a case-control study within the population-based Ontario Familial Colorectal Cancer Registry. Cancer Causes Control 2005 Sep;16(7):865-75. PMID: 16132797. **KQ1E4.**
92. Samadder NJ, Curtin K, Tuohy TM, et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology 2014 Apr;146(4):950-60. PMID: 24417818. **KQ1E4.**
93. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012 Feb 23;366(8):687-96. PMID: 22356322. **KQ1E4a.**
94. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prevention Research 2011 Oct;4(10):1563-71. PMID: 21750209. **KQ1E5.**
95. Multicentre Austrailian Colorectal-neoplasia Screening (MACS) Group. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. Med J Aust 2006 Jun 5;184(11):546-50. PMID: 16768659. **KQ1E5.**
96. Kewenter J, Brevinge H, Engaras B, et al. Follow-up after screening for colorectal neoplasms with fecal occult blood testing in a controlled trial. Dis Colon Rectum 1994 Feb;37(2):115-9. PMID: 8306829. **KQ1E5a.**
97. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal

cancer with faecal-occult-blood test. Lancet 1996 Nov 30;348(9040):1467-71. PMID: 8942774. **KQ1E5a.**

98. Mandel JS, Church TR, Ederer F, et al. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999 Mar 3;91(5):434-7. PMID: 10070942. **KQ1E5a.**
99. Atkin WS, Edwards R, Wardle J, et al. Design of a multicentre randomised trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen 2001;8(3):137-44. PMID: 11678553. **KQ1E5a.**
100. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002 Jan;50(1):29-32. PMID: 11772963. **KQ1E5a.**
101. Scholefield JH, Moss S, Sufi F, et al. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002 Jun;50(6):840-4. PMID: 12010887. **KQ1E5a.**
102. Bonelli L, Sciallero S, Senore C, et al. History of negative colorectal endoscopy and risk of rectosigmoid neoplasms at screening flexible sigmoidoscopy. Int J Colorectal Dis 2006 Mar;21(2):105-13. PMID: 15864604. **KQ1E5a.**
103. Malila N, Oivanen T, Hakama M. Implementation of colorectal cancer screening in Finland: experiences from the first three years of a public health programme. Zeitschrift fur Gastroenterologie 2008 Apr;46:Suppl-8. PMID: 18368636. **KQ1E5a.**
104. Guittet L, Launoy G. Diagnostic accuracy of immunochemical faecal occult blood tests according to number of samples and positivity threshold. Journal of Medical Screening 2008;15(1):48-9. PMID: 18416958. **KQ1E5a.**
105. Hol L, Wilschut JA, van BM, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. British Journal of Cancer 2009 Apr 7;100(7):1103-10. PMID: 19337257. **KQ1E5a.**
106. Paimela H, Malila N, Palva T, et al. Early detection of colorectal cancer with faecal occult blood test screening. British Journal of Surgery 2010 Oct;97(10):1567-71. PMID: 20603855. **KQ1E5a.**
107. Whynes DK, Mangham CM, Balfour TW, et al. Analysis of deaths occurring within the Nottingham trial of faecal occult blood screening for colorectal cancer. Gut 2010 Aug;59(8):1088-93. PMID: 20639252. **KQ1E5a.**
108. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the randomized prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial: added yield from a second screening examination. J Natl Cancer Inst 2012 Feb 22;104(4):280-9. PMID: 22298838. **KQ1E5a.**
109. Castells A, Bessa X, Quintero E, et al. Risk of advanced proximal neoplasms according to distal colorectal findings: comparison of sigmoidoscopy-based strategies. J Natl Cancer Inst 2013 Jun 19;105(12):878-86. PMID: 23708054. **KQ1E5a.**
110. Shaukat A, Mongin S, Geisser M, et al. Long-term mortality following screening for colorectal cancer: Results from the minnesota fecal occult blood trial. Am J Gastroenterol 2013;108:S646-S647. **KQ1E5a.**
111. Salas D, Vanaclocha M, Ibanez J, et al. Participation and detection rates by age and sex for colonoscopy versus fecal immunochemical testing in colorectal cancer screening. Cancer Causes & Control 2014 Aug;25(8):985-97. PMID: 24859111. **KQ1E5a.**
112. Schoen RE, Pinsky PF, Weissfeld JL, et al. Results of repeat sigmoidoscopy 3 years after a negative examination. JAMA 2003 Jul 2;290(1):41-8. PMID: 12837710. **KQ1E5a, KQ2E2.**
113. Kewenter J, Brevinge H. Endoscopic and surgical complications of work-up in screening for colorectal cancer. Dis Colon Rectum 1996 Jun;39(6):676-80. PMID: 8646956. **KQ1E5a, KQ3E4a.**
114. Robinson MH, Hardcastle JD, Moss SM, et al. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. Gut 1999 Oct;45(4):588-92. PMID: 10486370. **KQ1E5a, KQ3E4a.**
115. Lindholm E, Berglund B, Kewenter J, et al. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997 Mar;32(3):238-45. PMID: 9085461. **KQ1E5a, KQ3E5.**
116. Schoen RE, Weissfeld JL, Bowen NJ, et al. Patient satisfaction with screening flexible sigmoidoscopy. Arch Intern Med 2000 Jun 26;160(12):1790-6. PMID: 10871972. **KQ1E5a, KQ3E5.**
117. Parker MA, Robinson MH, Scholefield JH, et al. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9(1):7-10. PMID: 11943790. **KQ1E5a, KQ3E5.**
118. Larsen IK, Grotmol T, Bretthauer M, et al. Continuous evaluation of patient satisfaction in

endoscopy centres. Scand J Gastroenterol 2002 Jul;37(7):850-5. PMID: 12190102. **KQ1E5a, KQ3E5.**

119. Wardle J, Williamson S, Sutton S, et al. Psychological impact of colorectal cancer screening. Health Psychol 2003 Jan;22(1):54-9. PMID: 12558202. **KQ1E5a, KQ3E5.**
120. Larsen IK, Grotmol T, Almendingen K, et al. Impact of colorectal cancer screening on future lifestyle choices: a three-year randomized controlled trial. Clin Gastroenterol Hepatol 2007 Apr;5(4):477-83. PMID: 17363335. **KQ1E5a, KQ3E5.**
121. Hol L, de J, V, van Leerdam ME, et al. Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. European Journal of Cancer 2010 Jul;46(11):2059-66. PMID: 20621736. **KQ1E5a, KQ3E5.**
122. Fracchia M, Senore C, Armaroli P, et al. Assessment of the multiple components of the variability in the adenoma detection rate in sigmoidoscopy screening, and lessons for training. Eur J Radiol 2010 Jun;42(6):448-55. PMID: 20414864. **KQ1E5a, KQ3E5.**
123. Denters MJ, Deutekom M, Essink-Bot ML, et al. FIT false-positives in colorectal cancer screening experience psychological distress up to 6 weeks after colonoscopy. Support Care Cancer 2013 Oct;21(10):2809-15. PMID: 23729229. **KQ1E5a, KQ3E5.**
124. Atkin WS, Hart A, Edwards R, et al. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. Gut 1998 Apr;42(4):560-5. PMID: 9616321. **KQ1E5a, KQ3E5a.**
125. Gondal G, Grotmol T, Hofstad B, et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scandinavian Journal of Gastroenterology 38(6):635-42, 2003 Jun PMID: 12825872. **KQ1E5a.**
126. Hoff G, Grotmol T, Skovlund E, et al. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846. PMID: 19483252. **KQ1E5a.**
127. Thiis-Evensen E, Kalager M, Bretthauer M, et al. Long-term effectiveness of endoscopic screening on incidence and mortality of colorectal cancer: A randomized trial. United European Gastroenterology Journal 2013 Jun;1(3):162-8. PMID: 24917955. **KQ1E7.**
128. Hillyer GC, Schmitt KM, Freedberg DE, et al. Fecal-based colorectal cancer screening among the uninsured in northern Manhattan. American Journal of Preventive Medicine 2014 Aug;47(2):182-7. PMID: 24951037. **KQ1E7.**
129. Shuhaibar M, Walsh C, Lindsay F, et al. A comparative study of faecal occult blood kits in a colorectal cancer screening program in a cohort of healthy construction workers. Irish Journal of Medical Science 2011 Mar;180(1):103-8. PMID: 20953981. **KQ1E7, KQ2E2b.**
130. Thiis-Evensen E, Hoff GS, Sauar J, et al. The effect of attending a flexible sigmoidoscopic screening program on the prevalence of colorectal adenomas at 13-year follow-up. Am J Gastroenterol 2001 Jun;96(6):1901-7. PMID: 11419846. **KQ1E7, KQ3E5a.**
131. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007 Oct 4;357(14):1403-12. PMID: 17914041. **KQ1E7.**
132. Hoff G, Sauar J, Vatn MH, et al. Polypectomy of adenomas in the prevention of colorectal cancer: 10 years' follow-up of the Telemark Polyp Study I. A prospective, controlled population study. Scand J Gastroenterol 1996 Oct;31(10):1006-10. PMID: 8898422. **KQ1E7.**
133. Thiis-Evensen E, Hoff GS, Sauar J, et al. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999 Apr;34(4):414-20. PMID: 10365903. **KQ1E7.**
134. Towler B, Irwig L, Glasziou P, et al. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ 1998;317:559-65. PMID: 9721111. **KQ1E9.**
135. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database of Systematic Reviews 2007(1):CD001216. PMID: 17253456. **KQ1E9.**
136. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol 2008 Jun;103(6):1541-9. PMID: 18479499. **KQ1E9.**
137. Elmunzer BJ, Hayward RA, Schoenfeld PS, et al. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Medicine / Public Library of Science

2012;9(12):e1001352. PMID: 23226108. **KQ1E9.**

138. Littlejohn C, Hilton S, Macfarlane GJ, et al. Systematic review and meta-analysis of the evidence for flexible sigmoidoscopy as a screening method for the prevention of colorectal cancer. British Journal of Surgery 2012 Nov;99(11):1488-500. PMID: 23001715. **KQ1E9.**
139. Holme O, Bretthauer M, Fretheim A, et al. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database of Systematic Reviews 2013;9:CD009259. PMID: 24085634. **KQ1E9.**
140. Whitlock, EP, Lin, J, Liles, E, et al. Screening for Colorectal Cancer: An Updated Systematic Review. 2008. PMID: 20722162. **KQ1E9, KQ2E9, KQ3E9.**
141. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010 May 8;375(9726):1624-33. PMID: 20430429. **KQ3E5.**
142. Ferrandez A, Navarro M, Diez M, et al. Risk factors for advanced lesions undetected at prior colonoscopy: not always poor preparation. Eur J Radiol 2010 Dec;42(12):1071-6. PMID: 20960390. **KQ2E1.**
143. Cash BD, Stamps K, McFarland EG, et al. Clinical use of CT colonography for colorectal cancer screening in military training facilities and potential impact on HEDIS measures. Journal of the American College of Radiology 2013 Jan;10(1):30-6. PMID: 23290671. **KQ2E1.**
144. Brenner H, Altenhofen L, Tao S. Matching of controls may lead to biased estimates of specificity in the evaluation of cancer screening tests. Journal of Clinical Epidemiology 2013 Feb;66(2):202-8. PMID: 23257151. **KQ2E1.**
145. Sikka S, Ringold DA, Jonnalagadda S, et al. Comparison of white light and narrow band high definition images in predicting colon polyp histology, using standard colonoscopes without optical magnification. Eur J Radiol 2008 Oct;40(10):818-22. PMID: 18668472. **KQ2E1a.**
146. Matsuda T, Saito Y, Fu KI, et al. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate?--a pilot study. The American journal of gastroenterology 2008;103:1926-32. PMID: 18647285. **KQ2E1a.**
147. Van den Broek FJ, Reitsma JB, Curvers WL, et al. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon. Gastrointest Endosc 2009;69(1):124-35. PMID: 19111693. **KQ2E1a.**
148. Rastogi A, Keighley J, Singh V, et al. High accuracy of narrow band imaging without magnification for the real-time characterization of polyp histology and its comparison with high-definition white light colonoscopy: a prospective study. Am J Gastroenterol 2009 Oct;104(10):2422-30. PMID: 19584829. **KQ2E1a.**
149. Hewett DG, Rex DK. Cap-fitted colonoscopy: a randomized, tandem colonoscopy study of adenoma miss rates. Gastrointest Endosc 2010 Oct;72(4):775-81. PMID: 20579648. **KQ2E1a.**
150. Chung SJ, Kim D, Song JH, et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. Gastrointest Endosc 2010 Jul;72(1):136-42. PMID: 20493487. **KQ2E1a.**
151. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. Am J Gastroenterol 2010 Jun;105(6):1301-7. PMID: 20179689. **KQ2E1a.**
152. Gross SA, Buchner AM, Crook JE, et al. A comparison of high definition-image enhanced colonoscopy and standard white-light colonoscopy for colorectal polyp detection. Eur J Radiol 2011 Dec;43(12):1045-51. PMID: 21971929. **KQ2E1a.**
153. Lee CK, Lee SH, Hwangbo Y. Narrow-band imaging versus I-Scan for the real-time histological prediction of diminutive colonic polyps: a prospective comparative study by using the simple unified endoscopic classification. Gastrointest Endosc 2011 Sep;74(3):603-9. PMID: 21762907. **KQ2E1a.**
154. Leufkens AM, DeMarco DC, Rastogi A, et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. Gastrointest Endosc 2011 Mar;73(3):480-9. PMID: 21067735. **KQ2E1a.**
155. Ikematsu H, Saito Y, Tanaka S, et al. The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy. Journal of Gastroenterology 2012 Oct;47(10):1099-107. PMID: 22441532. **KQ2E1a.**
156. Siersema PD, Rastogi A, Leufkens AM, et al. Retrograde-viewing device improves adenoma detection rate in colonoscopies for surveillance

and diagnostic workup. World Journal of Gastroenterology 2012 Jul 14;18(26):3400-8. PMID: 22807609. **KQ2E1a.**

