Evidence Synthesis
Number 65, Part 1

Screening for Colorectal Cancer: An Updated Systematic Review

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

Prepared by:
Oregon Evidence-based Practice Center
Center for Health Research, Kaiser Permanente
3800 North Interstate Avenue
Portland, OR 97227

Investigators:
Evelyn P. Whitlock, MD MPH
Jennifer Lin, MD
Elizabeth Liles, MD
Tracy Beil, MS
Rongwei Fu, PhD
Elizabeth O'Connor, PhD
Rebecca Newton Thompson, MD, MSc
Taryn Cardenas, BS

AHRQ Publication No. 08-05-05124-EF-1

October 2008

This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10057-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. 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.

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The final version of this updated systematic review was submitted to the Agency for Healthcare Research and Quality in May 2008. This report was not made available to the public until the United States Preventive Services Task Force (USPSTF) updated recommendation for colorectal cancer screening was finalized and published through *Annals of Internal Medicine* (electronically on October 7, 2008 and in print on November 4, 2008).

A manuscript derived from this report statement (Whitlock, E.P., Lin J.S., Liles, E, Beil TL, Fu R. Screening for Colorectal Cancer: An updated systematic review for the US Preventive Services Task Force. *Ann of Intern Med* 2008; 149:638-658) was also published through *Annals of Internal Medicine* simultaneously with the updated USPSTF recommendation. This manuscript contains additional data not available at the time this evidence report was finalized, including the published results from the largest study of screening computed tomographic (CT) colonography conducted, the American College of Radiology Imaging Network (ACRIN) National CT colonography Trial 6664. Data from the ACRIN study have been incorporated into the manuscript to update the estimates of CT colonography sensitivity and specificity, referral rates after CT colonography, extracolonic findings with CT colonography, and harms with CT colonography and from screening colonoscopy. Please refer to the manuscript for updated information.

Suggested citation: Whitlock, EP, Lin J, Liles E, Beil T, Fu R, O'Connor E, Thompson RN, Cardenas T. Screening for Colorectal Cancer: An Updated Systematic Review. Evidence Synthesis No. 65, Part 1. AHRQ Publication No. 08-05124-EF-1. Rockville, Maryland, Agency for Healthcare Research and Quality, October 2008.

Acknowledgments

The authors of this report thank the peer reviewers for the evidence report (alphabetical)—James Allison, MD, Carrie Klabunde, PhD, Ted Levin, MD, Perry Pickhardt, MD, Margaret Piper, PhD, MPH, David Ransohoff, MD, Laura Seef, MD, Robert Smith, PhD, and Steve Woolf, MD, MPH; and the staff at the Oregon Evidence-based Practice Center staff— Mark Helfand, MD, MS, MPH, Kevin Lutz, MA, and Daphne Plaut, MLS.

Structured Abstract

Purpose: We conducted a systematic review of five key questions to assist the U.S. Preventive Services Task Force (USPSTF) in updating its 2002 recommendation for colorectal cancer (CRC) screening in average-risk adults aged 50 years or older using home fecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), FS *and* FOBT, colonoscopy, or double-contrast barium enema (DCBE). Key questions for this updated review primarily focused on evidence gaps from the previous review: 1) the accuracy (one-time test performance characteristics) and potential harms of newer CRC screening tests—fecal immunochemical tests (FIT), high-sensitivity FOBT, fecal DNA testing, and CT colonography (CTC)—as possible substitutes for currently recommended CRC screening modalities; 2) updating of evidence on the impact of CRC screening on mortality and to estimate the accuracy and harms of colonoscopy and FS in the community setting. A concurrent decision analysis done by others addressed screening program performance, and compared the life-years gained using different CRC screening tests, test intervals, and stopping ages.

Study Selection: We conducted five literature searches of MEDLINE and the Cochrane Library through January 2008. We identified 3948 abstracts from these searches and 488 articles identified from literature searches and outside sources, which we reviewed against specified inclusion-exclusion criteria. Articles were also excluded for quality reasons. Two reviewers' assents were required to exclude a study.

Data Extraction: One investigator abstracted key elements of all included studies into standardized evidence tables. A second reviewer verified these data. Two investigators critically appraised and quality-rated all studies. Disagreements were resolved by consensus.

Data Synthesis: We reported quantitative synthesis for results of each key question, where possible, and qualitative synthesis otherwise.

***Impact of Screening on CRC Mortality*.** We found no new studies of CRC screening that report mortality outcomes; longer-term follow-up of four biennial FOBT screening trials indicates CRC mortality was reduced 13 to 21 percent after 8 to 13 years of screening in two trials, although another two trials did not show mortality benefit until after 15 to18 years of screening. The Cochrane Collaboration's pooled estimate of CRC mortality reduction in all four FOBT trials at last follow-up was 15 percent, using either random or fixed-effect models (RR 0.85, CI: 0.78,0.92).

FITs, HemeSensa, fecal DNA. The largest body of evidence to evaluate screening test performance of newer fecal tests in average-risk screening populations is for fecal immunochemical tests (FITs), which cannot be analyzed as a class, but as individual assay types. Specifically, four individual FITs (Magstream/HemeSelect; FlexSure OBT/Hemoccult ICT; OC-Hemodia; Monohaem) have higher sensitivity for CRC (61 to 91 percent) than estimates for nonrehydrated Hemoccult II (25 to 38 percent) from another recent systematic review, with somewhat reduced specificity (91 to 97 percent). Sensitivity for advanced neoplasia or large adenomas is less commonly reported, but ranges between 20 and 67 percent in FITs, which is comparable or superior to the sensitivity for nonrehydrated Hemoccult II. Better detection appears to occur with 2 to 3

days of sample collection. For FITs, however, there is a mismatch between tests with clinical accuracy data and those with FDA approval and current US market availability. Of the four FITs discussed here, FlexSure OBT/Hemoccult ICT is the only FIT that is both FDA approved and on the US market at the time of this article.

Fewer acceptable-quality studies evaluate Hemoccult Sensa, and although it appears to improve sensitivity for CRC (64 to 80 percent), it may also lower specificity (87 to 90 percent). Clinical accuracy data on fecal DNA tests is still too limited to support population screening, and there is a mismatch between available clinical studies and commercially available tests. Where test accuracy results do not indicate superior test sensitivity with comparable specificity, determining the trade-offs between sensitivity and specificity of newer tests for fecal CRC screening in a program of CRC screening requires modeling.

CT Colonography. Published reports on CT colonography (CTC) screening suggest at least comparable sensitivity to colonoscopy for CRC and large adenomas (10 mm or larger). For smaller polyps (6 mm or larger), published data are inconsistent, with some studies suggesting reduced sensitivity or sensitivity, perhaps contingent upon the CT technology used and the individual reader. Published specificity estimates for CTC are consistently high (≥ 96 percent) for large polyps, but appear lower and more variable (80 to 94 percent) for smaller polyps (6 mm or larger). Test performance estimates will be more precise (more than doubling the number of average-risk patients studied with CTC screening) when currently unpublished data from the ACRIN study are made available. Based on currently published studies, as few as 1 in 8 to 1 in 13 of those screened with CTC would be referred for colonoscopy (if the referral threshold is CTC-detected lesions of 10 mm or greater), or, as many as 1 in 3 to 1 in 5 would be referred for colonoscopy (if the referral threshold is CTC-detected lesions of 6 mm or greater). Few procedure-related harms associated with CTC have been reported, although low-dose ionizing radiation is a potential harm. Additionally, extracolonic findings are relatively common (27 to 69 percent have any findings; 4 to 10 percent have findings of high clinical significance that require treatment or diagnostic evaluation; 5 to 27 percent have findings that would likely require investigation and/or further treatment); the net impact of all of these, in terms of added benefit (or harms), is uncertain.

Accuracy and Harms of FS and Colonoscopy in Community Settings. In community settings, FS (with or without biopsy to determine colonoscopy referral) has an estimated sensitivity of 58 to 75 percent for CRC in the entire colon (based on small numbers) and an estimated sensitivity of 72 to 86 percent for advanced neoplasia. Variations in these estimates are likely due to differences in examiner skill and the patient's risks for proximal lesions in the unexamined colon. The performance of FS screening will become more clear after results of current randomized controlled trials (RCT) are reported. While colonoscopy remains the most accurate screening test for CRC at a single application, recent CTC studies have confirmed that colonoscopy misses polyps and may also miss CRC. Colonoscopy also presents a higher risk for harms than other tests. Serious harms from community endoscopies are about ten times more common with colonoscopy (3.1 per 1000 procedures) than with FS (3.4 per 10,000 procedures). The estimates for harms from FS, however, have much wider confidence intervals.

Limitations: We reviewed the accuracy or harms of a CRC screening test in a single application for each question in this systematic review. The USPSTF commissioned a simultaneous decision analysis comparing different CRC screening programs that addressed repeated screening. Other topics beyond the scope of this review include barium enema for CRC screening, the adherence or acceptability of various CRC screening methods, methods to improve CRC screening rates, and cost-effectiveness.

Conclusions: Based on currently available evidence, refinements in current CRC screening recommendations to add some fecal tests appear warranted. Given potential harms and variation in test accuracy, emphasis on quality standards for implementation of recommended operator-dependent CRC screening tests also appears prudent. Re-evaluation may be appropriate once ongoing RCTs, particularly evaluating CTC, but also evaluating FS and fecal DNA, report their results. Screening for CRC has a rapidly evolving science base, such that guidance may be expected to change as additional research becomes available.

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I. Introduction

Scope and Purpose

We conducted this systematic review to support the USPSTF in updating its 2002 recommendation on screening for colorectal cancer (CRC).[1] The previous systematic review, on which this recommendation was based,[1,2] found direct evidence supporting the effectiveness of home fecal occult blood testing (FOBT) for decreasing disease-specific mortality. Three high-quality randomized controlled trials (RCT) of FOBT showed CRC-mortality reductions of 15 percent to 33 percent over 8 to 13 years.[3-5] The review reported a reduction in CRC incidence with flexible sigmoidoscopy (FS) screening (RR 0.20, CI: 0.03, 0.95) and a nonsignificant, but possible, reduction in CRC mortality based on the results of a small RCT of FS.[6]

The review also found evidence that sigmoidoscopy, and possibly colonoscopy, are associated with decreased mortality from CRC within reach of the endoscope. One high-quality, case-control study of rigid sigmoidoscopy found nine percent of those dying from CRC within 20 cm of the anus had had a previous sigmoidoscopy, while 24 percent of persons with CRC within 20 cm of the anus who did not die of this cancer had received the test.[7] The reduction in distal CRC mortality (adjusted OR 0.41,CI: 0.25, 0.69 was not seen in those dying of more proximal colonic cancers (adjusted OR 0.96), suggesting that screening reduced risk for death from CRC located in the sections of the colon reached by the sigmoidoscope. Evidence to support FOBT combined with sigmoidoscopy came from a nonrandomized trial suggesting a 43 percent reduction in CRC-mortality after nine years from combined testing compared with rigid sigmoidoscopy alone, although differences were not statistically significant.[8] One case-control study showed lower odds of having had a previous colonoscopy in those dying from CRC (OR 0.43, CI: 0.30, 0.73), compared to controls without CRC.[9] The previous review also cited support for colonoscopy screening from the National Polyp Study (NPS), which shows a 76 to 90 percent reduction of CRC incidence (compared to historical controls).[10] The effectiveness of barium enemas and virtual colonoscopy using CT colonography (CTC) in reducing CRC death or incidence was unknown.