157. Leufkens AM, van Oijen MG, Vleggaar FP, et al. Factors influencing the miss rate of polyps in a back-to-back colonoscopy study. Eur J Radiol 2012 May;44(5):470-5. PMID: 22441756. **KQ2E1a.**
158. Hong SN, Choe WH, Lee JH, et al. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. Gastrointest Endosc 2012 May;75(5):1011-21. PMID: 22381530. **KQ2E1a.**
159. Chan JL, Lin L, Feiler M, et al. Comparative effectiveness of i-SCAN and high-definition white light characterizing small colonic polyps. World Journal of Gastroenterology 2012 Nov 7;18(41):5905-11. PMID: 23139606. **KQ2E1a.**
160. Kakol D, Fraczek M, Banaszkiewicz A, et al. Narrow-band imaging and white-light endoscopy for detection of colorectal polyps: a randomized study. Polskie Archiwum Medycyny Wewnetrznej 2013;123(10):519-25. PMID: 23928892. **KQ2E1a.**
161. Chung SJ, Kim D, Song JH, et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. Gut 2013 Jul 12 PMID: 23853211. **KQ2E1a.**
162. Foutch PG, Mai H, Pardy K, et al. Flexible sigmoidoscopy may be ineffective for secondary prevention of colorectal cancer in asymptomatic, average-risk men. Dig Dis Sci 1991 Jul;36(7):924-8. PMID: 2070706. **KQ2E2.**
163. Schoenfeld P, Lipscomb S, Crook J, et al. Accuracy of polyp detection by gastroenterologists and nurse endoscopists during flexible sigmoidoscopy: a randomized trial. Gastroenterology 1999 Aug;117(2):312-8. PMID: 10419911. **KQ2E2.**
164. Burke CA, Elder K, Lopez R. Screening for colorectal cancer with flexible sigmoidoscopy: is a 5-yr interval appropriate? A comparison of the detection of neoplasia 3 yr versus 5 yr after a normal examination. Am J Gastroenterol 2006 Jun;101(6):1329-32. PMID: 16771957. **KQ2E2.**
165. Yang KC, Liao CS, Chiu YH, et al. Colorectal cancer screening with faecal occult blood test within a multiple disease screening programme: an experience from Keelung, Taiwan. J Med Screen 2006;13 Suppl 1:S8-13. PMID: 17227635. **KQ2E2.**
166. Summers RM, Handwerker LR, Pickhardt PJ, et al. Performance of a previously validated CT colonography computer-aided detection system in a new patient population. AJR 2008 Jul;American(1):168-74. PMID: 18562741. **KQ2E2.**
167. Taylor SA, Charman SC, Lefere P, et al. CT colonography: investigation of the optimum reader paradigm by using computer-aided detection software. Radiology 2008 Feb;246(2):463-71. PMID: 18094263. **KQ2E2.**
168. Taylor SA, Greenhalgh R, Ilangovan R, et al. CT colonography and computer-aided detection: effect of false-positive results on reader specificity and reading efficiency in a low-prevalence screening population. Radiology 2008 Apr;247(1):133-40. PMID: 18292478. **KQ2E2.**
169. Taylor SA, Burling D, Roddie M, et al. Computer-aided detection for CT colonography: incremental benefit of observer training. British Journal of Radiology 2008 Mar;81(963):180-6. PMID: 18180260. **KQ2E2.**
170. Pohl J, Lotterer E, Balzer C, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. Gut 2009 Jan;58(1):73-8. PMID: 18838485. **KQ2E2.**
171. ECRI Institute. Computed tomographic (CT) colonography for colorectal cancer screening and diagnosis. Or Manager 2009 Jun;25(6):15-8. PMID: 19558018. **KQ2E2.**
172. Park SH, Kim SY, Lee SS, et al. Sensitivity of CT colonography for nonpolypoid colorectal lesions interpreted by human readers and with computer-aided detection. AJR 2009 Jul;American(1):70-8. PMID: 19542397. **KQ2E2.**
173. Pickhardt PJ, Kim DH, Hassan C. Advanced neoplasia detection rates at colonoscopy screening: implications for CT colonography. Gastroenterology 2009;136(3):1121-2. PMID: 19167389. **KQ2E2.**
174. Rosenberg JA, Rubin DT. Performance of CT colonography in clinical trials. Gastrointestinal Endoscopy Clinics of North America 2010 Apr;20(2):193-207. PMID: 20451810. **KQ2E2.**
175. Suzuki K, Rockey DC, Dachman AH. CT colonography: advanced computer-aided detection scheme utilizing MTANNs for detection of "missed" polyps in a multicenter clinical trial. Medical Physics 2010 Jan;37(1):12-21. PMID: 20175461. **KQ2E2.**
176. Leung K, Pinsky P, Laiyemo AO, et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc

2010 Jan;71(1):111-7. PMID: 19647250. **KQ2E2.**

177. Hewett DG, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: an observational study. Gastrointest Endosc 2011 Aug;74(2):246-52. PMID: 21679946. **KQ2E2.**
178. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clinical Gastroenterology & Hepatology 2011 Jan;9(1):42-6. PMID: 20888435. **KQ2E2.**
179. Lathroum L, Ramos-Mercado F, Hernandez-Marrero J, et al. Ethnic and sex disparities in colorectal neoplasia among Hispanic patients undergoing screening colonoscopy. Clinical Gastroenterology & Hepatology 2012 Sep;10(9):997-1001. PMID: 22542749. **KQ2E2.**
180. Westwood DA, Alexakis N, Connor SJ. Transparent cap-assisted colonoscopy versus standard adult colonoscopy: a systematic review and meta-analysis. Diseases of the Colon & Rectum 2012 Feb;55(2):218-25. PMID: 22228167. **KQ2E2.**
181. Fraser CG, Allison JE, Young GP, et al. Quantitation of hemoglobin improves fecal immunochemical tests for noninvasive screening. Clinical Gastroenterology & Hepatology 2013 Jul;11(7):839-40. PMID: 23591278. **KQ2E2.**
182. Kearns B, Whyte S, Chilcott J, et al. Guaiac faecal occult blood test performance at initial and repeat screens in the English Bowel Cancer Screening Programme. British Journal of Cancer 2014 Oct 28;111(9):1734-41. PMID: 25180767. **KQ2E2.**
183. Zhang H, Qi J, Wu YQ, et al. Accuracy of early detection of colorectal tumours by stool methylation markers: a meta-analysis. World Journal of Gastroenterology 2014 Oct 14;20(38):14040-50. PMID: 25320544. **KQ2E2.**
184. Raginel T, Puvinel J, Ferrand O, et al. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. Gastroenterology 2013 May;144(5):918-25. PMID: 23376426. **KQ2E2, KQ1E2.**
185. Pox CP, Schmiegel W. Role of CT colonography in colorectal cancer screening: risks and benefits. Gut 2010 May;59(5):692-700. PMID: 20427403. **KQ2E2, KQ3E2.**
186. Tao S, Hundt S, Haug U, et al. Sensitivity estimates of blood-based tests for colorectal cancer detection: impact of overrepresentation of advanced stage disease. [Review]. Am J Gastroenterol 2011 Feb;106(2):242-53. PMID: 20959816. **KQ2E2a.**
187. Warren JD, Xiong W, Bunker AM, et al. Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. BMC Medicine 2011;9:133. PMID: 22168215. **KQ2E2a.**
188. Septin 9 (SEPT9) methylation analysis for colorectal cancer. 2012. **KQ2E2a.**
189. Ahlquist DA, Zou H, Domanico M, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012;142(2):248-56. PMID: 22062357. **KQ2E2a.**
190. Toth K, Sipos F, Kalmar A, et al. Detection of methylated SEPT9 in plasma is a reliable screening method for both left- and right-sided colon cancers. PLoS ONE [Electronic Resource] 2012;7(9):e46000. PMID: 23049919. **KQ2E2a.**
191. Ahlquist DA, Taylor WR, Mahoney DW, et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clinical Gastroenterology & Hepatology 2012 Mar;10(3):272-7. PMID: 22019796. **KQ2E2a.**
192. Heigh RI, Yab TC, Taylor WR, et al. Detection of Colorectal Serrated Polyps by Stool DNA Testing: Comparison with Fecal Immunochemical Testing for Occult Blood (FIT). PLoS ONE [Electronic Resource] 2014 Jan 20;9(1):e85659. PMID: 24465639. **KQ2E2a.**
193. Teoh ML, Puvan R, Cheah PY, et al. Colorectal cancer screening: yield of faecal occult blood testing. Asian Pacific Journal of Cancer Prevention: Apjcp 2010;11(1):153-6. PMID: 20593948. **KQ2E2b.**
194. Pickhardt PJ, Wise SM, Kim DH. Positive predictive value for polyps detected at screening CT colonography. European Radiology 2010 Jul;20(7):1651-6. PMID: 20069423. **KQ2E2b.**
195. Pickhardt PJ, Durick NA, Pooler BD, et al. Left-sided polyps detected at screening CT colonography: do we need complete optical colonoscopy for further evaluation?.[Erratum appears in Radiology. 2011 Jul;260(1):308]. Radiology 2011 May;259(2):429-34. PMID: 21357518. **KQ2E2b.**
196. Van Turenhout ST, van Rossum LG, Oort FA, et al. Similar fecal immunochemical test results in screening and referral colorectal cancer. World Journal of Gastroenterology 2012 Oct 14;18(38):5397-403. PMID: 23082056. **KQ2E2b.**
197. Pooler BD, Kim DH, Hassan C, et al. Variation in diagnostic performance among radiologists at screening CT colonography. Radiology 2013 Jul;268(1):127-34. PMID: 23449954. **KQ2E2b.**

198. Liao CS, Lin YM, Chang HC, et al. Application of quantitative estimates of fecal hemoglobin concentration for risk prediction of colorectal neoplasia. World Journal of Gastroenterology 2013 Dec 7;19(45):8366-72. PMID: 24363529. **KQ2E2b.**
199. Senore C, Armaroli P, Arrigoni A, et al. Neoplasia yield of repeated immunochemical fobt following a negative screening sigmoidoscopy. Gastroenterology 2013;144:S96-S97. **KQ2E2b.**
200. Poskus T, Strupas K, Mikalauskas S, et al. Initial results of the National Colorectal Cancer Screening Program in Lithuania. Eur J Cancer Prev 2014 Nov 3 PMID: 25370682. **KQ2E2b.**
201. Li S, Wang H, Hu J, et al. New immunochemical fecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: results of a prospective multicenter study in Chinese patients. Int J Cancer 2006 Jun 15;118(12):3078-83. PMID: 16425283. **KQ2E3a.**
202. Miutescu B, Sporea I, Popescu A, et al. Effectiveness of the immunochemical fecal test (FIT) for detection of advanced adenomas in colorectal carcinoma screening in an asymptomatic population. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi 2013 Apr;117(2):302-7. PMID: 24340508. **KQ2E3a.**
203. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. Dig Dis Sci 1997 Oct;42(10):2064-71. PMID: 9365136. **KQ2E4.**
204. Wessling J, Fischbach R, Domagk D, et al. Colorectal polyps: Detection with multi-slice CT colonography. Rofo 2001 Dec;173(12):1069-71. PMID: 11740665. **KQ2E4.**
205. Yoshida H, Nappi J, MacEneaney P, et al. Computer-aided diagnosis scheme for detection of polyps at CT colonography. Radiographics 2002 Jul;22(4):963-79. PMID: 12110726. **KQ2E4.**
206. Yoshida H, Masutani Y, MacEneaney P, et al. Computerized detection of colonic polyps at CT colonography on the basis of volumetric features: pilot study. Radiology 2002 Feb;222(2):327-36. PMID: 11818596. **KQ2E4.**
207. Lefere PA, Gryspeerdt SS, Dewyspelaere J, et al. Dietary fecal tagging as a cleansing method before CT colonography: initial results polyp detection and patient acceptance. Radiology 2002 Aug;224(2):393-403. PMID: 12147834. **KQ2E4.**
208. George ML, Tutton MG, Jadhav VV, et al. Colonoscopy in older patients: a safe and sound practice. Age Ageing 2002 Jan;31(1):80-1. PMID: 11850317. **KQ2E4.**
209. Wong BC, Wong WM, Cheung KL, et al. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. Aliment Pharmacol Ther 2003 Nov 1;18(9):941-6. PMID: 14616158. **KQ2E4.**
210. Vvan Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. [Review] [26 refs]. Am J Gastroenterol 2006 Feb;101(2):343-50. PMID: 16454841. **KQ2E4.**
211. Kaltenbach T, Friedland S, Soetikno R. A randomised tandem colonoscopy trial of narrow band imaging versus white light examination to compare neoplasia miss rates. Gut 2008 Oct;57(10):1406-12. PMID: 18523025. **KQ2E4.**
212. Heresbach D, Barrioz T, Lapalus MG, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Eur J Radiol 2008 Apr;40(4):284-90. PMID: 18389446. **KQ2E4.**
213. Hock D, Ouhadi R, Materne R, et al. Virtual dissection CT colonography: evaluation of learning curves and reading times with and without computer-aided detection. Radiology 2008 Sep;248(3):860-8. PMID: 18710980. **KQ2E4.**
214. Chaparro M, Gisbert JP, Del CL, et al. Accuracy of computed tomographic colonography for the detection of polyps and colorectal tumors: a systematic review and meta-analysis. [Review] [80 refs]. Digestion 2009;80(1):1-17. PMID: 19407448. **KQ2E4.**
215. Young PE, Ray QP, Hwang I, et al. Gastroenterologists' interpretation of CTC: a pilot study demonstrating feasibility and similar accuracy compared with radiologists' interpretation. Am J Gastroenterol 2009 Dec;104(12):2926-31. PMID: 19672252. **KQ2E4.**
216. Taylor SA, Brittenden J, Lenton J, et al. Influence of computer-aided detection false-positives on reader performance and diagnostic confidence for CT colonography. AJR 2009 Jun;American(6):1682-9. PMID: 19457835. **KQ2E4.**
217. Zhu H, Liang Z, Pickhardt PJ, et al. Increasing computer-aided detection specificity by projection features for CT colonography. Medical Physics 2010 Apr;37(4):1468-81. PMID: 20443468. **KQ2E4.**

218. Oort FA, Terhaar sive Droste JS, van der Hulst RW, et al. Colonoscopy-controlled intra-individual comparisons to screen relevant neoplasia: faecal immunochemical test vs. guaiac-based faecal occult blood test. Alimentary Pharmacology & Therapeutics 2010 Feb 1;31(3):432-9. PMID: 19878150. **KQ2E4.**
219. Pickhardt PJ, Hassan C, Halligan S, et al. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology 2011 May;259(2):393-405. PMID: 21415247. **KQ2E4.**
220. Oort FA, van Turenhout ST, Coupe VM, et al. Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study. BMC Cancer 2011;11:434. PMID: 21985604. **KQ2E4.**
221. Omata F, Shintani A, Isozaki M, et al. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. European Journal of Gastroenterology & Hepatology 2011 Nov;23(11):1036-41. PMID: 21897207. **KQ2E4.**
222. Chiang TH, Lee YC, Tu CH, et al. Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract. CMAJ Canadian Medical Association Journal 2011 Sep 20;183(13):1474-81. PMID: 21810951. **KQ2E4.**
223. Kalimutho M, Del Vecchio BG, Cretella M, et al. A simplified, non-invasive fecal-based DNA integrity assay and iFOBT for colorectal cancer detection. International Journal of Colorectal Disease 2011 May;26(5):583-92. PMID: 21225430. **KQ2E4.**
224. Chen JG, Cai J, Wu HL, et al. Colorectal cancer screening: comparison of transferrin and immuno fecal occult blood test. World Journal of Gastroenterology 2012 Jun 7;18(21):2682-8. PMID: 22690078. **KQ2E4.**
225. Hong SN, Sung IK, Kim JH, et al. The Effect of the Bowel Preparation Status on the Risk of Missing Polyp and Adenoma during Screening Colonoscopy: A Tandem Colonoscopic Study. Clinical Endoscopy 2012 Nov;45(4):404-11. PMID: 23251889. **KQ2E4.**
226. Martin Lopez JE, Calvo CB, Lopez RR, et al. Comparison of the accuracy of CT Colonography and colonoscopy in the diagnosis of colorectal cancer. Colorectal Dis 2013 Dec 3 PMID: 24299052. **KQ2E4.**
227. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. Int J Cancer 2013 Jul 1 PMID: 23818169. **KQ2E4.**
228. Johnson DA, Barclay RL, Mergener K, et al. Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. PLoS ONE [Electronic Resource] 2014;9(6):e98238. PMID: 24901436. **KQ2E4.**
229. Taylor SA, Halligan S, Saunders BP, et al. Use of multidetector-row CT colonography for detection of colorectal neoplasia in patients referred via the Department of Health "2-Week-wait" initiative. Clin Radiol 2003 Nov;58(11):855-61. PMID: 14581009. **KQ2E4a.**
230. Cotton PB, Durkalski VL, Pineau BC, et al. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. JAMA 2004 Apr 14;291(14):1713-9. PMID: 15082698. **KQ2E4a.**
231. Vogt C, Cohnen M, Beck A, et al. Detection of colorectal polyps by multislice CT colonography with ultra-low-dose technique: comparison with high-resolution videocolonoscopy. Gastrointest Endosc 2004 Aug;60(2):201-9. PMID: 15278045. **KQ2E4a.**
232. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007 Feb 20;146(4):244-55. PMID: 17310056. **KQ2E4a.**
233. Bose M, Bell J, Jackson L, et al. Virtual vs. optical colonoscopy in symptomatic gastroenterology out-patients: the case for virtual imaging followed by targeted diagnostic or therapeutic colonoscopy. Aliment Pharmacol Ther 2007 Sep 1;26(5):727-36. PMID: 17697206. **KQ2E4a.**
234. Chaparro SM, del C, V, Mate JJ, et al. Computed tomography colonography compared with conventional colonoscopy for the detection of colorectal polyps. Gastroenterol Hepatol 2007 Aug;30(7):375-80. PMID: 17692193. **KQ2E4a.**
235. Florie J, van Gelder RE, Schutter MP, et al. Feasibility study of computed tomography colonography using limited bowel preparation at normal and low-dose levels study. Eur Radiol 2007 Dec;17(12):3112-22. PMID: 17549490. **KQ2E4a.**
236. Taylor SA, Slater A, Burling DN, et al. CT colonography: optimisation, diagnostic performance and patient acceptability of reduced-laxative regimens using barium-based faecal tagging. European Radiology 2008 Jan;18(1):32-42. PMID: 17404739. **KQ2E4a.**
237. Roberts-Thomson IC, Tucker GR, Hewett PJ, et al. Single-center study comparing computed

tomography colonography with conventional colonoscopy. World Journal of Gastroenterology 2008 Jan 21;14(3):469-73. PMID: 18200672. **KQ2E4a.**

238. Jensch S, de Vries AH, Peringa J, et al. CT colonography with limited bowel preparation: performance characteristics in an increased-risk population. Radiology 2008 Apr;247(1):122-32. PMID: 18292475. **KQ2E4a.**
239. Nagata K, Okawa T, Honma A, et al. Full-laxative versus minimum-laxative fecal-tagging CT colonography using 64-detector row CT: prospective blinded comparison of diagnostic performance, tagging quality, and patient acceptance. Academic Radiology 2009 Jul;16(7):780-9. PMID: 19375954. **KQ2E4a.**
240. van den Broek FJ, Fockens P, van ES, et al. Clinical evaluation of endoscopic trimodal imaging for the detection and differentiation of colonic polyps. Clinical Gastroenterology & Hepatology 2009 Mar;7(3):288-95. PMID: 19168154. **KQ2E4a.**
241. White TJ, Avery GR, Kennan N, et al. Virtual colonoscopy vs conventional colonoscopy in patients at high risk of colorectal cancer--a prospective trial of 150 patients. Colorectal Disease 2009 Feb;11(2):138-45. PMID: 18462241. **KQ2E4a.**
242. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, et al. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. European Journal of Gastroenterology & Hepatology 2009 Sep;21(9):1062-7. PMID: 19307978. **KQ2E4a.**
243. Regge D, Laudi C, Galatola G, et al. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA 2009 Jun 17;301(23):2453-61. PMID: 19531785. **KQ2E4a.**
244. Rozen P, Levi Z, Hazazi R, et al. Identification of colorectal adenomas by a quantitative immunochemical faecal occult blood screening test depends on adenoma characteristics, development threshold used and number of tests performed. Alimentary Pharmacology & Therapeutics 2009 Apr 15;29(8):906-17. PMID: 19183147. **KQ2E4a.**
245. de Vries AH, Jensch S, Liedenbaum MH, et al. Does a computer-aided detection algorithm in a second read paradigm enhance the performance of experienced computed tomography colonography readers in a population of increased risk? European Radiology 2009 Apr;19(4):941-50. PMID: 18982331. **KQ2E4a.**
246. Rozen P, Levi Z, Hazazi R, et al. Quantitative colonoscopic evaluation of relative efficiencies of an immunochemical faecal occult blood test and a sensitive guaiac test for detecting significant colorectal neoplasms. Alimentary Pharmacology & Therapeutics 2009 Feb 15;29(4):450-7. PMID: 19035980. **KQ2E4a.**
247. Schonfeld V, Hinzmann S. Missed colonic adenomas in routine primary care endoscopy: a prospective tandem colonoscopy study. Zeitschrift fur Gastroenterologie 2010 Oct;48(10):1207-10. PMID: 20886425. **KQ2E4a.**
248. Horiuchi A, Nakayama Y, Kato N, et al. Hood-assisted colonoscopy is more effective in detection of colorectal adenomas than narrow-band imaging. Clinical Gastroenterology & Hepatology 2010 Apr;8(4):379-83. PMID: 19716434. **KQ2E4a.**
249. Wi JY, Kim SH, Lee JY, et al. Electronic cleansing for CT colonography: does it help CAD software performance in a high-risk population for colorectal cancer? European Radiology 2010 Aug;20(8):1905-16. PMID: 20309555. **KQ2E4a.**
250. Rozen P, Comaneshter D, Levi Z, et al. Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. Cancer 2010 May 1;116(9):2115-25. PMID: 20186820. **KQ2E4a.**
251. Liedenbaum MH, de Vries AH, Gouw CI, et al. CT colonography with minimal bowel preparation: evaluation of tagging quality, patient acceptance and diagnostic accuracy in two iodine-based preparation schemes. European Radiology 2010 Feb;20(2):367-76. PMID: 19707769. **KQ2E4a.**
252. Sofic A, Beslic S, Kocijancic I, et al. CT colonography in detection of colorectal carcinoma. Radiology & Oncology 2010 Mar;44(1):19-23. PMID: 22933886. **KQ2E4a.**
253. Keedy AW, Yee J, Aslam R, et al. Reduced cathartic bowel preparation for CT colonography: prospective comparison of 2-L polyethylene glycol and magnesium citrate. Radiology 2011 Oct;261(1):156-64. PMID: 21873253. **KQ2E4a.**
254. Rozen P, Shabtai EI, Liphshitz I, et al. Risk for colorectal cancer in elderly persons and possible methodologies for their screening. European Journal of Gastroenterology & Hepatology 2011 May;23(5):431-7. PMID: 21448071. **KQ2E4a.**
255. Heresbach D, Djabbari M, Riou F, et al. Accuracy of computed tomographic colonography in a nationwide multicentre trial,

and its relation to radiologist expertise. Gut 2011 May;60(5):658-65. PMID: 21266723. **KQ2E4a.**

256. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiology, Biomarkers & Prevention 2011 Feb;20(2):272-80. PMID: 21135261. **KQ2E4a.**
257. Kim JH, Kim YS, Cheon JH, et al. Influence of the insertion time and number of polyps on miss rate in colonoscopy. Scand J Gastroenterol 2011 May;46(5):634-9. PMID: 21370993. **KQ2E4a.**
258. Zhang HM, Guo W, Liu GF, et al. Colonic polyps: application value of computer-aided detection in computed tomographic colonography. Chinese Medical Journal 2011 Feb;124(3):380-4. PMID: 21362337. **KQ2E4a.**
259. Rozen P, Liphshitz I, Barchana M. Follow-up of patients undergoing both semiquantitated immunochemical fecal occult blood and colonoscopy examinations. Eur J Cancer Prev 2012 May;21(3):247-53. PMID: 21955798. **KQ2E4a.**
260. Wong CK, Fedorak RN, Prosser CI, et al. The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer. International Journal of Colorectal Disease 2012 Dec;27(12):1657-64. PMID: 22696204. **KQ2E4a.**
261. Parente F, Marino B, Ilardo A, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. European Journal of Gastroenterology & Hepatology 2012 Oct;24(10):1145-52. PMID: 22735608. **KQ2E4a.**
262. Horiuchi A, Nakayama Y, Kajiyama M, et al. Invasive colorectal cancer within 5 years of negative colonoscopy in a Japanese population. Colorectal Disease 2012 Sep;14(9):1090-4. PMID: 22107065. **KQ2E4a.**
263. Kovarova JT, Zavoral M, Zima T, et al. Improvements in colorectal cancer screening programmes - quantitative immunochemical faecal occult blood testing - how to set the cut-off for a particular population. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic 2012 Jun;156(2):143-50. PMID: 22837135. **KQ2E4a.**
264. Munroe CA, Lee P, Copland A, et al. A tandem colonoscopy study of adenoma miss rates during endoscopic training: a venture into uncharted territory. Gastrointest Endosc 2012 Mar;75(3):561-7. PMID: 22341103. **KQ2E4a.**
265. Mang T, Bogoni L, Salganicoff M, et al. Computer-aided detection of colorectal polyps in CT colonography with and without fecal tagging: a stand-alone evaluation. Investigative Radiology 2012 Feb;47(2):99-108. PMID: 21934519. **KQ2E4a.**
266. Moore H, Dodd N. Computed tomographic colonography (CTC); colorectal cancer diagnosis with CTC in an Auckland population. Journal of Medical Imaging & Radiation Oncology 2013 Oct;57(5):572-5. PMID: 24119271. **KQ2E4a.**
267. Colvin H, Lukram A, Sohail I, et al. The performance of routine computed tomography for the detection of colorectal cancer. Annals of the Royal College of Surgeons of England 2013 Oct;95(7):473-6. PMID: 24112491. **KQ2E4a.**
268. Randell E, Kennell M, Taher A, et al. Evaluation of Hemo Techt NS-Plus system for use in a province-wide colorectal cancer screening program. Clinical Biochemistry 2013 Mar;46(4-5):365-8. PMID: 23262404. **KQ2E4a.**
269. Ou CH, Kuo FC, Hsu WH, et al. Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. Journal of Digestive Diseases 2013 Sep;14(9):474-83. PMID: 23701988. **KQ2E4a.**
270. Fini L, Laghi L, Hassan C, et al. Noncathartic CT Colonography to Screen for Colorectal Neoplasia in Subjects with a Family History of Colorectal Cancer. Radiology 2013 Nov 22:130373. PMID: 24475809. **KQ2E4a.**
271. Plumb AA, Halligan S, Nickerson C, et al. Use of CT colonography in the English Bowel Cancer Screening Programme. Gut 2013 Aug 27 PMID: 23955527. **KQ2E4a.**
272. Regge D, Della MP, Galatola G, et al. Efficacy of computer-aided detection as a second reader for 6-9-mm lesions at CT colonography: Multicenter prospective trial. Radiology 2013;266:168-76. PMID: 23151831. **KQ2E4a.**
273. Cubiella J, Castro I, Hernandez V, et al. Characteristics of adenomas detected by fecal immunochemical test in colorectal cancer screening. Cancer Epidemiology, Biomarkers & Prevention 2014 Sep;23(9):1884-92. PMID: 24962836. **KQ2E4a.**
274. Rosenfeld G, Fu YT, Quiney B, et al. Does training and experience influence the accuracy of computed tomography colonography interpretation? World Journal of Gastroenterology 2014 Feb 14;20(6):1574-81. PMID: 24587633. **KQ2E4a.**