During 2006, while planning the updated evidence review on colorectal cancer screening, AHRQ decided to devote some funding to a decision analysis on CRC screening to be conducted in parallel with this systematic review. The Task Force members who were designated to the colorectal cancer screening topic saw this as an opportunity to bring useful information to the Task Force's deliberations that a systematic review would not likely address, such as the optimal age to begin or end screening and considerations of repeated screening over time (screening programs).

The Task Force determined the scope for both the systematic evidence review and the decision analysis, with an eye toward these two reports providing complementary information about the important clinical questions that could inform effective use of screening in practice. The systematic review focused on the accuracy and potential harms

of newer CRC screening technologies and, to a lesser extent, on updating test accuracy and harms data on already-recommended screening tests. The decision analysis focused on projected benefits to a cohort beginning CRC screening at age 40 years or later for different screening strategies, different beginning and ending ages, and different intervals for re-screening after a normal test, with varying screening test adherence.[11] These two reports were used together by the USPSTF to make its updated recommendation on CRC screening.

As an update, this report extends the time period of the previous report to update information on several currently recommended CRC screening tests (e.g., FOBT, FS, and colonoscopy); the update is limited to important supplemental data on screening test performance, benefits, and harms. The scope of this report was expanded to include the evidence for screening test performance, benefits, and harms of newer CRC screening tests not previously recommended by the USPSTF (e.g., high-sensitivity guaiac fecal occult blood tests (HS-FOBT), fecal immunochemical fecal tests (FITs), fecal DNA tests, and CTC). The USPSTF chose not to update the evidence on DCBE as a CRC screening test (see Methods section for rationale). This report does not address the effectiveness of screening programs based on these tests, as the concurrent decision analysis addresses this topic.

Background

Condition Definition

Colorectal cancer or colorectal adenocarcinoma (CRC) is a malignant tumor arising within the walls of the large intestine, including the segments in 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 that are considered precancerous lesions. Adenomas can have different degrees of dysplasia or different histologic characteristics (tubular, tubulovillous, and villous) associated with increasing malignant potential. Carcinoma *in situ* refers to adenomas with severe dysplasia, while lesions that invade the muscularis mucosa are considered adenocarcinomas. Advanced neoplasia refers to a composite outcome including adenocarcinoma, adenomas with high grade dysplasia or villous histology, and adenomas 10 mm or greater in diameter.

Burden of Preventable Illness

CRC continues to cause significant morbidity and mortality in the United States. Among all cancers, CRC ranks third in incidence and second in cause of cancer death for both men and women.[12] While overall CRC-related death rates in both men and women have recently declined, the increasing proportion of individuals over the age of 65 in the US is expected to increase the absolute number of CRC deaths.[13] Statistics from the National Cancer Institute (NCI) indicate that the annual incidence of CRC in the US is 52.0 cases per 100,000 persons,[14] with more than 90 percent of diagnoses occurring in individuals over the age of 50 years.[15] The lifetime risk of CRC is approximately 5.9 percent for men and 5.4 percent women, with a lifetime mortality rate of 2.4 percent and 3.3 percent respectively.[16]

Screening for CRC can impact both primary prevention (finding precancerous polyps that could later become malignant) and secondary prevention (detecting early cancers that can be more effectively treated). While there is general consensus that CRC screening reduces disease-specific mortality, newer screening tests have created uncertainty about the optimal methods for CRC screening in the general population.

Burden of disease by socio-demographic factors. Increasing age, male sex, and Black race are associated with an increased incidence of new CRC cases (see Table 1). Age-adjusted incidence rates for CRC are higher in men than women: 60.8 versus 44.6 per 100,000 persons (see Table 2). Blacks have the highest incidence of CRC among the racial/ethnic subgroups, 72.6 and 55.0 per 100,000 persons, respectively (See Table 1). Blacks also have a disproportionately high disease-specific mortality.[17-21] Over the past 20 years, CRC mortality rates have decreased more among Whites than Blacks.[22] While the overall annual CRC-related death rate is 19.2 deaths per 100,000 persons, the rate for Blacks is 26.4 per 100,000 persons, which is nearly double the mortality for Hispanics, Asian/PI, and AI/AN individuals.[15]

Anatomic location of CRC by socio-demographic factors. Age, sex, and race/ethnicity also appear to influence the anatomic distribution of CRC (see Table 2). Data from the NCI's Surveillance, Epidemiology, and End Results Program (SEER) demonstrate a proximal migration of CRC over the past two decades, which is attributed to a decrease in incidence of distal CRCs, and an aging population in which proximal lesions are more common.[23] This proximal migration appears in both men and women, and in Whites and Blacks.[23] SEER data from 2000 to 2004 suggest that the current age-adjusted ratio for proximal CRC incidence is highest among Blacks for both men and women (Table 2).[24] This difference between Whites and Blacks was not evident during the 1970s.[22]

Risk Factors

Most cases of CRC are sporadic, with 75 percent of cases developing in average-risk persons, versus about 20 percent of cases 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 genetic mutation, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), and I1307K, which is prevalent in Ashkenazi Jews.[24-27]

Case-control and cohort studies indicate an approximately two-fold increase in CRC risk for persons with a first-degree relative (e.g., parent, sibling, or child) with CRC. This increased risk is also applicable to first-degree relatives of individuals with colorectal adenomas.[26,28-37] CRC may be associated with nongenetic risk factors, such as smoking or obesity, although evidence is limited to case-control and cross-sectional data.[38] There has been substantial progress in understanding the molecular genetics of colorectal cancer, and these scientific advances underpin the efforts to develop DNA testing (fecal or plasma) for CRC detection.

Natural History

Impact of polypectomy on natural history and CRC incidence. It is estimated that at least 95 percent of colorectal cancers arise from preexisting polypoid or flat

adenomas.[39,40] The notion of an adenoma-carcinoma sequence stems from observations of a greatly elevated CRC risk status for patients with hereditary polyposis syndromes[41,42] and from observational studies showing an estimated 60 to 90 percent reduction in CRC incidence after polypectomy during colonoscopy or FS.[6,7,10,43-46]

The most commonly cited study, the National Polyp Study (NPS), reported a 76 to 90 percent reduction in observed CRC incidence over about 6 years in a surveillance cohort following colonoscopy and polypectomy for newly detected adenomas, compared with expected rates derived from three historical control cohorts.[10] In a similar Italian study, the observed CRC incidence over 10 years was reduced by about 66 percent in a surveillance cohort of persons with newly detected adenomas (5mm or larger) who underwent colonoscopy and polypectomy, compared with expected rates derived from a statistically modeled reference cohort.[44] While these estimates are widely cited, they should be interpreted with caution as both studies relied on historical controls for comparison, which can be unreliable. In addition, these estimates may have limited generalizability, given the extremely low incidence of CRC in these two observational studies. Large dietary-intervention and chemoprevention trials to prevent CRC report post-polypectomy CRC incidence rates three to four times higher than those seen in the two aforementioned observational studies.[47-51] While the difference in CRC incidence rates between these studies are likely multi-factorial (i.e., due to both population and study design characteristics), this issue is beyond the scope of our review, but is explored elsewhere.[40,52]

Additional evidence for the reduction in CRC incidence or mortality comes from FS studies. The most convincing evidence from sigmoidoscopy studies comes from well done case-control studies that have demonstrated a decrease in CRC mortality, and in some cases, in CRC incidence. The landmark case-control study by Selby and colleagues found a 60 percent reduction in mortality from distal CRC over 10 years in persons who received rigid sigmoidoscopes with polypectomy, compared to matched contemporaneous controls (adjusted for previous CRC, family history of CRC, and number of periodic health checkups).[7] These results have been reproduced in subsequent well done case-control studies,[9,45] one of which showed a probable reduction in CRC incidence.[46] In the Telemark Polyp Study, the observed CRC incidence was reduced by about 80 percent after 13 years in a screening cohort of 400 adults undergoing FS, followed by colonoscopy and polypectomy, and by surveillance, compared with a concurrent control cohort of 399 adults receiving no CRC screening (10 cancers in the control group compared with 2 in the screening group).[6] However, no clear CRC mortality benefit was seen (1 CRC death vs. 3 deaths in the controls) and there was a higher overall mortality rate reported in the screening group (RR 1.57, CI: 1.03, 2.4), which is difficult to interpret.

Despite the uncertainty around magnitude of benefit, these studies give us the best available estimates of polypectomy's impact on CRC incidence. We cannot definitively articulate the degree of CRC incidence reduction, however, due to CRC screening and resulting polypectomies without randomized controlled trials.

Significance of polyp size. While there is general agreement that the risk of in-dwelling cancer, or progression to cancer, for polyps 10 mm or larger is sufficient to require immediate removal, the necessity and benefit of removing small polyps is not clear.[53,54]

Sensitivity estimates for optical methods (e.g., CTC, FS, and colonoscopy) depend on the threshold for the size of polyp considered clinically meaningful. The threshold for polyp size also determines the number of colonscopy referrals that will result from primary CTC and other visualization-only screening methods.

No large observational studies are available to determine the consequences of untreated adenomas. One small observational study (n=226) of patients with unresected polyps greater than 10 mm found that 37 percent of polyps enlarged over a mean followup time of 68 months. The cumulative risk of malignancy at the polyp site at 5, 10, and 20 years was 2.5 percent, 8 percent, and 24 percent respectively.[55] The natural history of smaller adenomas, particularly those of different sizes (e.g., 5 mm or under, 6 to 9 mm), is unknown. Pilot-sized studies of all small (<10 mm) adenomatous polyps observed *in situ* by serial endoscopy suggest that many remain dormant or regress during a 2-3 year period. The tendency towards 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.[56,57]

Cross-sectional studies using colonoscopy registries report CRC prevalence in polyps of various sizes. The overall CRC prevalence in any-sized lesion found in screening colonoscopy studies in the US is approximately 0.4 percent.[58-69] A study from the Clinical Outcomes Research Initiative (CORI) database of 1,137 average-risk patients, whose largest polyp was 6-9 mm on screening colonoscopy, found invasive cancer in only two patients at the time of colonoscopy (0.2 percent).[70] Other colonoscopy database studies (that include high-risk populations) indicate that the prevalence of CRC in lesions less than 6 mm in diameter ranges from zero to 0.8 percent. The prevalence in lesions 6-9 mm ranges from 0.4 percent to 1.1 percent.[71-75] While advanced neoplasia (see below) is somewhat more common than CRC in small polyps, the clinical significance of advanced neoplasia is unknown.

Advanced neoplasia. Current efforts to characterize the accuracy of optical screening methods have evaluated the sensitivity of different tests not only for CRC, but also for advanced neoplasia. Advanced neoplasia is a composite endpoint defined as an adenoma 10 mm or greater in size, or a smaller adenoma with at least 25 percent villous histology, or those containing high-grade dysplasia or invasive carcinoma. It is therefore important to understand both the impact of polypectomy of advanced neoplasias on risk of future CRC, and conversely the impact of leaving an advanced neoplastic lesion intact on risk of future CRC. In a followup of 1618 patients with rectosigmoid adenomas removed during sigmoidoscopy and polypectomy, the risk of subsequent CRC was increased at least three-fold in those with tubulovillous, villous, or large ($\geq$ 10 mm) adenomas, compared with those with other types of rectosigmoid adenomas.[76] The perceived increase in malignant potential of advanced neoplastic lesions is also derived from examining the prevalence of adenocarcinoma polyps removed during colonoscopies or from consecutive surgical specimens at a single institution. In these cross-sectional studies, the approximate prevalence of invasive carcinoma among polyps varied by histology. Invasive carcinomas in polyps with surface villous histology ranged from 10 to 40 percent, from 6 to 23 percent among polyps with surface tubulovillous histology, from 2 to 5 percent among polyps with surface tubular histology,[77-80] and were 34.1 percent among polyps with surface advanced dysplasia.[77]

There have been no prospective studies describing the natural history of advanced neoplasia, and no longitudinal studies have validated the clinical benefit of targeting advanced neoplasia in screening populations. The results of three FS trials using advanced neoplasia criteria as a threshold for colonoscopy referral are pending.[81-83]

Flat and depressed adenomas. The prevalence of flat and depressed (nonpolypoid) adenomas in screening populations is largely unknown. However, one recent study in US veterans suggests that nonpolypoid colorectal neoplasms are relatively common, present in about 6 percent of the screening group and in about 15 percent of the asymptomatic surveillance group.[84] The advent of dye-spraying and magnified examination of the colon using chromoendoscopy allows better detection of flat and depressed lesions than standard colonoscopy.[84-87] In British studies of high-risk populations, flat and depressed lesions were more likely to contain advanced dysplasia or invasive cancer than polypoid lesions,[88,89] with a doubling of the odds of carcinoma in flat or depressed lesions compared with polypoid lesions in US veterans undergoing screening (OR 2.01, CI: 0.27, 15.3).[84] In contrast, investigators in the National Polyp study found no increase in risk for high-grade dysplasia initially, or at surveillance, within flat adenomas when compared to polypoid adenomas.[90-92] The Japan Polyp Study is currently examining the incidence of CRC during a followup surveillance exam at 2 versus 4 years after patients have had two serial chromoendoscopy clearing examinations.[93]

Colorectal Cancer Screening

Rationale and current practice. Colorectal cancer meets the criteria for a screening condition—it is prevalent and has a known preclinical period during which the majority of CRC develops from precursor lesions, such as adenomatous or other histologically advanced polyps. Based on evidence from randomized controlled trials (RCT), a screening program using simple, reasonably acceptable, guaiac fecal occult blood screening tests reduces CRC mortality when used with repeated application over time and endoscopic followup of positive results.[94] Other screening approaches are recommended based on extrapolation from the RCT evidence of screening program effectiveness, on specific test accuracy, and on other studies supporting an expected benefit from these tests when applied in a program of screening. No current CRC screening tests, however, are without drawbacks, including potential harms, limited accessibility, or imperfect acceptability to patients. Ongoing research aims to make more accurate screening tests available to further improve CRC screening programs.

Despite multiple professional organizations recommending CRC screening for all individuals 50 years of age or older,[95-98] serial national surveys document relatively low rates of CRC screening in the US, although these rates do appear to be increasing over time.[99-104] Between 2002 and 2004, the number of states (including District of Columbia) where 60 percent or more of the population aged 50 years or older had been screened for CRC increased from eight states in 2002 to 15 in 2004.[105] In the 2006 Behavioral Risk Factor Surveillance survey 60.8 percent of adults 50 years or older reported recent colorectal screening using either endoscopy in the preceeding 10 years, or FOBT within the past year.[104] There is also increasing evidence of race/ethnic and sex disparities in CRC screening, with lower rates of CRC screening in Nonwhite and Hispanic

populations,[103,106,107] fewer colonoscopies in women,[103,106] and lower screening rates in areas with higher poverty rates.[108]

CRC screening tests commonly used in primary care include home FOBT, FS, and colonoscopy.[100,103,109] Colonoscopy utilization for CRC screening has increased recently, and use of FS has decreased,[110] due largely to the Center for Medicare and Medicaid Service's 2001 decision to cover screening colonoscopy for patients on Medicare, and similar decisions by private pay insurers. Public perceptions of accuracy also play an important role in this issue.[103] Significant variation in community CRC screening practices, which may impact effectiveness of screening, has also been reported. Some primary care providers rely on in-office FOBT, for example, which has different test characteristics than home FOBT, the test which has been shown to be efficacious.[111] There also appears to be variation in practice for followup of positive FOBT (e.g., using FS instead of colonoscopy).[112] Lastly, there remains significant variation in operator characteristics for endoscopies, both FS and colonoscopy, which may affect test characteristics for screening and confirmatory endoscopy.[52]

While issues of test acceptability to patients and available capacity are important concepts for considering screening tests, exploring these issues was beyond the scope of this report. Similarly, recommended methods of surveillance in those who have screened positive was beyond the scope of this report, but has been reviewed by others.[96,113]

Previous USPSTF Recommendation

In 2002, the USPSTF issued the following recommendations about screening for colorectal cancer:

> *The USPSTF strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer. (A Recommendation)*
>
> *Rationale: The USPSTF found fair-to-good evidence that several screening methods are effective in reducing mortality from colorectal cancer. The USPSTF concluded that the benefits from screening substantially outweigh potential harms, but the quality of evidence, magnitude of benefit, and potential harms vary with each method.*
>
> *The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality. The USPSTF did not find direct evidence that screening colonoscopy is effective in reducing colorectal cancer mortality; efficacy of colonoscopy is supported by its integral role in trials of FOBT, extrapolation from sigmoidoscopy studies, limited case-control evidence, and the ability of colonoscopy to inspect the proximal colon. Double-contrast barium enema offers an alternative means of whole-bowel examination, but it is less sensitive than colonoscopy, and there is no direct evidence that it is effective in reducing mortality rates. The USPSTF found insufficient evidence that newer screening technologies (for example, computed tomographic colonography) are effective in improving health outcomes.*

II. Methods

This review's methods were based primarily on established USPSTF methods for systematic reviews.[114] Appendix A includes a more detailed description of our methods.

Under the guidance of the USPSTF, we developed an analytic framework and five key questions (Figure 1), which received final approval from USPSTF liaisons. This report's scope differed from the 2002 USPSTF evidence report in several important ways:

1. We did not update the direct evidence on standard FOBT screening. We did, however, examine longer-term followup results from the original trials included in the 2002 report, as this evidence was foundational for the last recommendation.
2. We did not update evidence on CRC screening methods not recommended after the last review (e.g., digital rectal exam) or omitted from this review by the USPSTF during the scoping phase (e.g. DCBE) due to poor test-performance characteristics. A single study (n=580) from the previous 2002 evidence report found that DCBE as a surveillance method after adenomatous polypectomy (with comparison to colonoscopy as the gold standard) showed a sensitivity of only 48 percent (CI: 24, 67) for polyps larger than 10 mm. A more recent study in a high-risk screening and diagnostic-evaluation population compared DCBE to both colonoscopy and CTC. This study found similarly low sensitivity estimates for large polyps.[115] Given its confirmed low sensitivity for one of the main targets of screening (lesions 10 mm or larger), DCBE as a primary CRC screening test was excluded from the review.
3. We did not systematically review screening-test adherence, acceptability, and feasibility. Similarly, the USPSTF judged that a thorough review of cost-effectiveness analyses was beyond the scope of our review, particularly since the USPSTF was conducting a simultaneous decision analysis. Since the separate decision analysis also examined screening intervals and ages to begin and end screening, these were not included in this systematic review.

KQ1 examined direct evidence from RCT, cohort studies, or case-control studies, that screening programs (single or repeated application of screening tests) for colorectal cancer in average-risk adults, aged 40 years and older, reduce mortality. KQ2a examined the accuracy of colonoscopy and/or FS for CRC screening in average-risk persons in the community practice setting. KQ2b examined the accuracy of CTC and fecal screening tests, including high-sensitivity guaiac FOBT, fecal immunochemical test (FIT), and fecal DNA tests in average-risk persons. For KQ2a and 2b, test accuracy was derived from comparison with a valid reference standard (e.g., colonoscopy to all participants) or an acceptable reference standard (e.g., colonoscopy to all positive tests with adequate followup of test negatives). KQ3a examined the adverse effects of colonoscopy or sigmoidoscopy for CRC screening in the community practice setting. KQ3b examined the adverse effects of CTC and fecal screening tests for CRC screening. Summarized results of each key question (text and tables) are presented within the body of the report. Additional study details and corresponding evidence tables can be found in the appendices, along with the corresponding evidence tables.

We searched PubMed, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), Institute of Medicine (IOM), National Institute for Health and Clinical Excellence (NICE), and Health Technology Assessment (HTA) databases for recent systematic reviews (1999-2006) for all key questions. We used fair- or good-quality existing research syntheses when available, supplemented with primary literature searches bridging the search windows of relevant systematic reviews and meta-analyses. We developed literature search strategies and terms for each KQ (see Appendix A, Table 1), with search dates guided by existing systematic reviews (including the 2002 UPSPTF report) and the timing of screening technology development.

We conducted five separate literature searches through January 2008 in both Medline and Cochrane Central Register of Controlled Trials (CCRCT) (detailed in Appendix A, Table 1). All abstracts were coded for inclusion/exclusion for all key questions.

For KQ1 (mortality outcomes of screening) and KQ2a (accuracy of FS and colonoscopy), we found no systematic reviews conforming to our inclusion and exclusion criteria more recent than the 2002 USPSTF review. Therefore, we searched for newly published primary literature beginning in January, 2000.

KQ2b (test performance characteristics of newer screening tests) required separate approaches for each of the three test types. For CTC, we used a good-quality systematic review published in 2005[116] as a foundation, supplemented with additional studies identified through five other systematic reviews (published between 2003 and 2006)[117-121] and our own search of primary literature beginning in January, 2006. For FIT, we conducted our own searches beginning in 1990, when the early literature was first being published. We confirmed our search results using two technical reports published during the review.[122,123] We used a good-quality Technical Evaluation Center assessment that searched through June 2006[124] as the basis for fecal DNA test literature, supplemented by two additional systematic reviews.[125,126] Using this review as our foundation, we searched for new primary literature published since January 2006.

For KQ3a and KQ3b (harms of screening tests) we found no synthesized evidence that could be used as a foundation for the current review. Therefore, we searched Medline and CCRCT beginning in January 2000 for newly published studies conducted in a community setting or, at a minimum, studies that included only asymptomatic individuals, the majority of whom are at average risk for CRC. We developed two search strategies: one comprehensive strategy that yielded many irrelevant abstracts, and one more focused strategy that produced fewer irrelevant abstracts. Although our pilot-testing of the more focused strategy suggested that it was sufficiently comprehensive, we coded all the abstracts from the broader strategy for articles published between January 2006 and January 2007.

Two investigators reviewed all 3948 abstracts identified by these searches. We evaluated 488 articles located through the searchs, the previous 2002 evidence report and outside sources against a set of inclusion/exclusion criteria for each key question, including design-specific quality criteria based on the USPSTF's methods (Appendix A, Table 3). We supplemented these methods with the National Institute for Health and

Clinical Excellence (NICE) and Oxman criteria for systematic reviews.[127,128] Detailed inclusion and exclusion criteria are included in Appendix A, Detailed Methods. Two investigators reviewed articles against inclusion and exclusion criteria and critically appraised all studies fulfilling inclusion criteria. Some articles were then excluded for quality reasons. One investigator abstracted data from included studies into evidence tables. A second investigator verified the evidence tables' content.

Due to study design and limitations in reporting for two of the studies evaluating CTC test performance, we calculated point estimates for per person sensitivity and specificity and their respective confidence intervals. For additional details see Appendix A, Detailed Methods.

Because of the stringency of our inclusion criteria for studies to estimate rates of endoscopy harms in the community practice setting (KQ3a), included studies were clinically homogeneous to pool. We conducted full meta-analyses using Stata v9.2 "meta" command for KQ3a to estimate combined complication rates for serious bleeding (with colonoscopy), perforation (with colonoscopy), and any serious complications (with colonoscopy or FS). Several studies reported that their patients experienced no adverse events. Therefore, we used a random-effects logistic model to include studies without adverse events[129,130] and estimate combined complication rates. A description of our model is included in Appendix A, Detailed Methods. Exploratory meta-regressions were conducted using random-effects logistic models to examine the association of the following study-level characteristics: study design; study setting by country; and population characteristics, including age range and indication for endoscopy, with complication rate. The analyses were performed using the NLMIXED procedure in SAS v9.1.