275. Castro I, Estevez P, Cubiella J, et al. Diagnostic Performance of Fecal Immunochemical Test and Sigmoidoscopy for Advanced Right-Sided Colorectal Neoplasms. Dig Dis Sci 2014 Nov 19 PMID: 25407805. **KQ2E4a.**
276. Zappa M, Castiglione G, Paci E, et al. Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. Int J Cancer 2001 Apr 1;92(1):151-4. PMID: 11279619. **KQ2E5.**
277. Grazzini G, Visioli CB, Zorzi M, et al. Immunochemical faecal occult blood test: number of samples and positivity cutoff. What is the best strategy for colorectal cancer screening? British Journal of Cancer 2009 Jan 27;100(2):259-65. PMID: 19142185. **KQ2E5.**
278. Zorzi M, Fedato C, Grazzini G, et al. High sensitivity of five colorectal screening programmes with faecal immunochemical test in the Veneto Region, Italy. Gut 2011 Jul;60(7):944-9. PMID: 21193461. **KQ2E5.**
279. Parente F, Marino B, DeVecchi N, et al. Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. British Journal of Surgery 2009 May;96(5):533-40. PMID: 19358181. **KQ2E5, KQ3E5a.**
280. Parente F, Boemo C, Ardizzoia A, et al. Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. Eur J Radiol 2013;45(1):27-34. PMID: 23254404. **KQ2E5.**
281. Pickhardt PJ, Nugent PA, Choi JR, et al. Flat colorectal lesions in asymptomatic adults: implications for screening with CT virtual colonoscopy. AJR American journal of roentgenology 2004 Nov;183(5):1343-7. PMID: 15505301. **KQ2E5a.**
282. Pickhardt PJ, Choi JR, Hwang I, et al. Nonadenomatous polyps at CT colonography: prevalence, size distribution, and detection rates. Radiology 2004 Sep;232(3):784-90. PMID: 15247435. **KQ2E5a.**
283. Pickhardt PJ, Choi JR, Nugent PA, et al. The effect of diagnostic confidence on the probability of optical colonoscopic confirmation of potential polyps detected on CT colonography: prospective assessment in 1,339 asymptomatic adults. AJR Am J Roentgenol 2004 Dec;183(6):1661-5. PMID: 15547207. **KQ2E5a.**
284. Kim SH, Lee JM, Eun HW, et al. Two- versus Three-dimensional Colon Evaluation with Recently Developed Virtual Dissection Software for CT Colonography. Radiology 2007 Sep;244(3):852-64. PMID: 17709833. **KQ2E5a.**
285. Pickhardt P, Lee A, Taylor A, et al. Primary 2D versus Primary 3D Polyp Detection at Screening CT Colonography. Am J Roentgenol 2007 Dec;189(6):1451-6. PMID: 18029884. **KQ2E5a.**
286. Sutradhar R, Paszat L, Rabeneck L. Accuracy of CT colonography for colorectal cancer screening. N Engl J Med 2008 Dec 25;359(26):2843-4. PMID: 19115493. **KQ2E5a.**
287. Juchems MS, Ernst A, Johnson P, et al. Electronic colon-cleansing for CT colonography: diagnostic performance. Abdominal Imaging 2009 May;34(3):359-64. PMID: 18343970. **KQ2E5a.**
288. Van Rossum LG, van Rijn AF, Laheij RJ, et al. Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme. British Journal of Cancer 2009 Oct 20;101(8):1274-81. PMID: 19755997. **KQ2E5a.**
289. Fletcher JG, Chen MH, Herman BA, et al. Can radiologist training and testing ensure high performance in CT colonography? Lessons From the National CT Colonography Trial. AJR Am J Roentgenol 2010 Jul;195(1):117-25. PMID: 20566804. **KQ2E5a.**
290. Haug U, Hundt S, Brenner H. Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests. Am J Gastroenterol 2010 Mar;105(3):682-90. PMID: 19953091. **KQ2E5a.**
291. Hara AK, Kuo MD, Blevins M, et al. National CT colonography trial (ACRIN 6664): comparison of three full-laxative bowel preparations in more than 2500 average-risk patients. AJR Am J Roentgenol 2011 May;196(5):1076-82. PMID: 21512073. **KQ2E5a.**
292. Hara AK, Blevins M, Chen MH, et al. ACRIN CT colonography trial: does reader's preference for primary two-dimensional versus primary three-dimensional interpretation affect performance? Radiology 2011 May;259(2):435-41. PMID: 21364081. **KQ2E5a.**
293. Mang T, Hermosillo G, Wolf M, et al. Time-efficient CT colonography interpretation using an advanced image-gallery-based, computer-aided "first-reader" workflow for the detection of colorectal adenomas. European Radiology 2012 Dec;22(12):2768-79. PMID: 22903619. **KQ2E5a.**
294. Stegeman I, de Wijkerslooth TR, Stoop EM, et al. Risk factors for false positive and for false negative test results in screening with fecal

occult blood testing. International Journal of Cancer 2013 Nov 15;133(10):2408-14. PMID: 23649826. **KQ2E5a.**

295. Tao S, Brenner H. Well adjusted qualitative immunochemical faecal occult blood tests could be a promising alternative for inexpensive, high-quality colorectal cancer screening. Eur J Cancer Prev 2013 Jul;22(4):305-10. PMID: 23702679. **KQ2E5a.**
296. Rex DK, Vining D, Kopecky KK. An initial experience with screening for colon polyps using spiral CT with and without CT colography (virtual colonoscopy). Gastrointest Endosc 1999 Sep;50(3):309-13. PMID: 10462648. **KQ2E6.**
297. Macari M, Milano A, Lavelle M, et al. Comparison of time-efficient CT colonography with two- and three-dimensional colonic evaluation for detecting colorectal polyps. AJR Am J Roentgenol 2000 Jun;174(6):1543-9. PMID: 10845478. **KQ2E6.**
298. Sung JJ, Chan FK, Leung WK, et al. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. Gastroenterology 2003 Mar;124(3):608-14. PMID: 12612899. **KQ2E6.**
299. Mesihovic R, Vanis N, Gribajcevic M. Test for obscure bleeding vs colonoscopy in the prevention of colorectal cancer. Medicinski Arhiv 2008;62(3):153-5. PMID: 18822943. **KQ2E6.**
300. Brenner H, Hoffmeister M, Birkner B, et al. Diagnostic Performance of Guaiac-Based Fecal Occult Blood Test in Routine Screening: State-Wide Analysis from Bavaria, Germany. Am J Gastroenterol 2013 Dec 17 PMID: 24343548. **KQ2E6.**
301. Spada C, Hassan C, Barbaro B, et al. Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial. Gut 2014 Jun 24 PMID: 24964317. **KQ2E6.**
302. Nakazato M, Yamano H, Matsushita H, et al. Immunologic fecal occult blood test for colorectal cancer screening. Japan Medical Association Journal 2006;49(5-6):203-7. PMID: None. **KQ2E7.**
303. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. Journal of Gastroenterology 2010 Jul;45(7):703-12. PMID: 20157748. **KQ2E7.**
304. Wong MC, Ching JY, Chan VC, et al. Factors associated with false-positive and false-negative fecal immunochemical test results for colorectal cancer screening. Gastrointest Endosc 2014 Oct 4 PMID: 25293827. **KQ2E7.**
305. Imperiale TF, Wagner DR, Lin CY, et al. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000 Jul 20;343(3):169-74. PMID: 10900275. **KQ2E8.**
306. Ikeda Y, Mori M, Miyazaki M, et al. Significance of small distal adenoma for detection of proximal neoplasms in the colorectum. Gastrointest Endosc 2000 Sep;52(3):358-61. PMID: 10968850. **KQ2E8.**
307. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000 Jul 20;343(3):162-8. PMID: 10900274. **KQ2E8.**
308. Imperiale TF, Wagner DR, Lin CY, et al. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003 Dec 16;139(12):959-65. PMID: 14678915. **KQ2E8.**
309. Anderson JC, Alpern Z, Messina CR, et al. Predictors of proximal neoplasia in patients without distal adenomatous pathology. Am J Gastroenterol 2004 Mar;99(3):472-7. PMID: 15056088. **KQ2E8.**
310. Betes-Ibanez M., Munoz-Navas MA, Duque JM, et al. Diagnostic value of distal colonic polyps for prediction of advanced proximal neoplasia in an average-risk population undergoing screening colonoscopy. Gastrointest Endosc 2004 May;59(6):634-41. PMID: 15114305. **KQ2E8.**
311. Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005 May;352(20):2061-8. PMID: 15901859. **KQ2E8.**
312. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clinical Gastroenterology & Hepatology 2009 Dec;7(12):1341-6. PMID: 19426835. **KQ2E8.**
313. Jaboori KA, Domagalski JE, Eckert LD, et al. Colonoscopy by a family physician: detecting proximal neoplasia in asymptomatic adults. Military Medicine 2011 May;176(5):573-7. PMID: 21634304. **KQ2E8, KQ3E5.**
314. Zhu MM, Xu XT, Nie F, et al. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis. Journal of Digestive Diseases 2010 Jun;11(3):148-60. PMID: 20579218. **KQ2E9.**