USPSTF Involvement

The authors worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework questions, to address methodological decisions on applicable evidence, 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, reviewed the draft report, and assisted in external review of the draft-evidence synthesis.

III. Key Questions & Results

We condensed the findings for each key question into a summary table and abbreviated text summarizing these studies, which makes presenting the large number of detailed studies possible. Details for each of the studies included in each key question are addressed in the detailed evidence tables and descriptive text included in the Appendices. Where 95 percent confidence intervals are reported, they are abbreviated as "CI".

Key Question 1. What is the effectiveness of the following screening methods (alone or in combination) in reducing *mortality* from colorectal cancer: flexible sigmoidoscopy (FS), colonoscopy, CT colonography (CTC), fecal screening tests?

We found no new trials or well-designed cohort or case-control studies of FOBT screening programs reporting mortality. Recent publications, however, provide data on longer-term followup after 12-18 years in two of the three RCTs of FOBT screening programs included in the previous USPSTF report.[131,132] Additionally, another FOBT trial[133] included in the previous report has made mortality data available to other authors for meta-analysis.[94] For other established CRC screening modalities (e.g., colonoscopy or FS), and for newer CRC screening methods (e.g., CTC, new fecal screening tests), we found no new trials or well-designed cohort or case-control studies that reported CRC mortality, and no reports of longer-term followup of previously identified trials.

Mortality data from the longest time point of followup for each of the FOBT screening trials is included in Table 3. While biennial FOBT screening programs generally reduced CRC mortality 13 to 21 percent after 8 to 13 years of screening,[3,4,132,134] two trials did not show mortality benefit until after 15-18 years of screening.[94,135] All trials used the Hemoccult II brand of FOBT, but screening programs differed in several important ways: 1) whether they rehydrated the FOBT samples prior to testing; 2) what number of positive FOBT results defined a "test positive"; and 3) the work-up used for positive FOBT results. In one trial that reported a 16 percent CRC mortality reduction after 17 years of biennial screening using nonrehydrated FOBT,[131] recalculation of CRC mortality after including CRC treatment-related deaths, however, reduced this benefit to 11 percent (no longer a statistically significant reduction). We were unable to interpret this finding, due to very limited details about how deaths were classified. And, while none of these trials found a reduction in all-cause mortality from screening, two issues in these trials undermine the expectation for an effect on all-cause mortality; first, CRC mortality was a relatively low contributor to overall mortality; and, second, there was limited power. Both issues lead to a loss of precision in estimates of all-cause mortality.

Key Question 2a. What are the sensitivity and specificity of (1) colonoscopy, and (2) flexible sigmoidoscopy (FS) when used to screen for CRC in the community practice setting?

Colonoscopy

Estimating the sensitivity and specificity for screening colonoscopy is challenging due to lack of a true gold standard. Also, most available studies have selected practitioners who were quite experienced and not necessarily representative of community practice. We considered studies that estimated sensitivity of colonoscopy in average-risk screening patients using tandem colonoscopy, or by analyzing the accuracy of initial colonoscopy in studies primarily examining the accuracy of CTC screening. No tandem colonoscopy studies evaluated average-risk populations, and most included only very experienced, as opposed to community-based, examiners. Thus, none of the tandem colonoscopy studies met our inclusion/exclusion criteria. Sensitivity estimates for colonoscopy were available from three CTC screening studies in average-risk screening patients that used segmental unblinding or second-look colonoscopy to evaluate lesions detected by CTC but missed on initial colonoscopy. While these studies all addressed average-risk patients and used an enhanced reference standard (second-look colonoscopy), they are limited in providing an accurate estimate of relative test performance and of community test performance for these two CRC screening approaches. First, the number of patients studied is small. Second, the designs compared the performance of larger number (between five and 50) of experienced colonoscopists to the performance of a smaller number (between two and six) of experienced radiologists using a range of technological approaches to CTC.

Sensitivity of screening colonoscopy. In a good-quality cross-sectional comparison, Pickhardt et al.[136] examined the sensitivity of same-day colonoscopy compared with CTC in 1,233 individuals in three medical centers in the United States. Subjects were asymptomatic adults (mean age 57.8 years) with no personal history of polyps, CRC, inflammatory bowel disease, or familial polyposis syndrome who were referred for colorectal cancer screening. CTC was conducted using fecal tagging with oral contrast. One of 6 trained radiologists using a commercially available CTC system interpreted the results. The radiologists viewed the colon initially using the 3D endoluminal fly-through view for detecting polyps (using 1.25-2.5 mm collimation), then used 2D images for confirmation and problem-solving. One of 17 experienced colonoscopists performed optical colonoscopy immediately after CTC interpretation using standard commercial video colonoscopes, with unblinding of the CTC results after examination of each segment of colon. For any suspected polyp seen on CTC that measured 5 mm or greater, which was not seen on the initial blinded colonoscopy, the colonoscopist closely reexamined that segment and could review the CTC images for guidance. The accuracy (represented by lower adenoma miss rates) of colonoscopy exceeded that of CTC for adenomas equal to or greater than 6 mm in size (10 vs. 14 percent), however miss rates

were higher for colonoscopy than for CTC for larger adenomas ≥10 mm; and none of these differences were statistically significant. Sensitivity (per person detection rate) for colonoscopy was 92 percent (155/168) for patients with adenomas ≥ 6 mm in size, compared with 89 percent (149/168) for CTC; sensitivity of colonoscopy was 92 percent (75/82) for patients with an adenoma ≥ 8 mm in size, compared with 94 percent (77/82) for CTC; and sensitivity of colonoscopy was 88 percent (42/48) for patients with an adenoma ≥ 10 mm, compared with 94 percent (45/48) for CTC; none of these differences was statistically significant. Colonoscopy detected only one of two colorectal cancers (50 percent sensitivity), whereas CTC detected both colorectal cancers. The six radiologists reading the CTC had received training reading a minimum of 25 studies, and two had interpreted > 100 studies. The 17 colonoscopists were characterized as "experienced."

A smaller fair-quality study by Kim et al.[137] compared various approaches to CTC in 96 individuals agreeing to participate in a screening study in Seoul, Korea, and also reported on the the detection of polyps by colonoscopy. Subjects were adults (mean age 54.8 years) with no history of polypectomy during the previous year, no positive FOBT or iron-deficiency anemia during the previous six months, no history of colorectal surgery, and no history of inflammatory bowel disease or familial adenomatous polyposis. Initial CTC readings were conducted by 1 of 2 radiologists with previous experience from at least 100 colonoscopy-proven CTC examinations. All images were 2 mm-slice thickness. One of the two radiologists initially viewed 2D transverse images, with 2D coronal and sagittal images and 3D endoluminal views as secondary techniques to better characterize any lesions. The other radiologist used a 3D-380 degree (virtual dissection) circular view for primary viewing, with 2D tranverse or multiplanar reconstruction images used to clarify any lesions found. Within 2 hours after CTC was completed, one of five board-certified gastroenterologists, each with 7-15 years of clinical experience, performed a colonoscopy with segmental unblinding to the CTC results. Colonoscopy detected 90 percent (35/39) of polyps ≥ 6 mm in size and all polyps 10 mm or larger (12/12). This study detected no CRC. Per-person detection (sensitivity) for colonoscopy was not directly reported.

A fair-quality study by Johnson et al[138] comparing various CTC approaches in 452 asymptomatic, average-risk patients at the Mayo Clinic also reported colonoscopy performance using retrospective review of videotaped colonoscopies. Subjects were adults (mean age 65 years.) with no personal history of gastrointestinal symptoms, inflammatory bowel disease, or familial adenomatous polyposis. Initial CTC readings were conducted by two of three experienced radiologists using one of two search methods: 2D or 3D. The primary 2D search method utilized a conventional 2D image display with 3D endoluminal problem solving, whereas the primary 3D search method utilized a 360-degree virtual dissection image display, which can display both multiplanar 2D and 3D perspective volume-rendered images for problem solving. Different slice thicknesses for CTC, 1.25 vs 2.5 mm, were also viewed within each subgroup. All three CTC reviewers had interpreted more than 1,000 colonoscopy-verified CTC examinations before this study, and had trained on at least 50 cases using 360-degree virtual dissection software before the study. Same-day index colonoscopy was performed (or supervised) by one of 50 experienced staff gastroenterologists and colorectal surgeons, blinded to the CTC results (and without segmental unblinding). Colonoscopy videotapes were reviewed

if lesions of > 5 mm were identified on CTC but not during colonoscopy. Repeat colonoscopy was performed in six patients in whom a large (≥ 10 mm) missed lesion was deemed by consensus to have a high likelihood of being a true neoplasm. Colonoscopy detected 77 percent (20/26) of all neoplasms ≥10 mm in diameter. Four of the missed lesions were later determined to be adenocarcinomas. Colonoscopy therefore detected one of the five CRCs detected by CTC (20 percent). This study is limited since not all cases with a discrepancy between CTC and colonoscopy had a confirmatory examination. Further, the performance of three very experienced radiologists was compared to that of 50 experienced endoscopists (or more, since some examinations were only supervised and not performed by this group).

Flexible Sigmoidoscopy (FS)

No studies reported the sensitivity and specificity of flexible sigmoidoscopy (FS) for CRC, advanced neoplasia, or adenomas by size, based on conducting both FS and colonoscopy in all average-risk screening patients. We therefore relied on three approaches to estimate accuracy of community FS. The first method is tandem FS studies that determine miss rates for the distal colon only, i.e. can apply only to lesions that lie within the reach of the sigmoidoscope. Although the reach of FS is variable, and may be better with current generation instruments, estimates are of a mean insertion depth ranging from approximately 40 up to 60 cm.[139,140] Another method for determining miss rates for the distal colon is to conduct repeated FS examination up to 3 years after a negative FS examination. While some lesions detected at three years may not have been present at the initial FS, given the natural history of adenoma progression, a maximum of three years for followup of negative lesions on an initial FS can fairly approximate miss rates. A final method was using studies of screening colonoscopy to simulate how screening FS, followed by colonoscopy examinations in those with findings on FS, would perform in detecting lesions in the entire colon. Researchers have used this approach to estimate the sensitivity of various FS protocols (i.e., FS with and without biopsy to determine referral for colonoscopy). The results from this FS protocol are estimates using findings of the initial FS and the results of that followup examination. This construct assumes 100 percent referral and compliance with followup colonoscopy for positive FS examinations. Sensitivity calculations from the studies reviewed here were for either a FS protocol using biopsy and referral for adenomas, or a FS protocol using visualization alone (without biopsy) and referral for all distal lesions. We calculated sensitivity of each type of FS protocol for all outcomes (CRC, adenomas by size, and advanced neoplasia), when possible.

Adenoma miss rates for flexible sigmoidoscopy. We found a single tandem FS study[141] describing adenoma miss rates, and two large, high-quality prospective studies that reported the incidence of advanced neoplasia and CRC in the distal colon during repeat FS 3 years after a negative screening FS exam.[142,143] All three FS studies were conducted in average-risk screening populations, predominantly involving people with no family history of colorectal cancer. Among 328 patients undergoing tandem FS in a community setting, the overall adenoma miss rate for polyps of any size was 20 percent.[141] The miss rate for large adenomas (≥ 10 mm in diameter) was 14.3 percent (2/14). The miss rate for adenomas 6 mm or greater was 19 percent (4/21). Both prospective followups of negative

screening FS in average-risk populations (combined n=10,232) showed that approximately 0.8 percent of patients had advanced neoplasia in the distal colon viewed on a second FS conducted three years later. There were no adenocarcinomas detected in the distal colon three years after a negative screening examination.

Calculated sensitivity of flexible sigmoidoscopy with and without biopsy. The relationship of distal colon findings to proximal lesions has recently been studied in large cohorts of average-risk patients undergoing screening colonoscopy (see Table 4).[58,60,61,144-146] Three studies included up to 16 percent of patients with CRC in a first-degree relative, although many studies did not report this data. The distal examination of the colon (defined as the rectum, sigmoid, and descending colon up to, but not including, the splenic flexure) served as a surrogate for the reach of a FS examination. All investigators excluded patients who had gastrointestinal symptoms (e.g., abdominal pain, change in bowel habits, rectal bleeding) and patients with a history of colon disease (e.g., inflammatory bowel disease, polyps, or colorectal cancer). Four of the six studies[58,60,61,144] also excluded patients who had been screened with a FS or colonoscopy during the previous 5-10 years. Four of these six studies were conducted in the US.[58,60,61,146] The prevalence of CRC (0.1 to 1.0 percent) in a single examination with standard colonoscopy was fairly consistent among the five studies reporting this data. The prevalence of advanced neoplasms (defined as any adenoma 10 mm or larger, or with villous features, severe dysplasia, or carcinoma) anywhere in the colon varied more widely between the six studies, ranging from 2.4 to 10.5 percent. These lesions were more prevalent in studies of male veterans[60] and females from military medical centers.[61] The prevalence of proximal advanced neoplasia ranged from 0.9 percent to 4.1 percent. Isolated proximal advanced neoplasia (proximal neoplasias in those with no adenomas in the distal colon) varied from 0.8 percent to 3.2 percent among average-risk patients. It is important to bear in mind that, for all of these sensitivity estimates, using colonoscopic examination of the distal colon as a surrogate for FS may result in an overestimation of sensitivity due to superior bowel preparation for colonoscopy. And, examiner skill for colonoscopy may also vary from that for FS, particularly in the community setting.

Simulated protocol for flexible sigmoidoscopy without biopsy. FS without biopsy is the traditional and lower-risk method of performing this test. The appropriate polyp size threshold for referral to colonoscopy is not well-established, and thus colonoscopy referral often follows detection of any lesion on FS. The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening trial in the United States is currently examining CRC incidence and mortality rates after FS without biopsy, and pending results may also clarify how screening outcomes are related to different distal polyp size thresholds for referral. Our estimates of sensitivity for the FS without biopsy protocol assumed that a polyp of any size found on FS would prompt colonoscopy referral, which is the same protocol as for the PLCO trial.[147]

Only two screening colonoscopy studies (in three publications) provided data allowing the calculation of the sensitivity of FS without biopsy in average-risk adults.[59,60,146] Sensitivity for CRC in the entire colon (75 percent) could be estimated from a single study of 1994 adults with a total of 12 CRCs detected,[59] while sensitivity for advanced neoplasia in the entire colon ranged from 76.8 to 85.6 percent in two studies of 6146 adults with a total of 514 advanced neoplasias detected.[60,146]

Simulated protocol for flexible sigmoidoscopy with biopsy. FS with biopsy is a protocol used in three FS trials whose CRC incidence and mortality outcomes are pending.[81-83] The criteria for colonoscopy referral in two of these studies is the FS detection of any single adenoma ≥10 mm, with tubulovillous or villous histology, severe dysplasia, or malignancy, or the detection of three or more adenomas of any size or histology.[82,83] We used these same criteria to calculate the sensitivity of FS with biopsy for six colonoscopy screening studies in a total of 14,938 average-risk patients. The sensitivity of FS with biopsy for CRC in the entire colon ranges from 58.3 to 62.5 percent, based on two studies in 3982 average-risk adults that detected a total of 20 cancers.[58,59] Sensitivity of FS with biopsy for advanced neoplasia (1,028 lesions throughout the entire colon) in six studies ranged from 71.8 to 85.3 percent, with an outlier study reporting 50 percent sensitivity in a sample of women examined at military medical centers.[61] The one other study that reported sex-specific sensitivity estimates suggested that FS was equally or more sensitive for advanced colonic neoplasia (32/41 lesions in the entire colon) in women (78 percent), compared with men (70 percent, 98/140 lesions).[146] These studies defined the distal colon reached by FS as up to the splenic flexure. As expected, using a more limited definition of the distal colon that would be reached by FS (up to the junction of the sigmoid and descending colons)[61] resulted in a decrease in sensitivity for advanced neoplasia in women (from 50 to 34 percent) and men (from 82 to 71 percent)[60,61] (see Table 4).

Key Question 2b. What are the test performance characteristics of (1) CT colonography (CTC) and (2) fecal screening tests (e.g., high-sensitivity guaiac fecal occult blood testing (HS-FOBT), fecal immunological test (FIT), or fecal DNA tests) for CRC screening as compared to an acceptable reference standard?

CT Colonography (CTC)

Recent systematic reviews[116-121] have identified 40 studies comparing CTC using a variety of imaging approaches and scanner types with a reference standard. These reviews summarized data across a large range of technological approaches to CTC and with varying patient populations, reference standards, study designs, and outcomes. The most comprehensive of these current reviews by Mulhall evaluated 33 prospective studies in 6393 adult patients comparing CTC (that met a minimum level for quality and technological sophistication) to colonoscopy or surgery.[116] Only four studies from this review, however, addressed average-risk patients.[136,148-150] While we identified no additional studies in average-risk patients after examining other systematic reviews, we did locate three additional studies comparing different CTC approaches (2D imaging and 3D imaging) to colonoscopy in average-risk patients.[137,138,151] We first discuss the Mulhall review to provide a context for considering the more limited research examining CTC screening in average-risk patients.

The reported CTC sensitivity varied widely among the 33 studies conducted in all patient populations in Mulhall's review.[116] Per-patient sensitivity ranged from 30

percent to 100 percent for polyps 6 mm or greater in diameter. These data could not be pooled due to significant between-study heterogeneity that persisted even within size-specific polyp strata (6-9 mm, ≥ 10 mm). Per-patient specificity estimates were more homogeneous across studies and pooled estimates varied significantly with polyp size. Specificity for polyps greater than 9 mm was 97 percent (CI: 96, 97), and was significantly better than for polyps 6-9 mm (93 percent, CI: 91, 95) and polyps < 6 mm (91 percent, CI: 89, 95). Meta-regression suggested that the CTC technology impacted CTC sensitivity. Sensitivity decreased 4.9 percent (CI: 0.8, 7.1) for every 1-mm increase in the width of the CTC slice thickness (based on collimation setting). Sensitivity was higher (95 percent, CI: 92, 99) and homogeneous (I^2 = 40 percent) in studies using multi-detector scanners, compared with nonhomogeneous estimates from studies using single-detector scanners. Similarly, studies that used standard two-dimensional (2D), with concomitant three-dimensional (3D) imaging, rather than 2D imaging with 3D imaging only for confirmation, were more sensitive and homogeneous in their findings. Fly-through (3D) technology was applied in only two studies, but had the highest sensitivity (99 percent, CI: 95,100).

We located six fair- or good-quality cross-sectional studies[136-138,148-150] that examined a total of 1937 average-risk patients screened for colorectal cancer with both CTC and colonoscopy on the same day. Three of these studies are not discussed here because: two of these studies involved very small samples (less than 50 patients) and used older, less consistent single detector technology;[148,150] the other study provided accuracy data that reflects a very small number (n=16) of polyps larger than 6 mm, and researchers used a questionable approach of assuming that CTC-located lesions not found on colonoscopy were false positives due to residual fecal materials.[149] These studies are included in Appendix D. In the three remaining studies, 40 to 45 percent of participants were women.[136-138] Most participants were aged 50 to 79 years. Information on race/ethnicity was provided in one study that included 15 percent Nonwhites,[138] and one study was conducted in Korea.[137] These three studies also provided data on sensitivity of colonoscopy (KQ2a).[136-138]

A good-quality study conducted by Pickhardt represents the largest single study on the accuracy of CTC screening compared with colonoscopy in average risk patients that has been published to date, and the only one whose primary purpose was to address this question. This study enrolled 1233 average-risk patients (41 percent female; ages 50 to 79 years; two percent under age 50 with a positive family history for CRC) and compared same-day colonoscopy with CTC using 3D fly-through endoluminal display, fecal tagging, and contrast-based luminal fluid opacification.[136] Trained radiologists conducted all readings. Seventeen experienced colonoscopists initially blinded to the CTC results conducted the colonoscopies. Segmental unblinding of results from the CTC permitted colonoscopists to recheck CTC findings that were not located on first-pass colonoscopy. This also allowed researchers to clearly separate false-positive CTC results from false-negative colonoscopy results. About half of the patients (50.4 percent) had a polyp and 13.6 percent had adenomas. Two patients had adenocarcinomas, 3.9 percent had large adenomas (10 mm or greater in diameter), and 13.6 percent had adenomas 6 mm or greater. Per-patient CTC sensitivity for adenomas did not differ by lesion size (89 to 94 percent) and was not significantly different between CTC and colonoscopy (see Table 5). However, one of two carcinomas was missed on colonoscopy. This study's

sensitivity estimates might be considered best estimates due to the use of 3D fly-through CT technology with fecal tagging and luminal fluid opacification, and the use of a limited number (six) of reasonably experienced radiologist readers. Per-patient CTC specificity varied significantly by lesion size, with significantly worse per-patient specificity (79.6 percent) for lesions 6 mm or greater, compared with 96 percent specificity for lesions 10 mm or greater. Specificity estimates may be affected by two influential study factors: 1) CTC specificity could be underestimated due to the conservative assumption that polyps identified on CTC were false positives if they matched only with a nonadenomatous polyp; 2) CTC specificity could be overestimated due to the use of contrast materials to allow fecal tagging and residual fluid opacification. While these techniques are widely accepted[138] and are used in large screening studies, it is not clear if they are common in community practice. Depending on the referral threshold for CTC findings triggering a colonoscopy referral, as few as one out of 13 patients undergoing CTC would be referred based on a polyp of 10 mm diameter or greater, compared with as many as one out of three patients for a polyp of 6 mm diameter or greater. Considering sensitivity at the lesion level, the per-polyp sensitivity of CTC and colonoscopy for advanced neoplasia did not significantly differ. In a related publication, the sensitivity for flat adenomas 6 mm or larger (82.8 percent) was reported to be similar to the sensitivity for polypoid adenomas 6 mm or larger (86.2 percent), although this determination was based on a total of 29 flat adenomas 6 mm or greater, with flat polyps found in 52/1233 persons (4.9 percent).[152]

There is currently debate about the relative accuracy of primary 2D compared with primary 3D methods for displaying and reviewing CTC screening results.[153] While both visualization approaches are generally employed in current CTC reading, the difference lies in which approach is used for primary polyp detection (primary 2D or 3D approach), and which is used for confirmation or problem solving.[151] Two studies compared sensitivity between these approaches in patients who received no oral contrast, and therefore did not have fecal tagging.