315. Haug U, Knudsen AB, Brenner H, et al. Is fecal occult blood testing more sensitive for left- versus right-sided colorectal neoplasia? A systematic literature review. Expert Review of Molecular Diagnostics 2011 Jul;11(6):605-16. PMID: 21745014. **KQ2E9.**
316. de Haan MC, van Gelder RE, Graser A, et al. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. European Radiology 2011 Aug;21(8):1747-63. PMID: 21455818. **KQ2E9.**
317. Lee JK, Liles EG, Bent S, et al. Accuracy of Fecal Immunochemical Tests for Colorectal CancerSystematic Review and Meta-analysis. Ann Intern Med 2014 Feb 4;160(3):171-81. PMID: 24658694. **KQ2E9.**
318. Stermer E, Lavy A, Rainis T, et al. Incidental colorectal computed tomography abnormalities: would you send every patient for a colonoscopy? Canadian Journal of Gastroenterology 2008 Sep;22(9):758-60. PMID: 18818789. **KQ3E1.**
319. Sawhney MS, Salfiti N, Nelson DB, et al. Risk factors for severe delayed postpolypectomy bleeding. Eur J Radiol 2008 Feb;40(2):115-9. PMID: 18253906. **KQ3E1.**
320. Berzin TM, Blanco PG, Lamont JT, et al. Persistent psychological or physical symptoms following endoscopic procedures: an unrecognized post-endoscopy adverse event. Digestive Diseases & Sciences 2010 Oct;55(10):2869-73. PMID: 20393877. **KQ3E1.**
321. Randriamarolahy A, Cucchi JM, Brunner P, et al. Two rare cases of spontaneous splenic rupture. Clinical Imaging 2010 Jul;34(4):306-8. PMID: 20630345. **KQ3E1.**
322. Siewert B, Kruskal JB, Eisenberg R, et al. Quality initiatives: quality improvement grand rounds at Beth Israel Deaconess Medical Center: CT colonography performance review after an adverse event. Radiographics 2010 Jan;30(1):23-31. PMID: 19901086. **KQ3E1.**
323. Ko CW, Dominitz JA, Green P, et al. Accuracy of Medicare claims for identifying findings and procedures performed during colonoscopy. Gastrointest Endosc 2011 Mar;73(3):447-53. PMID: 20950800. **KQ3E1.**
324. Gimeno-Garcia AZ, de Ganzo ZA, Sosa AJ, et al. Incidence and predictors of postpolypectomy bleeding in colorectal polyps larger than 10 mm. European Journal of Gastroenterology & Hepatology 2012 May;24(5):520-6. PMID: 22465971. **KQ3E1.**
325. La TM, Velluti F, Giuliani G, et al. Promptness of diagnosis is the main prognostic factor after colonoscopic perforation. Colorectal Disease 2012 Jan;14(1):e23-e26. PMID: 21831176. **KQ3E1.**
326. Hamilton W, Coleman MG, Rubin G. Colorectal cancer. BMJ 2013;346:f3172. PMID: 23693056. **KQ3E1.**
327. Callejas MF, Errazuriz JI, Castillo F, et al. Incidental venous thromboembolism detected by PET-CT in patients with cancer: prevalence and impact on survival rate. Thrombosis Research 2014 May;133(5):750-5. PMID: 24565275. **KQ3E1.**
328. Neri E, Laghi A, Regge D. Re: Colonic perforation during screening CT colonography using automated CO2 insufflation in an asymptomatic adult. Abdominal Imaging 2008 Nov;33(6):748-9. PMID: 18546033. **KQ3E2.**
329. Liedenbaum MH, Venema HW, Stoker J. Radiation dose in CT colonography--trends in time and differences between daily practice and screening protocols. European Radiology 2008 Oct;18(10):2222-30. PMID: 18491095. **KQ3E2.**
330. Consolo P, Luigiano C, Strangio G, et al. Efficacy, risk factors and complications of endoscopic polypectomy: ten year experience at a single center. World Journal of Gastroenterology 2008 Apr 21;14(15):2364-9. PMID: 18416463. **KQ3E2.**
331. Berland LL. Incidental extracolonic findings on CT colonography: the impending deluge and its implications. Journal of the American College of Radiology 2009 Jan;6(1):14-20. PMID: 19111266. **KQ3E2.**
332. Araujo SE, Seid VE, Caravatto PP, et al. Incidence and management of colonoscopic colon perforations: 10 years' experience. Hepatogastroenterology 2009 Nov;56(96):1633-6. PMID: 20214207. **KQ3E2.**
333. Panteris V, Haringsma J, Kuipers EJ. Colonoscopy perforation rate, mechanisms and outcome: from diagnostic to therapeutic colonoscopy. Eur J Radiol 2009 Nov;41(11):941-51. PMID: 19866393. **KQ3E2.**
334. Yee J, Sadda S, Aslam R, et al. Extracolonic findings at CT colonography. Gastrointestinal Endoscopy Clinics of North America 2010 Apr;20(2):305-22. PMID: 20451819. **KQ3E2.**
335. Oka S, Tanaka S, Kanao H, et al. Current status in the occurrence of postoperative bleeding, perforation and residual/local recurrence during colonoscopic treatment in Japan. Digestive Endoscopy 2010 Oct;22(4):376-80. PMID: 21175503. **KQ3E2.**
336. Berrington de GA, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. Gastrointestinal Endoscopy

Clinics of North America 2010 Apr;20(2):279-91. PMID: 20451817. **KQ3E2.**
337. Berrington de GA, Kim KP, Knudsen AB, et al. Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis. AJR 2011 Apr;American(4):816-23. PMID: 21427330. **KQ3E2.**
338. ASGE Standards of Practice Committee, Fisher DA, Maple JT, et al. Complications of colonoscopy. Gastrointest Endosc 2011 Oct;74(4):745-52. PMID: 21951473. **KQ3E2.**
339. Ghevariya V, Kevorkian N, Asarian A, et al. Splenic injury from colonoscopy: a review and management guidelines. Southern Medical Journal 2011 Jul;104(7):515-20. PMID: 21886052. **KQ3E2.**
340. Buddingh KT, Herngreen T, Haringsma J, et al. Location in the right hemi-colon is an independent risk factor for delayed post-polypectomy hemorrhage: a multi-center case-control study. Am J Gastroenterol 2011 Jun;106(6):1119-24. PMID: 21266961. **KQ3E2.**
341. Khan JS, Moran BJ. Iatrogenic perforation at colonic imaging. Colorectal Disease 2011 May;13(5):481-93. PMID: 20015266. **KQ3E2.**
342. Kapetanos D, Beltsis A, Chatzimavroudis G, et al. Postpolypectomy bleeding: incidence, risk factors, prevention, and management. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2012 Apr;22(2):102-7. PMID: 22487620. **KQ3E2.**
343. Sarkar S, Geraghty J, Moore AR, et al. A multicentre study to determine the incidence, demographics, aetiology and outcomes of 6-day emergency readmission following day-case endoscopy. European Journal of Gastroenterology & Hepatology 2012 Dec;24(12):1438-46. PMID: 23114746. **KQ3E2.**
344. DeRoux SJ, Sgarlato A. Upper and lower gastrointestinal endoscopy mortality: the medical examiner's perspective. Forensic Science, Medicine & Pathology 2012 Mar;8(1):4-12. PMID: 21667169. **KQ3E2.**
345. Raju GS, Vadyala V, Slack R, et al. Adenoma detection in patients undergoing a comprehensive colonoscopy screening. Cancer Medicine 2013 Jun;2(3):391-402. PMID: 23930215. **KQ3E2.**
346. Pendse DA, Taylor SA. Splenic rupture: an uncommon complication after colonoscopy. European Journal of Radiology 2013 Aug;82(8):1159-65. PMID: 22595505. **KQ3E2.**
347. Yao J, Burns JE. Extracolonic findings on CT colonography: does the benefit outweigh the cost? Academic Radiology 2013 Jun;20(6):665-6. PMID: 23664396. **KQ3E2.**
348. Wu XR, Church JM, Jarrar A, et al. Risk factors for delayed postpolypectomy bleeding: how to minimize your patients' risk. International Journal of Colorectal Disease 2013 Aug;28(8):1127-34. PMID: 23440363. **KQ3E2.**
349. Gimeno-Garcia AZ, Quintero E. Post-polypectomy complications: high risk in the cecum. Eur J Radiol 2014 Feb;46(2):88-9. PMID: 24477362. **KQ3E2.**
350. Tagg W, Woods S, Razdan R, et al. Hemoperitoneum after colonoscopy. Eur J Radiol 2008 Sep;40:Suppl-7. PMID: 18633865. **KQ3E2c.**
351. Bassett JT, Liotta RA, Barlow D, et al. Colonic perforation during screening CT colonography using automated CO2 insufflation in an asymptomatic adult. Abdominal Imaging 2008 Sep;33(5):598-600. PMID: 18446401. **KQ3E2c.**
352. Ahlawat SK, Charabaty A, Benjamin S. Rectal perforation caused by retroflexion maneuver during colonoscopy: closure with endoscopic clips. Gastrointest Endosc 2008 Apr;67(4):771-3. PMID: 18206880. **KQ3E2c.**
353. Gross RG, Reiter B, Korsten MA. Pyogenic liver abscess complicating colonoscopic polypectomy. Gastrointest Endosc 2008 Apr;67(4):767-8. PMID: 18155212. **KQ3E2c.**
354. Sarhan M, Ramcharan A, Ponnapalli S. Splenic injury after elective colonoscopy. Journal of the Society of Laparoendoscopic Surgeons 2009 Oct;13(4):616-9. PMID: 20202406. **KQ3E2c.**
355. Patselas TN, Gallagher EG. Splenic rupture: an uncommon complication after colonoscopy. American Surgeon 2009 Mar;75(3):260-1. PMID: 19350865. **KQ3E2c.**
356. Lewis SR, Ohio D, Rowley G. Splenic injury as a rare complication of colonoscopy. Emergency Medicine Journal 2009 Feb;26(2):147. PMID: 19164635. **KQ3E2c.**
357. Desai B. Splenic laceration following routine colonoscopy. Southern Medical Journal 2010 Nov;103(11):1181-3. PMID: 20890252. **KQ3E2c.**
358. Hlivko JT, Esber EJ, Porter JA, et al. Small-bowel obstruction precipitated by bowel preparation for screening colonoscopy. Eur J Radiol 2010;42:Suppl. PMID: 20878603. **KQ3E2c.**
359. Gonzalez-Candelas F, Guiral S, Carbo R, et al. Patient-to-patient transmission of hepatitis C virus (HCV) during colonoscopy diagnosis. Virology Journal 2010;7:217. PMID: 20825635. **KQ3E2c.**
360. Alder AC, Scott DL, Browning JD. Colonoscopy: an unusual complication. Gastroenterology 2010;138(2):434. PMID: 20034601. **KQ3E2c.**

361. Pothula A, Lampert J, Mazeh H, et al. Splenic rupture as a complication of colonoscopy: report of a case. Surgery Today 2010;40(1):68-71. PMID: 20037844. **KQ3E2c.**
362. Maddur H, Agrawal S, Fayad N, et al. Acute cholecystitis after colonoscopy: a case series. Gastrointest Endosc 2011 Jul;74(1):211-3. PMID: 21549374. **KQ3E2c.**
363. Langer K, Kriegler S, Moser M. Colonoscopy complicated by arterial avulsion and retroperitoneal hemorrhage. Eur J Radiol 2011;43:Suppl. PMID: 21590605. **KQ3E2c.**
364. Rustagi T. Intestinal obstruction from diaphragmatic hernia following colonoscopy. American Journal of the Medical Sciences 2011 May;341(5):423-5. PMID: 21358390. **KQ3E2c.**
365. Bildzukewicz NA, Weinstein MS. Appendicitis following virtual colonoscopy: a case report. Journal of Gastrointestinal Surgery 2012 Dec;16(12):2291-3. PMID: 22918862. **KQ3E2c.**
366. Cheng YC, Wu CC, Lee CC, et al. Rare complication following screening colonoscopy: ischemic colitis. Digestive Endoscopy 2012 Sep;24(5):379. PMID: 22925295. **KQ3E2c.**
367. Singla S, Keller D, Thirunavukarasu P, et al. Splenic injury during colonoscopy--a complication that warrants urgent attention. Journal of Gastrointestinal Surgery 2012 Jun;16(6):1225-34. PMID: 22450952. **KQ3E2c.**
368. Saludes V, Esteve M, Casas I, et al. Hepatitis C virus transmission during colonoscopy evidenced by phylogenetic analysis. Journal of Clinical Virology 2013 Jul;57(3):263-6. PMID: 23567025. **KQ3E2c.**
369. Lee CK, Shim JJ, Jang JY. Ceco-colic intussusception with subsequent bowel infarction as a rare complication of colonoscopic polypectomy. Eur J Radiol 2013;45:Suppl-7. PMID: 23526500. **KQ3E2c.**
370. Hammadah M, Gaber L, Raghavan R. Renal cortical necrosis following a colonoscopy. Clinical Nephrology 2013 Jan;79(1):67-71. PMID: 22913920. **KQ3E2c.**
371. April MD, Simmons JR, Nielson AS. An unusual cause of postcolonoscopy abdominal pain. American Journal of Emergency Medicine 2013 Jan;31(1):273-4. PMID: 22795421. **KQ3E2c.**
372. Shaw D, Gallardo G, Basson MD. Post-colonoscopy appendicitis: A case report and systematic review. World Journal of Gastrointestinal Surgery 2013 Oct 27;5(10):259-63. PMID: 24179623. **KQ3E2c.**
373. Yu JY, Kim SK, Jang EC, et al. Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding. World Journal of Gastrointestinal Endoscopy 2013 May 16;5(5):270-2. PMID: 23678383. **KQ3E2c.**
374. Ignjatovic M, Jovic J. Tension pneumothorax, pneumoretroperitoneum, and subcutaneous emphysema after colonoscopic polypectomy: a case report and review of the literature. Langenbecks Archives of Surgery 2009 Jan;394(1):185-9. PMID: 18283482. **KQ3E3a.**
375. Aswakul P, Prachayakul V, Lohsiriwat V, et al. Screening colonoscopy from a large single center of Thailand - something needs to be changed? Asian Pacific Journal of Cancer Prevention: Apjcp 2012;13(4):1361-4. PMID: 22799332. **KQ3E3a.**
376. Rogge JD, Elmore MF, Mahoney SJ, et al. Low-cost, office-based, screening colonoscopy. Am J Gastroenterol 1994 Oct;89(10):1775-80. PMID: 7942665. **KQ3E4.**
377. Newcomer MK, Shaw MJ, Williams DM, et al. Unplanned work absence following outpatient colonoscopy. J Clin Gastroenterol 1999 Jul;29(1):76-8. PMID: 10405238. **KQ3E4.**
378. Dafnis G, Ekbom A, Pahlman L, et al. Complications of diagnostic and therapeutic colonoscopy within a defined population in Sweden. Gastrointest Endosc 2001 Sep;54(3):302-9. PMID: 11522969. **KQ3E4.**
379. Edwards JK, Norris TE. Colonoscopy in rural communities: can family physicians perform the procedure with safe and efficacious results? J Am Board Fam Pract 2004 Sep;17(5):353-8. PMID: 15355949. **KQ3E4.**
380. Syn WK, Tandon U, Ahmed MM. Colonoscopy in the very elderly is safe and worthwhile. Age Ageing 2005 Sep;34(5):510-3. PMID: 16107458. **KQ3E4.**
381. Newman RJ, Nichols DB, Cummings DM. Outpatient colonoscopy by rural family physicians. Ann Fam Med 2005 Mar;3(2):122-5. PMID: 15798037. **KQ3E4.**
382. Lee YC, Wang HP, Chiu HM, et al. Factors determining post-colonoscopy abdominal pain: prospective study of screening colonoscopy in 1000 subjects. Journal of Gastroenterology & Hepatology 21(10):1575 -80 , 2006 Oct PMID: 16928219. **KQ3E4.**
383. Duncan JE, Sweeney WB, Trudel JL, et al. Colonoscopy in the elderly: low risk, low yield in asymptomatic patients. Dis Colon Rectum 2006 May;49(5):646-51. PMID: 16482421. **KQ3E4.**
384. Russmann S, Lamerato L, Marfatia A, et al. Risk of impaired renal function after colonoscopy: a cohort study in patients receiving either oral sodium phosphate or polyethylene glycol. Am J