In a fair-quality retrospective study, primary 2D and primary 3D virtual dissection CTC technology using a multidetector scanner with IV contrast, but without oral contrast, were compared with same-day colonoscopy in 96 patients referred for screening colonoscopy.[137] Twenty-three percent of patients had polyps ≥ 6 mm. Two very experienced radiologists read the studies on the same patients, separated by 2 months between 2D and 3D viewings. Using either approach, both readers had 100 percent sensitivity and 99-100 percent specificity for large polyps (10 mm or greater). For lesions 8 mm or larger, one lesion was missed on 3D by one reader (resulting in 85 percent sensitivity instead of 92 percent sensitivity for 3D CTC), but 2D and 3D sensitivity were otherwise the same, as were specificity (98-99 percent). Sensitivity of 3D CTC appeared to be better for lesions 6 mm or larger (73-77 percent for 3D CTC vs. 59-64 percent for 2D CTC), but these differences reflect detecting three fewer lesions, showing the imprecision associated with small numbers. For one reader, specificity for lesions 6 mm or larger appeared lower for 2D than for 3D CTC (specificity estimates 89 to 99 percent), but small numbers again affected the precision of these estimates.

In a fair-quality study, primary 2D and primary 3D virtual dissection CTC technology using a multidetector scanner without contrast were compared with same-day

colonoscopy in 452 asymptomatic patients referred for screening colonoscopy.[138] Investigators also examined the impact of CTC slice thickness (1.25 vs. 2.5 mm) on sensitivity and specificity. They also reviewed differences between very experienced readers. A little over twelve percent of patients had one or more adenomatous lesions—5.8 percent with adenomas 10 mm or larger in size and 6.6 percent with adenomas 6-9 mm. Limited power suggested no significant difference in test performance for 1.25 vs. 2.5 mm collimation, and we report here the most sensitive (1.25 mm) test results. When averaged across readers looking at different sets of randomly assigned patient images, per-patient sensitivity of 2D or 3D reading for adenomas 10 mm or greater was 76 percent and 73 percent, respectively. Sensitivity was much higher (95 percent) when 2D and 3D reading results were combined. Compared with the sensitivity for larger adenomas, lower sensitivity was seen for adenomas 6-9 mm using 2D (53 percent) and 3D (60 percent); sensitivity for smaller adenomas also improved if the two approaches were combined (71 percent). Specificity was similarly good between 2D and 3D approaches for large adenomas (98-99 percent) and for smaller (6-9 mm) adenomas (above 94-95 percent), with lower overall specificity for smaller adenomas. These results were achieved without the use of oral contrast for fecal tagging. Due to this study's primary aims of comparing readers and different CTC technical parameters, results were reported for subsets of the total patients and result in small numbers, affecting the precision of these estimates of test accuracy.

Pickhardt, et al. have recently published a fair-to-good quality reanalysis of 730 of the original 1233 cases from their study of a primary 3D endoluminal fly-through approach. This study compared the sensitivity of this approach with that of more experienced CTC readers using primarily 2D methods, with 3D displays reserved for problem solving.[151] Per-patient sensitivity for large adenomas (10 mm or greater) in the subset of 730 patients using primary 2D CTC was 81 percent, compared with 94 percent for 3D CTC in the entire cohort. Including smaller adenomas (6 mm or greater), 2D CTC sensitivity was markedly reduced (49 percent), compared with 3D CTC (89 percent). Specificity for 2D CTC was the same as 3D CTC for large polyps (97 percent compared with 98 percent, respectively), but higher for smaller polyps (95 percent for 2D CTC compared with 85 percent for 3D CTC). A strength of this study was using one software system (Viatronix) for both approaches, the sample size, and the use of fecal tagging which likely improved the specificity of 2D. Study limitations include the comparison of the subset for 2D to the entire cohort for 3D and possible conflicts resulting from the author serving as a consultant to the manufacturer.

At the time of our review, results from a large CTC study had been presented but not yet published. These preliminary results from the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial, an NIH-funded multicenter study of 2,531 average-risk individuals, examining the accuracy of CTC are described in the Discussion section on CTC.

Fecal Screening Tests

Fecal screening test summary. Recent systematic reviews[122,123] identified more than 130 studies evaluating the analytic and clinical test performance of 18 fecal occult blood tests (FOBTs)---17 fecal immunochemical tests (FITs) and one high-sensitivity guaic

FOBT (Hemoccult Sensa)---that were developed after Hemoccult and Hemoccult II. We further identified 18 additional published studies through searching. We excluded case-control studies of screening accuracy, since these consistently reported higher sensitivity for FOBTs than did cohort studies.[122] Case-control studies have been shown to overestimate sensitivity as a design-related source of bias.[154] Among cohort studies we evaluated, very few compared fecal screening test results to a valid reference standard (e.g., colonoscopy) or to an acceptable reference standard (e.g., colonoscopy for positives and systematic followup for negatives). To represent test performance in average-risk screening populations, we retained studies including participants enrolled from mass screening programs (community-, worksite-, or population-based) or non-CRC-focused health appraisal programs. Given the relatively few number of cohort studies available for individual tests, we also retained several studies with a higher potential for selectivity (e.g., not clearly representing average-risk screening participants, e.g. screening programs at cancer centers, doctor-initiated screening activities, and medical checkups for colorectal cancer).

Recent systematic reviews[124,126,155] have identified 24 studies evaluating the analytic test performance of fecal DNA tests in selected groups of patients with colorectal cancer, adenomas, hyperplastic polyps, other GI diseases, or normal colonoscopy findings. We identified one additional published analytic test performance study.[156] None of these studies were cohort studies conducted in average-risk patients undergoing screening. We found two clinical studies providing information on fecal DNA testing for CRC screening.[157,158]

High-sensitivity guaiac testing. None of the cohort studies we found examined the test performance characteristics of high-sensitivity guaiac testing (Hemoccult Sensa) by ensuring that all participants received the same reference standard test. Two at least fair-quality cohort studies in average-risk screening populations from the same managed care institution in the United States evaluated Hemoccult Sensa in a total of 13,945 average-risk adults aged 50 years and older. These studies used endoscopy for those testing positive and medical record/tumor registry followup over 2 years for those testing negative (supplemented by FS in those with negative FOBTs in the second study)[159,160] (See Table 6). The first study compared four FOBT screening strategies: high-sensitivity guaiac (Hemoccult Sensa), nonrehydrated Hemoccult II, FIT alone (using HemeSelect), and a Hemoccult Sensa/HemeSelect screening sequence in 8104 adults (47 percent Nonwhite; 59 percent female, 31 percent aged 70 years or older) who were advised to undertake dietary and medication restriction prior to screening.[160] Hemoccult Sensa had a much higher test positivity rate (13.6 percent) than Hemoccult II (2.5 percent), which improved sensitivity for CRC (79.4 percent compared with 37.1 percent), but reduced specificity (86.7 percent vs. 97.7 percent). Performance for FIT testing is discussed in the following section. The sensitivity of Hemoccult Sensa was likely overestimated, and the specificity was likely underestimated, since not all participants received a colonoscopy. Followup of some screen-positive patients was completed through FS, which would not detect proximal lesions and thereby underestimates specificity. The screen-negative patients were followed through medical records, which would overestimate sensitivity. In a recently published followup study of 5841 average-risk screening patients (26 percent Nonwhite, 53 percent female, 11 percent aged 70 years and older), Hemoccult Sensa was compared to a fecal immunochemical test (FlexSure), alone or in combination with

Hemoccult Sensa. The screen-positive patients received colonoscopy, while test negative patients received FS.[159] Hemoccult Sensa had the highest test positivity (10 percent) of the three fecal occult blood testing approaches, with possibly lower sensitivity for left-sided (distal) CRC than the fecal immunochemical test (FIT) alone (64.3 percent sensitivity compared with 81.8 percent, estimates not statistically different). Hemoccult Sensa also had a clearly lower specificity for left-sided CRC (90.1 percent compared with 96.9 percent). A combination Hemoccult Sensa/FlexSure screening approach, where the FIT was developed only if the guaiac-based test was positive, had identical sensitivity and better specificity than Hemoccult Sensa alone (98.1 percent compared with 90.1 percent). Absolute sensitivity or specificity for whole-colon CRC cannot be inferred from these estimates, although the authors' provision of estimates for left-sided lesions is reliable.

Fecal immunochemical tests (FIT). We identified 12 types of FITs representing 20 different proprietary names. Differences in test methodology do not allow these tests to be analyzed as a class, although some tests are part of the same developmental test sequence.

FITs vary in terms of their FDA approval status and their availability in the United States (see Appendix D Table 5). We found admissible studies (cohort design, average-risk population, acceptable reference standard) that evaluated the test performance characteristics of five different FITs (OC-Hemodia, FlexSure OBT [now called Hemoccult ICT], Monohaem, Magstream, and HemeSelect). HemeSelect, Immudia HemSP, and Magstream are related tests, with more current versions allowing quantitative results from an automated reader. HemeSelect, Monohaem, and FlexSure OBT are FDA approved. Only FlexSure OBT (Hemoccult ICT) appears to currently be marketed in the US (see Table 6). We found no eligible studies evaluating other FITs─InSure (Inform is the same test), Quickvue, and Hemosure─that are both FDA approved and currently on the US market.

Nine fair- or good-quality cohort studies in a total of 86,498 average-risk patients evaluated FIT using a valid reference standard (colonoscopy in all patients regardless of FIT results),[159,161-164] or an acceptable reference standard (followup of negatives as a substitute for conducting endoscopy in all participants).[160,165-167] (See Table 6) We did not include an additional study[168] that used an identical screening population as an included study, and thus appeared redundant.[161]

Since optimal test performance for one of the FITs (Monohaem) was achieved with a 2-day specimen collection, compared with a 1-day or 3-day approach, we preferentially describe 2-day collection results when available.

We found the largest evidence base (3 fair-quality studies in 37,330 persons) for the Magstream-related FITs.[160,163,166] One study was conducted in a representative US primary care population.[160] Two of these studies evaluated Magstream or Immudia-SP and provided quantitative (as opposed to qualitative) test results from an automated reader.[163,166] Only one study, done in 7421 average-risk adults,[166] provided quantitative results across a range of cutpoints for the 2-day sampling approach, however, and this study used observation for development of CRC for those testing negative as the reference standard (instead of colonoscopy). As such, this study could provide test

accuracy for CRC only and may overestimate sensitivity and underestimate specificity. In this study, test positivity for Magstream ranged from a high of 5.8 percent at 20 ng/ml to a low of 2.0 percent at 75 ng/ml, with higher sensitivity for CRC (85 percent) at the 20 ng/ml cutpoint and as low as 61 percent at the 75 ng/ml cutpoint. Specificity was reasonable at the lower cutpoint (94 percent) and better at the higher cutpoint (98 percent). Sensitivity for advanced neoplasia in a separate study employing colonoscopic evaluation of all patients was 27 percent (based on a single day sample), with a specificity of 95 percent.[163] When directly compared to Hemoccult II, qualitative results from HemeSelect had a higher sensitivity for CRC (69 percent compared to 37 percent for Hemoccult II) and a lower specificity (94 percent compared with 98 percent).[160] Using Hemoccult Sensa/HemeSelect in sequence achieved virtually the same sensitivity for CRC as HemeSelect alone, thought it had much better specificity (97 percent). The specificity of this sequence was comparable to the specificity of Hemoccult II.

Three fair-quality studies evaluated OC-Hemodia in 35,171 average-risk patients with unknown applicability to the US population, and with some differences in study design from already-described studies.[161,162,165] One study in 27,680 persons used a 1-day sampling scheme, but also used followup (rather than endoscopy) to estimate false negatives from FIT screening.[165] Test positivity was lower for the 1-day sampling (5.3 percent) than for the 3-day sampling approaches (9.2 to 18.8 percent, although this latter estimate is based on small numbers). Sensitivity for CRC in the 1-day sampling approach (86.5 percent) was comparable to the larger study using 3-day sampling (87.5 percent).[161] The 1-day sample had a higher specificity (94.9 percent compared with 91.0 percent). Sensitivity for advanced neoplasia in the study employing colonoscopic evaluation of all patients was 48 percent (based on a 3-day sample), with a specificity of 91 percent.[161] Estimates for OC-Hemodia accuracy in the small subgroup of persons who met our criteria for average risk (n=80) from a larger study of diagnostic colonoscopy were imprecise, due to small numbers.[162]

Two fair-quality studies evaluated Monohaem in 7976 average-risk Japanese patients. In the largest study (n=4611) using colonoscopy for the entire screening population, sensitivity for CRC for a 2-day sample was 83 percent and specificity was 96 percent. Sensitivity for advanced neoplasia was 51 percent.[169] In a separate study by the same group, much higher sensitivity was reported using followup of negatives, illustrating how this method may inflate sensitivity estimates.[167]

A single good-quality prospective study in 5841 screening patients aged 50 and older (26 percent Nonwhite, 53 percent female, 11 percent aged 70 years and older) evaluated FlexSure OBT (now Hemoccult ICT) and sequential screening using Hemoccult Sensa followed by FlexSure OBT for any positives. This study was conducted in a real-world managed care setting in the US.[159] FOBT-positives received a colonoscopy and FOBT-negatives were referred for FS (with about 80 percent completion of endoscopy), with 2-year followup for CRC detection. Fourteen cancers were detected along with 128 large adenomas. Test positivity was slightly higher for FlexSure (3.2 percent) than for the combination (2.1 percent). Both rates were much lower than Hemoccult Sensa alone (10.1 percent). FlexSure had similar sensitivity for distal CRC (82 percent) and for large distal adenomas (30 percent) as Hemoccult Sensa and the combination test power for differences was limited due to small numbers. The

combination test had the best specificity for either outcome, with FlexSure a close second (96.9 percent and 98.1 percent for CRC, respectively). While absolute sensitivity or specificity for whole-colon CRC cannot be inferred from these estimates, these estimates for left-sided (distal) lesions are reliable.

Fecal DNA testing. Applicable fecal DNA screening studies are limited to one fair-quality large cohort study using a multitarget fecal DNA panel test (the pre-commercial version of Pre-Gen Plus™, version 1.0), in 4404 average-risk patients undergoing colonoscopy,[158] and a smaller cohort study of a test for a single mutation of the K-ras gene.[157] In the best study available, researchers compared a one-time multitarget fecal DNA panel (PreGen Plust ™, version 1.0) with 3-card non-rehydrated Hemoccult II in 4404 average-risk asymptomatic patients who all underwent colonoscopy.[158] The study only provides data on a one-time screening approach, rather than a screening program. Of the 5486 enrolled participants, 1082 (19.7 percent) did not complete some aspect of the testing: 770 (71 percent) did not complete the colonoscopy, 641 (59 percent) did not provide an adequate fecal DNA sample, and 426 (43 percent) did not provide an adequate Hemoccult II sample. A higher percentage of incomplete samples for fecal DNA testing, which required at minimum a 30g stool sample with receipt within 72 hours, compared with Hemoccult II, which required a sampling strategy from multiple stools, may signal differences in feasibility or acceptability to patients. From the 4404 that were fully tested, a subset (n=2507) with a mean age of 69.5 years, 44.5 percent male, 87 percent white, 13.9 percent positive family history, were selected for fecal DNA testing based on results of the colonoscopy and histopathology. The multitarget fecal DNA test, PreGen Plus ™, tested for 21 DNA mutations in the K-ras, APC, and p53 genes, along with markers for miscrosatellite-instability and long DNA.

Patients who received multitarget fecal DNA testing included those with invasive adenocarcinomas (n=31) or advanced adenoma (n=403), one rectal carcinoid tumor, one cloacogenic tumor, and a randomly selected subgroup with minor (n=648) or no (n=1423) detected polyps. Among this subset, 8.2 percent were test-positive on the fecal DNA panel and 5.8 percent had a positive Hemoccult II. One-time fecal DNA testing was more sensitive for adenocarcinoma than Hemoccult II (51.6 percent, [CI: 34.8, 68.0] and 12.9 percent [CI: 5.1, 28.9], respectively). Sensitivity for advanced adenomas was similarly poor for fecal DNA testing (15.1 percent, [CI: 12.0, 19.0] and for Hemoccult II (10.7 percent, [CI: 8.0, 14.0])). While specificity for minor polyps (92.4 vs. 95.2) or no polyps (94.4 vs. 95.2) did not differ between fecal DNA and Hemoccult II, respectively; power to detect a difference was limited since the full sample was not tested. Other study limitations include poor precision in the estimates of test performance characteristics due to sample size issues, not including the other two nonadenocarcinomatous cancers in any calculations of relative test performance, excluding 20 percent of the study population for incomplete data, and questions about the generalizability of these findings to widespread population screening using fecal DNA. Generalizability concerns reflect the older age of study participants relative to the usual age of CRC screening (three-quarters over 65 years of age) and uncertainty about the accuracy of fecal DNA test performance in a community (as opposed to a specialized) laboratory setting. And, since this study was

completed, the test version is no longer available on the commercial market and has been supplanted by other versions (1.1 and higher) for which there are not currently clinical cohort studies in screening populations.

One other fair-quality analysis from a population-based cohort study examined baseline stool samples for a single mutation of the K-ras gene in 441 older adults (aged 50-75 years) undergoing colonoscopy within two years.[157] These participants were similar to the overall study population, except that more reported a first-degree relative with CRC. The fecal test had zero percent sensitivity, testing positive in none of the 31 participants with advanced colorectal neoplasia, including seven patients with invasive CRC. The highest rate of mutant K-ras was reported in participants with a negative colonoscopy (7.5 percent). Limitations of this study include bias in the spectrum of patients self-selecting for colonoscopy, and the lag-time between stool collection and clinical diagnosis which could have affected test performance.

Key Question 3a. What are age-specific rates of harm from colonoscopy and flexible sigmoidoscopy in the community practice setting?

Colonoscopy

We found 16 fair- or good-quality studies evaluating clinically significant adverse events from colonoscopy conducted in predominantly asymptomatic persons (see Table 7). Three of these 16 studies were retrospective cohort studies,[170-172] while the other 13 studies were prospective.[6,82,136,173-182] Six of the prospective studies were conducted in trial settings and used colonoscopy as followup to FOBT, FS, or as a comparator for CTC.[6,82,136,173,175,181] Seven of these 15 studies were conducted primarily in community settings.[170-172,174,177,180,181] The 2002 review included only one of these studies.[180] In light of the stringency of our inclusion criteria, focusing on estimates of harms in the community practice setting, our studies were homogeneous enough to pool rates of complications. All studies were conducted in explicitly asymptomatic persons, or, at a minimum, in the case of 3 studies[170,172,180] in the community setting.

We pooled the proportion of total serious complications from the 11 studies that reported all significant complications using a random-effects logistic model (n= 55,211).[6,82,136,171,172,174-177,179,181,183] Only three of these eleven studies reported the number or proportion of polypectomies performed, which ranged from 41 percent to 68 percent.[171,172,179] In these three studies, the majority (>85 percent) of serious complications, perforations, or major bleeding were in colonscopies with polypectomies. After pooling, we estimated that serious complications from colonoscopy in asymptomatic populations occurred in 3.1 per 1000 procedures (CI: 1.7, 5.8) (see Figure 2). We defined serious complications as adverse events requiring hospital admission, including perforation, major bleeding, diverticulitis, severe abdominal pain, cardiovascular events, and deaths attributable to colonoscopy. Based on pooling 13 studies (n= 173,391),[6,82,136,170-172,174-177,179,181,182] we found that perforations from colonoscopy in asymptomatic populations occurred in 5.6 per 10,000 procedures (CI: 2.2,

14.5). Based on pooling 12 studies (n= 55,461), we found that major bleeding from colonoscopy in asymptomatic populations occurred in 12 per 10,000 procedures (CI: 8.9, 16 per 10,000 procedures).[6,82,136,171,172,174-177,179-181] We were unable to obtain reliable pooled estimates for the proportion of other complications due to sparse data. We were also unable to obtain estimates for complications by age or age groups due to limitations in data reporting in the individual studies (see Discussion section).

While there was no significant statistical heterogeneity in combining studies to obtain pooled estimates, two studies appear to have slightly different estimates of harms.[175,176] In the first, Kewenter and colleagues used colonoscopies as followup exams for positive screening tests. Therefore, 113 of the 190 colonoscopies were conducted to remove proximal lesions seen on barium enema. In the second study by Ko and colleagues, both hospitalizations and emergency department visits were used to define major complications. These differences in study characteristics, along with relatively small study sizes, may account for the apparent, though not statistically significant, difference in harms estimates. We conducted a sensitivity analysis with and without the study by Ko and colleagues[177] because this study was only published as an abstract at the time of this report, though we were able to obtain additional information to assess quality from the authors. As shown on the respective forest plots, there was no meaningful difference in estimates when we excluded this study.

We also conducted exploratory meta-regressions to determine if study design, study setting by country, and population characteristics including age range and indication for endoscopy would affect estimates of harms for colonoscopy. None of these study-level characteristics appear to affect estimates of total serious complications in 11 studies (n= 55,211). However, the study setting by country is significantly associated with complications from perforations in 13 studies (n= 173,391) at p=0.04 level. Complications from perforations in the eight studies conducted in the US versus the five studies not conducted in the US were 2.5 to 28.0 per 10,000 procedures less common. Therefore, we conducted stratified analyses and report separately the estimates of harms from colonoscopy (Forest plots not shown). Total serious complications from colonoscopy in six studies conducted in the US were 2.9 per 1000 procedures (CI: 1.2, 7.6). Perforations from colonoscopy in eight studies conducted in the US occurred in 3.8 per 10,000 procedures (CI: 1.4 to 10.4 per 10,000 procedures). Major bleeding from colonoscopy in seven studies conducted in the US occurred in 12.3 per 10,000 procedures (CI: 7.8 to 19.3 per 10,000 procedures).

Flexible Sigmoidoscopy

We found 8 fair- or good-quality studies that evaluated clinically significant adverse events from FS for colorectal cancer screening in a general-risk population (Table 7).[6,82,173,175,184-187] Two of these eight studies were retrospective cohort studies.[184,185] The remaining six studies were prospective.[6,82,173,175,186-188] Two of these prospective studies were conducted in randomized controlled trial settings evaluating FS.[82,173] One was conducted in a randomized controlled trial setting evaluating FOBT that used FS in their followup.[175] Only one of these studies was included in the prior 2002 review.[173] Similar to the colonoscopy studies, given the stringency of our inclusion

criteria, focusing on estimates of harms in the community practice setting, our studies were homogeneous enough to pool rates of complications.

Using a random-effects logistic model, we pooled the proportion of total serious complications from the six studies that reported all significant complications from FS, not including those complications generated from followup colonoscopy (n= 126,985).[6,82,173,175,184-186] All of these studies, per their protocol, performed polypectomy with FS. Only two studies, however, reported the proportion of polypectomies performed, which was approximately 20 percent to 22 percent.[173,175] We found that serious complications from FS for colon cancer screening in average-risk populations are much lower than for colonoscopy screening, with a pooled point estimate of 3.4 per 10,000 procedures (CI: 0.6 to 19 per 10,000 procedures) (Figure 3). As with colonoscopy, we defined serious complications as adverse events requiring hospital admission, including perforation, major bleeding, severe abdominal complaints, myocardial infarction, syncope, and deaths attributable to FS. Based on seven studies (n= 134,119),[6,82,175,184-187] we found that perforations from FS in average-risk populations were relatively uncommon, with a pooled point estimate of 4.6 per 100,000 procedures (CI: 3.6 per million to 5.9 per 10,000 procedures) (forest plot not shown). We were unable to obtain reliable pooled estimates for the proportion of other complications due to sparse data. Again, we were also unable to obtain estimates for complications by age or age groups due to limitations in data reporting for the individual studies.