Gastroenterol 2007 Dec;102(12):2655-63. PMID: 17970832. **KQ3E4.**
385. Guerra JF, San F, I, Pimentel F, et al. Splenic rupture following colonoscopy. World Journal of Gastroenterology 2008 Nov 7;14(41):6410-2. PMID: 19009661. **KQ3E4.**
386. Ballas KD, Rafailidis SF, Triantaphyllou A, et al. Retroperitoneal, mediastinal, and subcutaneous emphysema, complicating colonoscopy and rectal polypectomy. Journal of Laparoendoscopic & Advanced Surgical Techniques 2008 Oct;Part(5):717-20. PMID: 18803515. **KQ3E4.**
387. Hough DM, Kuntz MA, Fidler JL, et al. Detection of occult colonic perforation before CT colonography after incomplete colonoscopy: perforation rate and use of a low-dose diagnostic scan before CO2 insufflation. AJR 2008 Oct;American(4):1077-81. PMID: 18806146. **KQ3E4.**
388. Michail O, Griniatsos J, Daskalaki M, et al. Two cases of cervical emphysema after colonoscopy. Eur J Radiol 2008 Sep;40:Suppl-2. PMID: 18668467. **KQ3E4.**
389. Saad A, Rex DK. Colonoscopy-induced splenic injury: report of 3 cases and literature review. Digestive Diseases & Sciences 2008 Apr;53(4):892-8. PMID: 17934832. **KQ3E4.**
390. Pasumarthy L, Srour J, Johnson D. Jejunal Perforation following Screening Colonoscopy. Case Reports Gastroenterology 2008;2(2):187-90. PMID: 21490886. **KQ3E4.**
391. Ha JF, Minchin D. Splenic injury in colonoscopy: a review. International Journal Of Surgery 2009 Oct;7(5):424-7. PMID: 19638324. **KQ3E4.**
392. Uraoka T, Kato J, Kuriyama M, et al. CO(2) insufflation for potentially difficult colonoscopies: efficacy when used by less experienced colonoscopists. World Journal of Gastroenterology 2009 Nov 7;15(41):5186-92. PMID: 19891018. **KQ3E4.**
393. Chalumeau C, Facy O, Radais F, et al. Colonoscopy-related esophageal perforation: report of two cases. Eur J Radiol 2009;41:Suppl. PMID: 19866419. **KQ3E4.**
394. Dellon ES, Lippmann QK, Galanko JA, et al. Effect of GI endoscopy nurse experience on screening colonoscopy outcomes. Gastrointest Endosc 2009 Aug;70(2):331-43. PMID: 19500788. **KQ3E4.**
395. Bechtold ML, Hammad HT, Arif M, et al. Perforation upon retroflexion: an endoscopic complication and repair. Eur J Radiol 2009;41:Suppl-6. PMID: 19544277. **KQ3E4.**
396. Rao KV, Beri GD, Sterling MJ, et al. Splenic injury as a complication of colonoscopy: a case series. Am J Gastroenterol 2009 Jun;104(6):1604-5. PMID: 19491881. **KQ3E4.**
397. Ranganath R, Selinger S. An uncommon complication of a common procedure. Postgraduate Medical Journal 2009 Apr;85(1002):224. PMID: 19417175. **KQ3E4.**
398. Nguyen HD, Borum ML. Acute hepatitis in a patient given propofol during colonoscopy. Southern Medical Journal 2009 Mar;102(3):333-4. PMID: 19204630. **KQ3E4.**
399. Kimberly JR, Phillips KC, Santago P, et al. Extracolonic findings at virtual colonoscopy: an important consideration in asymptomatic colorectal cancer screening. Journal of General Internal Medicine 2009 Jan;24(1):69-73. PMID: 18958531. **KQ3E4.**
400. Mai CM, Wen CC, Wen SH, et al. Iatrogenic colonic perforation by colonoscopy: a fatal complication for patients with a high anesthetic risk. International Journal of Colorectal Disease 2010 Apr;25(4):449-54. PMID: 19855987. **KQ3E4.**
401. Kipple JC. Bilateral tension pneumothoraces and subcutaneous emphysema following colonoscopic polypectomy: a case report and discussion of anesthesia considerations. AANA Journal 2010 Dec;78(6):462-7. PMID: 21309293. **KQ3E4.**
402. Michetti CP, Smeltzer E, Fakhry SM. Splenic injury due to colonoscopy: analysis of the world literature, a new case report, and recommendations for management. American Surgeon 2010 Nov;76(11):1198-204. PMID: 21140684. **KQ3E4.**
403. Theodoropoulos J, Krecioch P, Myrick S, et al. Delayed presentation of a splenic injury after colonoscopy: a diagnostic challenge. International Journal of Colorectal Disease 2010 Aug;25(8):1033-4. PMID: 20217421. **KQ3E4.**
404. Tribonias G, Konstantinidis K, Theodoropoulou A, et al. Rectal perforation caused by colonoscopic retroflexion. Gastrointest Endosc 2010 Mar;71(3):662. PMID: 20189536. **KQ3E4.**
405. Sheikh A, Watt J, Tee M, et al. Appendicitis as a complication of colonoscopy. Journal of Surgical Case Reports 2010;2010(9):1. PMID: 24946353. **KQ3E4.**
406. Akhtar AJ, Padda MS. Safety and efficacy of colonoscopy in the elderly: experience in an innercity community hospital serving African American and Hispanic patients. Ethnicity & Disease 2011;21(4):412-4. PMID: 22428343. **KQ3E4.**
407. Khan S, Ahmed J, Lim M, et al. Colonoscopy in the octogenarian population: diagnostic and survival outcomes from a large series of patients.

Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland 2011 Aug;9(4):195-9. PMID: 21672659. **KQ3E4.**
408. Wu AY, Oestreicher JH. Endogenous bacterial endophthalmitis after routine colonoscopy. Canadian Journal of Ophthalmology 2011 Dec;46(6):556-7. PMID: 22153651. **KQ3E4.**
409. Fishback SJ, Pickhardt PJ, Bhalla S, et al. Delayed presentation of splenic rupture following colonoscopy: clinical and CT findings. Emergency Radiology 2011 Dec;18(6):539-44. PMID: 21887533. **KQ3E4.**
410. Sutherland T, Coyle E, Lui B, et al. Extracolonic findings at CT colonography: a review of 258 consecutive cases. Journal of Medical Imaging & Radiation Oncology 2011 Apr;55(2):149-52. PMID: 21501403. **KQ3E4.**
411. Hasan AG, Brown WR. Colonic cleansing for colonoscopy: a risk to be taken seriously. Gastrointest Endosc 2011 Mar;73(3):616-8. PMID: 21353860. **KQ3E4.**
412. Emmanouilidis N, Jager MD, Winkler M, et al. Boerhaave syndrome as a complication of colonoscopy preparation: a case report. Journal of Medical Case Reports [Electronic Resource] 2011;5:544. PMID: 22054124. **KQ3E4.**
413. Azzopardi J, DeWitt DE. Quality and safety issues in procedural rural practice: a prospective evaluation of current quality and safety guidelines in 3000 colonoscopies. Rural & Remote Health 2012;12:1949. PMID: 22985075. **KQ3E4.**
414. Matharoo GS, Goldfarb MA. Treatment and outcomes of iatrogenic colon perforations at a community teaching hospital. American Surgeon 2012 Sep;78(9):975-8. PMID: 22964207. **KQ3E4.**
415. Hagel AF, Boxberger F, Dauth W, et al. Colonoscopy-associated perforation: a 7-year survey of in-hospital frequency, treatment and outcome in a German university hospital. Colorectal Disease 2012 Sep;14(9):1121-5. PMID: 22122526. **KQ3E4.**
416. Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc 2012 Aug;76(2):255-63. PMID: 22657404. **KQ3E4.**
417. DeMuro JP. Incarcerated spigelian hernia after colonoscopy. American Surgeon 2012 May;78(5):E260-E261. PMID: 22691321. **KQ3E4.**
418. Villafanez-Garcia MC, San Gil JG, Ortega-Abengozar H, et al. Massive pneumoperitoneum after colonoscopy. Journal of Emergency Medicine 2012 Jan;42(1):58-9. PMID: 19828276. **KQ3E4.**
419. Wernli KJ, Rutter CM, Dachman AH, et al. Suspected extracolonic neoplasms detected on CT colonography: literature review and possible outcomes. [Review]. Academic Radiology 2013 Jun;20(6):667-74. PMID: 23465379. **KQ3E4.**
420. Randall JK, Good CS, Gilbert JM. 22-year longitudinal study of repetitive colonoscopy in patients with a family history of colorectal cancer. Annals of the Royal College of Surgeons of England 2013 Nov;95(8):586-90. PMID: 24165342. **KQ3E4.**
421. Pineda L, Sarhan M, Suman P, et al. Splenic rupture after screening colonoscopy. American Surgeon 2013 Jan;79(1):E43-E44. PMID: 23317606. **KQ3E4.**
422. Okholm C, Hadikhadem T, Andersen LT, et al. No increased risk of perforation during colonoscopy in patients undergoing Nurse Administered Propofol Sedation. Scand J Gastroenterol 2013 Nov;48(11):1333-8. PMID: 24063514. **KQ3E4.**
423. Kotwal VS, Attar BM, Carballo MD, et al. Morning-only polyethylene glycol is noninferior but less preferred by hospitalized patients as compared with split-dose bowel preparation. Journal of Clinical Gastroenterology 2014;48:414-8. PMID: 24406474. **KQ3E4.**
424. Pierzchajlo RP, Ackermann RJ, Vogel RL. Colonoscopy performed by a family physician. A case series of 751 procedures. J Fam Pract 1997 May;44(5):473-80. PMID: 9152265. **KQ3E4a.**
425. Xiong T, Richardson M, Woodroffe R, et al. Incidental lesions found on CT colonography: their nature and frequency. Br J Radiol 2005 Jan;78(925):22-9. PMID: 15673525. **KQ3E4a.**
426. Paspatis GA, Vardas E, Theodoropoulou A, et al. Complications of colonoscopy in a large public county hospital in Greece. A 10-year study. Digestive & Liver Disease 2008 Dec;40(12):951-7. PMID: 18417433. **KQ3E4a.**
427. Baudet JS, Diaz-Bethencourt D, Arguinarena X, et al. Cat scratch colon is caused by barotrauma secondary to insufflation during colonoscopy. Eur J Radiol 2008 Oct;40(10):878-9. PMID: 18828090. **KQ3E4a.**
428. Avgerinos DV, Llaguna OH, Lo AY, et al. Evolving management of colonoscopic perforations. Journal of Gastrointestinal Surgery 2008 Oct;12(10):1783-9. PMID: 18683006. **KQ3E4a.**
429. Alabraba E, Gourevitch D, Hejmadi R, et al. Post-colonoscopy tension pneumothorax resulting from colonic barotrauma in a

previously unrecognised left-sided diaphragmatic hernia. Eur J Radiol 2008 Sep;40:Suppl-9. PMID: 18633881. **KQ3E4a.**

430. Yuksel O, Bolat AD, Koklu S, et al. Ischemic colitis, an unusual complication of colonoscopy. Southern Medical Journal 2008 Sep;101(9):972-3. PMID: 18708963. **KQ3E4a.**
431. Famularo G, Minisola G, De SC. Rupture of the spleen after colonoscopy: a life-threatening complication. American Journal of Emergency Medicine 2008 Sep;26(7):834. PMID: 18774051. **KQ3E4a.**
432. Atiq M, Aduli F, Refai W, et al. Postpolypectomy acute colonic pseudo-obstruction (Ogilvie's syndrome). Eur J Radiol 2008 Sep;40:Suppl. PMID: 18668452. **KQ3E4a.**
433. Sohns C, Heuser M, Sossalla S, et al. Current role and future potential of computed tomographic colonography for colorectal polyp detection and colon cancer screening-incidental findings. Clinical Imaging 2008 Jul;32(4):280-6. PMID: 18603183. **KQ3E4a.**
434. Siddiki H, Fletcher JG, McFarland B, et al. Incidental findings in CT colonography: literature review and survey of current research practice. Journal of Law, Medicine & Ethics 2008;36(2):320-31. PMID: 18547201. **KQ3E4a.**
435. Parker WT, Edwards MA, Bittner JG, et al. Splenic hemorrhage: an unexpected complication after colonoscopy. American Surgeon 2008 May;74(5):450-2. PMID: 18481509. **KQ3E4a.**
436. Tominaga K, Shigiyama F, Ito S, et al. Emergence of "cat scratch colon" during a colonoscopy. Eur J Radiol 2008 Apr;40(4):353. PMID: 18389454. **KQ3E4a.**
437. Ugajin T, Miyatani H, Momomura S, et al. Ventricular fibrillation during colonoscopy: a case report--colonoscopy in high-risk patients should be performed with ECG monitoring. Internal Medicine 2008;47(7):609-12. PMID: 18379145. **KQ3E4a.**
438. Petersen CR, Adamsen S, Gocht-Jensen P, et al. Splenic injury after colonoscopy. Eur J Radiol 2008 Jan;40(1):76-9. PMID: 18058621. **KQ3E4a.**
439. Quer J, Esteban JI, Sanchez JM, et al. Nosocomial transmission of hepatitis C virus during contrast-enhanced computed tomography scanning. European Journal of Gastroenterology & Hepatology 2008 Jan;20(1):73-8. PMID: 18090995. **KQ3E4a.**
440. Duarte CG. Splenic rupture after colonoscopy. American Journal of Emergency Medicine 2008 Jan;26(1):117-3. PMID: 18082812. **KQ3E4a.**
441. Hunter IA, Sarkar R, Smith AM. Small bowel obstruction complicating colonoscopy: a case report. Journal of Medical Case Reports [Electronic Resource] 2008;2:179. PMID: 18505563. **KQ3E4a.**
442. Cappellani A, Di VM, Zanghi A, et al. Splenic rupture after colonoscopy: Report of a case and review of literature. World Journal Of Emergency Surgery 2008;3:8. PMID: 18261241. **KQ3E4a.**
443. Skipworth JR, Raptis DA, Rawal JS, et al. Splenic injury following colonoscopy--an underdiagnosed, but soon to increase, phenomenon? Annals of the Royal College of Surgeons of England 2009 May;91(4):W6-11. PMID: 19416579. **KQ3E4a.**
444. Park SK, Park DI, Lee SY, et al. Extracolonic findings of computed tomographic colonography in Koreans. World Journal of Gastroenterology 2009 Mar 28;15(12):1487-92. PMID: 19322923. **KQ3E4a.**
445. Kolber M, Szafran O, Suwal J, et al. Outcomes of 1949 endoscopic procedures: performed by a Canadian rural family physician. Can Fam Physician 2009 Feb;55(2):170-5. PMID: 19221080. **KQ3E4a.**
446. Beetham M, Khan MI. Incarceration of an umbilical hernia following colonoscopy. New Zealand Medical Journal 2009 Dec 11;122(1307):97-9. PMID: 20148050. **KQ3E4a.**
447. Atalla MA, Rozen WM, Master M, et al. Education and Imaging. Colonic perforation during 'virtual' CT colonography. Journal of Gastroenterology & Hepatology 2009 Nov;24(11):1800. PMID: 20136963. **KQ3E4a.**
448. Witt DM, Delate T, McCool KH, et al. Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. Journal of Thrombosis & Haemostasis 2009 Dec;7(12):1982-9. PMID: 19719825. **KQ3E4a.**
449. Ho JM, Cavalcanti RB. A shocking bowel preparation: severe electrolyte disturbances after polyethylene glycol-based bowel preparation. Journal of the American Geriatrics Society 2009 Sep;57(9):1729-30. PMID: 19895448. **KQ3E4a.**
450. de VJ, Ronnen HR, Oomen AP, et al. Splenic rupture following colonoscopy, a rare complication. Netherlands Journal of Medicine 2009 Jun;67(6):230-3. PMID: 19749393. **KQ3E4a.**
451. Younes NA, Al-Ardah MI, Daradkeh SS. Rupture of spleen post colonoscopy. Saudi Medical Journal 2009 Aug;30(8):1095-7. PMID: 19668895. **KQ3E4a.**
452. Dong Q, Wang Q, Li Y. Ischemic colitis after colonoscopy in a female patient. Am J

Gastroenterol 2009 Aug;104(8):2123-4. PMID: 19455113. **KQ3E4a.**
453. Kume K, Yoshikawa I, Harada M. A rare complication: incarceration of a colonoscope in an inguinal hernia. Eur J Radiol 2009;41:Suppl. PMID: 19629941. **KQ3E4a.**
454. Kiosoglous AJ, Varghese R, Memon MA. Splenic rupture after colonoscopy: a case report. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2009 Jun;19(3):e104-e105. PMID: 19542830. **KQ3E4a.**
455. Fazeli MS, Keramati MR, Lebaschi AH, et al. Extensive subcutaneous emphysema due to colonic perforation following colonoscopy. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan 2009 Jun;19(6):383-5. PMID: 19486580. **KQ3E4a.**
456. Nogales RO, Yepes B, I, Hernando AA, et al. Large intramural colonic hematoma after polypectomy. Eur J Radiol 2009;41:Suppl. PMID: 19177292. **KQ3E4a.**
457. Exbrayat C, Poncet F, Billette d, V, et al. Colonoscopy practices, and colorectal cancer and polyp screening, as assessed in the French district of Isere from May to July in 2004. Gastroenterologie Clinique et Biologique 2010 Dec;34(12):702-11. PMID: 20970271. **KQ3E4a.**
458. Hardy D, Roach M. Hemothorax and splenic hematoma as complications of colonoscopy. American Surgeon 2010 Jun;76(6):E39-E40. PMID: 21418762. **KQ3E4a.**
459. Hutchinson B, Heeney A, Conneely J, et al. Splenic laceration following colonoscopy. Irish Journal of Medical Science 2010 Dec;179(4):633-4. PMID: 20865345. **KQ3E4a.**
460. Fortea JI, Marin J, I, Nogales RO, et al. Postcolonic polypectomy pancreatitis. Eur J Radiol 2010;42:Suppl-2. PMID: 20931450. **KQ3E4a.**
461. Sekino Y, Fujisawa N, Suzuki K, et al. A case of recurrent infective endocarditis following colonoscopy. Eur J Radiol 2010;42:Suppl. PMID: 20845280. **KQ3E4a.**
462. Moorman ML, Miller JP, Khanduja KS, et al. Postcolonoscopy appendicitis. American Surgeon 2010 Aug;76(8):892-5. PMID: 20726424. **KQ3E4a.**
463. Murariu D, Takekawa S, Furumoto N. Splenic rupture: a case of massive hemoperitoneum following therapeutic colonoscopy. Hawaii Medical Journal 2010 Jun;69(6):140-1. PMID: 20535686. **KQ3E4a.**
464. D'Ovidio V, Di CM, Pimpo MT, et al. An unusual complicated polypectomy and inverted colonic diverticula. Colorectal Disease 2010 May;12(5):491-2. PMID: 19486101. **KQ3E4a.**
465. DuCoin C, Acholonu E, Ukleja A, et al. Splenic rupture after screening colonoscopy: case report and literature review. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2010 Feb;20(1):e31-e33. PMID: 20173607. **KQ3E4a.**
466. Lee KJ, Ehrenpreis ED, Greenberg J, et al. Mesenteric panniculitis following colonoscopy, polypectomy, and epinephrine injection. Eur J Radiol 2010;42:Suppl-5. PMID: 20157883. **KQ3E4a.**
467. Sullivan JL, Maxwell PJ, Kastenberg DM, et al. Rectal perforation by retroflexion of the colonoscope managed by endoclip closure. American Surgeon 2010 Jan;76(1):108-10. PMID: 20135951. **KQ3E4a.**
468. Niv Y, Gershtansky Y, Kenett RS, et al. Complications in colonoscopy: analysis of 7-year physician-reported adverse events. European Journal of Gastroenterology & Hepatology 2011 Jun;23(6):492-8. PMID: 21537124. **KQ3E4a.**
469. Ahlawat SK, Gupta N, Benjamin SB, et al. Large colorectal polyps: endoscopic management and rate of malignancy: does size matter? Journal of Clinical Gastroenterology 2011 Apr;45(4):347-54. PMID: 20871408. **KQ3E4a.**
470. Tung LM, Co CS, Cheung HY, et al. A case report of small bowel perforation at colonoscopy. Asian Journal of Endoscopic Surgery 2011 Nov;4(4):171-3. PMID: 22776302. **KQ3E4a.**
471. Dumoulin FL, Textor J. An unusual presentation of a typical complication after endoscopic polypectomy. BMJ Case Reports 2011;2011,2011. PMID: 22679055. **KQ3E4a.**
472. Penkov P. Acute appendicitis following colonoscopy: causality or coincidence. ANZ Journal of Surgery 2011 Jun;81(6):491-2. PMID: 22295367. **KQ3E4a.**
473. Shih HY, Wu DC, Huang WT, et al. Glutaraldehyde-induced colitis: case reports and literature review. Kaohsiung Journal of Medical Sciences 2011 Dec;27(12):577-80. PMID: 22208542. **KQ3E4a.**
474. Peterlejtner T, Szewczyk T, Buczynska E, et al. Colonoscopic polypectomy--evaluation of the effectiveness and safety (single center experience). Polski Przeglad Chirurgiczny 2011 Aug;83(8):438-42. PMID: 22166717. **KQ3E4a.**
475. Khashram M, Frizelle FA. Colonoscopy--a rare cause of pancreatitis. New Zealand Medical Journal 2011 Nov 4;124(1345):74-6. PMID: 22072170. **KQ3E4a.**
476. Hong KD, Lee SI, Moon HY. Rectal diverticular perforation complicating diagnostic colonoscopy: a case report and review of the literature. Journal of Laparoendoscopic &

Advanced Surgical Techniques 2011 Oct;Part(8):745-8. PMID: 21819215. **KQ3E4a.**
477. Kocak E, Ergul B, Koklu S, et al. Abundant intraperitoneal bleeding after colonoscopy. Clinics & Research in Hepatology & Gastroenterology 2011 Sep;35(8-9):599-600. PMID: 21659014. **KQ3E4a.**
478. Singh-Ranger G, Halls A, Grundy A, et al. An unusual case of severe colitis after colonoscopy. Journal of Crohn's & colitis 2011 Jun;5(3):267-8. PMID: 21575897. **KQ3E4a.**
479. Aslinia FM, Von Rosenvinge EC. Case report: colonoscopy-associated splenic injury in a 56-year-old woman. American Family Physician 2011 Apr 1;83(7):786. PMID: 21524041. **KQ3E4a.**
480. Nguyen AB, Lee PC, Paul S. Crepitus: an uncommon complication of a common procedure. Annals of Thoracic Surgery 2011 Apr;91(4):e63. PMID: 21440112. **KQ3E4a.**
481. Alcaide N, Atienza R, Barrio J, et al. Hemoperitoneum caused by hemorrhage of tubal vessels, a previously undescribed complication of colonoscopy. Eur J Radiol 2011;43:Suppl. PMID: 21425027. **KQ3E4a.**
482. Meier RP, Toso C, Volonte F, et al. Splenic rupture after colonoscopy. American Journal of Emergency Medicine 2011 Feb;29(2):241-2. PMID: 20825894. **KQ3E4a.**
483. Seddik H, Rabhi M. Two cases of appendiceal intussusception: a rare diagnostic pitfall in colonoscopy. Diagnostic & Therapeutic Endoscopy 2011;2011:198984. PMID: 21603019. **KQ3E4a.**
484. Kim dH, Lim SW. Analysis of delayed postpolypectomy bleeding in a colorectal clinic. Journal of the Korean Society of Coloproctology 2011 Feb;27(1):13-6. PMID: 21431091. **KQ3E4a.**
485. Sewitch MJ, Jiang M, Joseph L, et al. Rate of serious complications of colonoscopy in Quebec. Canadian Journal of Gastroenterology 2012 Sep;26(9):611-3. PMID: 22993732. **KQ3E4a.**
486. Beitz A, Riphaus A, Meining A, et al. Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study (ColoCap Study). Am J Gastroenterol 2012 Aug;107(8):1205-12. PMID: 22641306. **KQ3E4a.**
487. Lee TJ, Rutter MD, Blanks RG, et al. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012 Jul;61(7):1050-7. PMID: 21940723. **KQ3E4a.**
488. Repici A, Hassan C, Vitetta E, et al. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. Eur J Radiol 2012 Jan;44(1):27-31. PMID: 22125197. **KQ3E4a.**
489. Carey JL, Napoli AM. Tension pneumoperitoneum during routine colonoscopy. American Journal of Emergency Medicine 2012 Jan;30(1):261-2. PMID: 21185666. **KQ3E4a.**
490. Loffeld RJ, Liberov B, Dekkers PE. Incidence and causes of colonoscopic perforations: a single-center case series. Geriatrics & gerontology international 2012 Apr;12(2):298-303. PMID: 22050603. **KQ3E4a.**
491. Alcaide N, Diez-Redondo P, Herranz-Bachiller MT, et al. Serosal lacerations during colonoscopy - a rare complication. Eur J Radiol 2012;44:Suppl. PMID: 22814914. **KQ3E4a.**
492. Yin AX, Park GH, Garnett GM, et al. Chilaiditi syndrome precipitated by colonoscopy: a case report and review of the literature. Hawai'i Journal of Medicine & Public Health : A Journal of Asia Pacific Medicine & Public Health 2012 Jun;71(6):158-62. PMID: 22787564. **KQ3E4a.**
493. Moore H, Dodd N. Computed tomographic colonography: colonic and extracolonic findings in an Auckland population. New Zealand Medical Journal 2012 Jun 8;125(1356):68-74. PMID: 22729061. **KQ3E4a.**
494. Lasithiotakis K, Grisbolaki E, Filis D, et al. Ileocolic intussusception precipitated by diagnostic colonoscopy: a case report. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2012 Jun;22(3):e161-e163. PMID: 22678343. **KQ3E4a.**
495. Lucendo AJ, Olveira A, Friginal-Ruiz AB, et al. Nonanesthesiologist-administered propofol sedation for colonoscopy is safe and effective: a prospective Spanish study over 1000 consecutive exams. European Journal of Gastroenterology & Hepatology 2012 Jul;24(7):787-92. PMID: 22517241. **KQ3E4a.**
496. Niv Y, Bogolavski I, Ilani S, et al. Impact of colonoscopy on quality of life. European Journal of Gastroenterology & Hepatology 2012 Jul;24(7):781-6. PMID: 22441512. **KQ3E4a.**
497. De J, V, Sint NJ, van BO, et al. The incidence of 30-day adverse events after colonoscopy among outpatients in the Netherlands. Am J Gastroenterol 2012 Jun;107(6):878-84. PMID: 22391645. **KQ3E4a.**
498. Tang RS, Hunt GC. Recurrent pneumothoraces after diagnostic colonoscopy. Gastroenterology 2012 May;142(5):e9-e10. PMID: 22449583. **KQ3E4a.**

499. Zandona C, Turrina S, Pasin N, et al. Medico-legal considerations in a case of splenic injury that occurred during colonoscopy. Journal of Forensic & Legal Medicine 2012 May;19(4):229-33. PMID: 22520377. **KQ3E4a.**
500. Sharma G, Boopathy SN, Juneja R, et al. Neurocardiogenic syncope during a routine colonoscopy: an uncommon malignant presentation. Internal Medicine 2012;51(8):891-3. PMID: 22504245. **KQ3E4a.**
501. Sachdev S, Thangarajah H, Keddington J. Splenic rupture after uncomplicated colonoscopy. American Journal of Emergency Medicine 2012 Mar;30(3):515-2. PMID: 21450434. **KQ3E4a.**
502. Agko M, Gociman B, Keilani ZM, et al. Cecal volvulus: a rare complication of colonoscopy. International Journal of Colorectal Disease 2012 Feb;27(2):265-6. PMID: 21538052. **KQ3E4a.**
503. Nachnani J, Burns E, Margolin D, et al. Colocolonic intussusception after colonoscopy. Gastrointest Endosc 2012 Jan;75(1):223-5. PMID: 21481863. **KQ3E4a.**
504. Sansoni I, Piccolo CL, Di G, I, et al. Portomesenteric Venous System Gas after CT Colonography: A Case Report. Case Reports in Radiology 2012;2012:420901. PMID: 23050186. **KQ3E4a.**
505. Falidas E, Anyfantakis G, Vlachos K, et al. Pneumoperitoneum, Retropneumoperitoneum, Pneumomediastinum, and Diffuse Subcutaneous Emphysema following Diagnostic Colonoscopy. Case Reports in Surgery 2012;2012:108791. PMID: 23024878. **KQ3E4a.**
506. Badiani S, Tomas-Hernandez S, Karandikar S, et al. Extracolonic findings (ECF) on CT colonography (CTC) in patients presenting with colorectal symptoms. Acta Radiologica 2013 Oct;54(8):851-62. PMID: 23761550. **KQ3E4a.**
507. Denis B, Gendre I, Sauleau EA, et al. Harms of colonoscopy in a colorectal cancer screening programme with faecal occult blood test: a population-based cohort study. Digestive & Liver Disease 2013 Jun;45(6):474-80. PMID: 23414583. **KQ3E4a.**
508. Pourmand A, Shokoohi H. Tension Pneumothorax, Pneumoperitoneum, and Cervical Emphysema following a Diagnostic Colonoscopy. Case Reports in Emergency Medicine Print 2013;2013:583287. PMID: 23819071. **KQ3E4a.**
509. Gavin DR, Valori RM, Anderson JT, et al. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK.[Erratum appears in Gut. 2013 Feb;62(2):249]. Gut 2013 Feb;62(2):242-9. PMID: 22661458. **KQ3E4a.**
510. Denadai R, Medeiros CC, Toledo AP, et al. Rectal perforation after colonoscopic polypectomy presented as subcutaneous emphysema, pneumomediastinum and pneumoretroperitoneum successfully treated conservatively in an elderly adult. Journal of the American Geriatrics Society 2013 Aug;61(8):1433-5. PMID: 23937504. **KQ3E4a.**
511. Singhal S, Changela K, Momeni M, et al. Outcome and safety of colonoscopy in minorities aged 85 and older. Journal of the American Geriatrics Society 2013 May;61(5):832-4. PMID: 23672553. **KQ3E4a.**
512. Blumenstein I, Tacke W, Bock H, et al. Prevalence of colorectal cancer and its precursor lesions in symptomatic and asymptomatic patients undergoing total colonoscopy: results of a large prospective, multicenter, controlled endoscopy study. European Journal of Gastroenterology & Hepatology 2013 May;25(5):556-61. PMID: 23283303. **KQ3E4a.**
513. Sopena-Falco J, Poch-Vall N, Brullet E, et al. Fatal massive air embolism following diagnostic colonoscopy. Eur J Radiol 2013;45:Suppl. PMID: 23526536. **KQ3E4a.**
514. Noordzij W, Slart RH, Zeebregts CJ, et al. Gastrocolocutaneous fistula detected by [8F]fluorodeoxyglucose positron emission tomography with low-dose computed tomography: a rare iatrogenic complication of colonoscopy. Eur J Radiol 2013;45:Suppl-8. PMID: 23526522. **KQ3E4a.**
515. Kim BH, Yoon SJ, Lee JY, et al. Subcutaneous emphysema, pneumomediastinum, pneumoretroperitoneum, and pneumoperitoneum secondary to colonic perforation during colonoscopy. Korean Journal of Anesthesiology 2013 Dec;65(6:Suppl):Suppl-4. PMID: 24478831. **KQ3E4a.**
516. Li Y, Li Q. Diaphragmatic hernia: a rare adverse event of colonoscopy. Eur J Radiol 2013 Nov;45:Suppl-1. PMID: 24285070. **KQ3E4a.**
517. Tan VP, Lee YT, Poon JT. Incarceration of a colonoscope in an inguinal hernia: Case report and literature review. World Journal of Gastrointestinal Endoscopy 2013 Jun 16;5(6):304-7. PMID: 23772270. **KQ3E4a.**
518. Severe rhabdomyolysis and hyponatremia induced by picosulfate and bisacodyl during the preparation of colonoscopy. Rev Esp Enferm Dig 2013 May;105(3):180-2. PMID: 23735032. **KQ3E4a.**
519. Lin BW, Thanassi W. Tension pneumoperitoneum. Journal of Emergency Medicine 2014 PMID: 18571362. **KQ3E4a.**

520. Taylor T, Williamson S, Wardle J, et al. Acceptability of flexible sigmoidoscopy screening in older adults in the United Kingdom. J Med Screen 2000;7(1):38-45. PMID: 10807146. **KQ3E5.**

521. Brasso K, Ladelund S, Frederiksen BL, et al. Psychological distress following fecal occult blood test in colorectal cancer screening--a population-based study. Scand J Gastroenterol 2010 Oct;45(10):1211-6. PMID: 20443744. **KQ3E5.**

522. Summers RM, Baecher N, Yao J, et al. Feasibility of simultaneous computed tomographic colonography and fully automated bone mineral densitometry in a single examination. Journal of Computer Assisted Tomography 2011 Mar;35(2):212-6. PMID: 21412092. **KQ3E5.**

523. Khalid-de Bakker CA, Jonkers DM, Hameeteman W, et al. Cardiopulmonary events during primary colonoscopy screening in an average risk population. Netherlands Journal of Medicine 2011 Apr;69(4):186-91. PMID: 21527807. **KQ3E5.**

524. Robb KA, Lo SH, Power E, et al. Patient-reported outcomes following flexible sigmoidoscopy screening for colorectal cancer in a demonstration screening programme in the UK. J Med Screen 2012;19(4):171-6. PMID: 23417540. **KQ3E5.**

525. Kilgert B, Rybizki L, Grottke M, et al. Prospective long-term assessment of sedation-related adverse events and patient satisfaction for upper endoscopy and colonoscopy. Digestion 2014;90(1):42-8. PMID: 25139268. **KQ3E5.**

526. Pickhardt P, Bodeen G, Brett A, et al. Comparison of Femoral Neck BMD Evaluation Obtained Using Lunar DXA and QCT With Asynchronous Calibration From CT Colonography. J Clin Densitom 2014 May 28 PMID: 24880495. **KQ3E5.**

527. Ko CW, Riffle S, Morris CG, et al. Complications after Screening and Surveillance Colonoscopy. Gastroenterology. 2007;132:A149. **KQ3E5a.**

528. Rabeneck L, Saskin R, Paszat LF. Onset and clinical course of bleeding and perforation after outpatient colonoscopy: a population-based study. Gastrointest Endosc 2011 Mar;73(3):520-3. PMID: 21195406. **KQ3E5a.**

529. Morse JW, Fowler SA, Morse AL. Endoscopist-administered propofol: a retrospective safety study. Canadian Journal of Gastroenterology 2008 Jul;22(7):617-20. PMID: 18629390. **KQ3E6.**

530. Rathore F, Sultan N, Byrne D. Tolerance of colonoscopy and questioning its utility in the elderly population. Irish Medical Journal 2014 Sep;107(8):247. PMID: 25282969. KQ3E7.

We found 12 fair-quality trials [110,111,117,121,122,126,127,129-133] in 16 articles[110,111,117,121,122,126,127,129-133,138,139,149,153] examining the comparative effectiveness of different screening tests in average-risk screening populations. We also found three fair-quality large prospective cohort studies[113,115,116] (in six articles[113,115,116,140-142]) 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);[117,131] in addition, three cohort studies[113,115,116] 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.[117,131] 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.[113,116] One cohort study did not show statistically significant difference in cancer detection between Immudia and Hemoccult II despite the higher test positivity of Immudia.[115] 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**).[130,133] 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.[130] 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.[133] 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[110,111,117,122,132] 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[110,122,132]) 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.[122] 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[117,126,127] 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%;[126] as compared to the other trial by Hol and colleagues in the Netherlands, the adherence to FIT (59%) was higher than to FS (28%).[117] 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.[126] 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[121,126] 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[126] 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[129] 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[133]	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*[130] (intervals)	1	FIT (OC-Sensor Micro), 1 year interval	64.7	8.4	4/1541	(0.3)	NR	
			FIT (OC-Sensor Micro), 2 year interval	61.0		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	6.0	1/1286	(0.08)	0/1285†	(0)
			FIT (OC-Sensor Micro), 2 year interval	62.5		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*[153] (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*[117]	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**[117,138,139]	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[116]	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[113,140]	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[141]	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 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[133]	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*[130] (intervals)	1	FIT (OC-Sensor Micro), 1 year interval	64.7	8.4	4/1541	(0.3)	NR	
			FIT (OC-Sensor Micro), 2 year interval	61.0		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	6.0	1/1286	(0.08)	0/1285†	(0)
			FIT (OC-Sensor Micro), 2 year interval	62.5		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*[153] (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*[117]	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**[117,138,139]	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[116]	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[113,140]	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[141]	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*[117]	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[126] 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[127] 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[122]	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[132]	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[121,149] COLONPREV	1	Colonoscopy	17.3	10.3	30/5059	(0.6)*	NR	
			FIT (OC-Sensor)	31.3	7.2	33/10507	(0.3)	NR	
	Segnan, 2007[126] SCORE III	1	Colonoscopy	26.5	5.1	13/1596	(0.8)‡	NR	
			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[129] COCOS	1	Colonoscopy	21.5	8.7	7/5924	(0.1)	NR	
			CTC	33.6	8.6	5/2920	(0.2)	NR	
	Segnan, 2007[126] SCORE III	1	Colonoscopy	26.5	5.1	13/1596	(0.8)	NR	
			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. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Adeyemo, 2014[210] 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[216] 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[217] 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 Fair	54,039 (1384 CTC)	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. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Chukmaitov, 2013[222] 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[223] 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[233] 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[264] 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. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Rutter, 2012‡[268] 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[246] 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[253] 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. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
Arora, 2009[213] 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[225] Fair	236,087	Mixed (including symptomatic)	Bleeding	OR (95% CI) for age squared, per year: 1.0001 (1.0001, 1.0002) p<0.0001
			Perforation	OR (95% CI) for age squared, per year: 1.0003 (1.0002, 1.0005) p<0.0001
			Cardiorespiratory complication	OR (95% CI) for age squared, per year: 1.0003 (1.0002, 1.0004) p<0.0001
Warren, 2009**[281] Good	53,220	Mixed (including symptomatic)	Serious GI events (perforation, GI bleeding, transfusion)	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)
			Cardiovascular events	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[255] 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[266] Fair	97,091	Mixed (including symptomatic)	Bleeding	OR (95% CI), multivariate Age 50-59: 1.00 60-75: 1.61 (1.20, 2.16) p= 0.001
			Perforation	Age 50-59: 1.00 60-75: 2.06 (1.79, 2.37) p<0.0001
Levin, 2006[250] 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)

Appendix E. Colonoscopy Harms by Age

Author, Year Quality	n	Recruited Population	Type of Outcome	Effect size difference by age
			Any serious complication	RR (95% CI) Age 40-59: 1.0 60+: 1.2 (0.9, 1.7)
Korman, 2003[248] 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. 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
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

Appendix F. Ongoing Studies

Study Reference Trial Identifier	Study Name	Location	Estimated N	Description	Relevant Outcomes	2015 Status
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.