We conducted similar exploratory meta-regressions to determine if certain study-level characteristics would affect estimates of FS harms. Study setting by country appears to be significantly associated with total serious complications in six studies (n= 126,985) at p=0.02 level. The total serious complications in the two studies conducted in the US, versus the four studies not conducted in the US, were 3.1 to 13.0 per 10,000 procedures less common. We therefore conducted stratified analyses and report separately the estimates of harms from FS (Forest plots not shown). Total serious complications from FS after pooling the two studies conducted in the US had a point estimate of 0.9 per 10,000 procedures with very wide 95% confidence intervals (CI: 2.0 per million to 49.5 per 10,000 procedures). Perforations from FS in three studies conducted in the US were similarly imprecise with a point estimate of 0.2 per 10,000 procedures (CI: 0.9 per million to 3.5 per 10,000 procedures).

Key Question 3b. What are the adverse effects of CT colonography (CTC) and/or fecal screening tests (high sensitivity fecal occult blood test (HS-FOBT), fecal immunochemical tests (FIT), and fecal DNA)?

CT Colonography (CTC)

We found five fair-quality cohort studies that addressed potential adverse effects of screening CTC (see Table 8).[136,189-191] Adverse effects, including clinically important events requiring medical attention and evaluation of extra-colonic findings on CT, are addressed in the discussion section. Overall, it appears that the risk of perforation for screening CTC ranges from zero to less than 0.06 percent (6 per 10,000 CTC procedures). Evidence for clinically significant adverse effects primarily comes from two large retrospective studies (n= 33,793), which included both asymptomatic and symptomatic populations.[190,191] The overall risk for perforation ranged from 0.9 to 6 per 10,000 CTCs (2/21,923 to 7/11,870). Both studies, however, suggest that perforation rates are higher for symptomatic persons undergoing CTC. No perforations were reported in one study's screening subgroup of 11,707 procedures.[190] There was one perforation in the screening subgroup of 11,870 procedures (number of CTC screening procedures not reported).[191] Furthermore, it is unclear how clinically important CTC -associated perforations compare with asymptomatic perforations visualized on CT, or with noniatrogenic perforations. In the study by Sosna and colleagues, for example, six of the seven perforations were detected on CTC (number of symptomatic perforations not reported), and only four of the seven perforations required surgical intervention.[191] In the study by Pickhardt and colleagues, only one of the two perforations was clinically symptomatic and required treatment.

The three prospective cohort studies (n= 4707), which were conducted in predominantly asymptomatic, average-risk screening populations, did not find any evidence of clinically significant adverse events from CTC.[136,182,189] One study reported three syncopal events related to a magnesium citrate/sodium picosupphate (SPS) bowel preparation, a procedure that has subsequently been discontinued.[189] We found two reviews providing estimates of ionizing radiation exposure per CTC exam.[192,193] Estimates of total radiation exposure per exam range from 1.6 to 24.4mSv for dual positioning (both supine and prone positions) with a median dose estimate of 8.8mSv or 10.2mSv.[192,193] These estimates are consistent with those provided in other primary articles and multiple background/reference articles.[117,118,120,194-201] We identified no studies that directly measured the risk for stochastic effects (e.g., cancer) caused by radiation exposure from CTC. We discuss the indirect evidence for the potential adverse effects of low-dose ionizing radiation in the discussion section.

Fecal screening tests. We found no studies meeting our inclusion criteria that addressed adverse effects of fecal screening tests, including HS-FOBT, FITs, or fecal DNA tests.

IV. Discussion

Research substantiating the mortality benefit of various CRC screening approaches is not significantly different from the evidence base for the 2002 USPSTF recommendation. There are still no screening trials reporting mortality outcomes for any screening methods except guaiac FOBT screening using Hemoccult or Hemoccult II. At the time of this report, results from a number of trials or studies of CRC screening methods are pending (see Ongoing Studies section and Appendix G), including four trials of FS addressing health and mortality outcomes. While two of these FS trials appear to be completed,[81,202] contact with investigators confirmed that their results are still unavailable.

A substantial body of research on other aspects of CRC screening has been published since the 2002 recommendation, and this remains a very active area of international research. We have organized the discussion of our findings by screening test, rather than by key question, to allow a synthesized consideration of the evidence on potential CRC screening test options. A summary of the overall evidence is provided in Table 9.

CRC Screening using FOBT and other Fecal Screening Tests

Guaiac FOBT screening programs

CRC mortality reductions due to FOBT screening reported in the previous review were generally maintained through longer-term followup. We found new reports of longer-term followup of biennial FOBT screening trials indicating CRC mortality was reduced 13 to 21 percent after 8 to 13 years of screening in two trials, although another two trials did not show mortality benefit until after 15-18 years of screening. A recent meta-analysis from the Cochrane Collaboration pooled CRC mortality reduction estimates for biennial screening at the last followup for four FOBT trials (i.e., at 11.7 years,[132] 15 years,[94] 17 years,[131] and 18 years[135]). The overall estimate of CRC mortality reduction was 15 percent using either random- or fixed-effect models (RR 0.85, CI: 0.78,0.92).[94] This analysis did not incorporate recently reported data from one of these trials, suggesting that CRC mortality benefit is no longer statistically significant at 17 years when deaths due to CRC treatment are included (RR 0.89, CI: 0.78,1.01).[131] 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. And, while meta-analysis of all four FOBT screening trials indicated no benefit for all-cause mortality (RR 1.00, CI: 0.99,1.03),[94,131,203] CRC screening would not be expected to reduce all-cause mortality in these trials due to the relatively low contribution of CRC mortality to overall mortality and power issues affecting the precision of all-cause mortality estimates.[204-208] Consistent with the USPSTF methodology, data on both cause-specific as well as all-cause mortality are considered relevant. However, in valuing the impact these data have on their recommendations, the USPSTF also considers methodological issues that may impact their interpretation.

Accuracy of newer fecal tests

Policymakers and clinicians seek evidence on test performance to guide decisions about substituting newer fecal tests for standard guaiac tests in order to improve FOBT screening programs for CRC. Screening tests that are more sensitive (but equally specific) may produce value by detecting extra cases of CRC with fecal screening without imposing a higher burden of false-positive test results (and associated risks). Methodologists suggest that, in the case of new diagnostic tests, evidence of this type of superior test accuracy provides a sufficient evidence basis for test substitution without conducting new randomized trials, if the additional cases are in patients that represent the same disease spectrum; this is likely if the reference standard is the same in the test accuracy studies as in the trials showing treatment benefit.[209] Based on this standard, and the use of colonoscopy in test accuracy as well as treatment trials, it is reasonable to assume that some fecal tests with improved sensitivity and similar specificity (relative to Hemoccult II) could be considered as substitutes in fecal screening programs. The best evidence to evaluate screening test performance of newer fecal tests in average-risk screening populations is available for four individual fecal immunochemical tests (FITs): Magstream/HemeSelect; FlexSure OBT/Hemoccult ICT; OC-Hemodia; and Monohaem. FITs cannot be analyzed as a class.[123] More limited data is available for Hemoccult Sensa, and very limited data is available for fecal DNA tests. Where test accuracy results do not indicate superior test sensitivity with comparable specificity, determining the trade-offs between sensitivity and specificity of these different fecal occult blood options, particularly in a program of repeated screening over time, requires modeling. The companion decision analysis[11] examines the comparative benefits and harms of Hemoccult Sensa, Hemoccult II, and FIT testing.

Fecal immunochemical tests (FIT). A large body of evidence (86,498 average-risk persons studied) from cohort studies has evaluated the screening test performance of specific FITs: OC-Hemodia, Monohaem, FlexSure OBT (now called Hemoccult ICT), Magstream, and HemeSelect (early generation, qualitative test related to Magstream). Qualitative and quantitative results from at least 2-day sampling suggest superior sensitivity for CRC of HemeSelect (68.8 percent) when directly compared with the sensitivity of concurrent nonrehydrated Hemoccult II of (37.1 percent).[160] The sensitivity for CRC of the other tested FITs (range: 61 percent to 88.9 percent) also exceeds that of nonrehydrated Hemoccult II (range: 25 to 38 percent, with one outlier study of 60 percent) as reported in four adequately powered cohort studies in average-risk patients in a recent systematic review.[122] Sensitivity for advanced neoplasia or large adenoma is less commonly reported, but ranges between 27 and 67 percent in FITs, which is at least comparable if not superior to the sensitivity for nonrehydrated Hemoccult II from a direct comparison (31 percent).[160] Specificity of FITs for CRC is generally lower (91 percent to 97 percent) than with nonrehydrated Hemoccult II (98 percent to 99 percent), although quantitative FITs (Magstream) using the higher cutpoint (75 ng/ml) and combination Hemoccult Sensa/FIT tests report specificity estimates comparable to nonrehydrated Hemoccult II. Almost all of these FIT studies used methods that could inflate estimates of diagnostic accuracy due to verification bias (partial or complete).[154] One also cannot assume that results from tested FITs are generalizable to other untested FITs.[122] As of this writing, only FlexSure OBT (Hemoccult ICT) appears to be currently on the US market.

Magstream, the only test with quantitative results and an automated reader, has been adopted for use in the Australian national screening program.[210] No adequate clinical accuracy data could be located for other FDA-approved tests, including the Insure test. Insure uses a promising brush sampling technique that has been reported to significantly increase FOBT program participation in a RCT comparing guaiac testing and another FIT, both based on spatula sampling.[211]

Hemoccult Sensa. Although this high-sensitivity guaiac test has been available for many years, no well-designed (i.e., cohort) studies have compared Hemoccult results to an adequate reference standard (e.g., colonoscopy) in all average-risk persons being screened. Another recent systematic review that comprehensively considered fecal occult blood tests for CRC screening also did not find a large body of research on Hemoccult Sensa.[122] These reviewers found a total of four screening accuracy studies examining Hemoccult Sensa.[160,212-214] We excluded two of these studies for the following reasons: 1) case-control design[213] (these designs exaggerate estimates of sensitivity);[122,154] 2) use of an inadequate reference standard for detecting both CRC and polyps, and inadequate data reporting to allow sensitivity calculations for CRC alone.[212] Another trial (reported in abstract) from this review is now published[159] and we had reviewed the fourth.[160] The best available evidence for Hemoccult Sensa is from two large cohort studies (n= 13,945 total) in a single managed care organization's health appraisal unit.[159,160] These studies compare Hemoccult Sensa with Hemoccult II and with two FITS, Hemeselect and FlexSure, which were analyzed as both primary screening tests and in combination with Hemoccult Sensa for CRC screening in average-risk adults. Hemoccult Sensa had five times the test-positivity rate as Hemoccult II and two to three times the test-positivity rate as FITs (alone or in series after a positive Hemoccult Sensa result). Although Hemoccult Sensa had significantly improved test sensitivity for CRC (79.4 percent compared with 37.1 percent for Hemoccult II), it was not more accurate than either FIT alone or combination Hemoccult Sensa/FIT testing. Of all the newer fecal tests we evaluated, limited data on Hemoccult Sensa suggested it has the lowest specificity.

Fecal DNA tests. Despite significant media attention, fecal DNA tests are still a developing technology and few have any clinical accuracy evaluations. One fair-quality cohort study evaluated average-risk patients (n=2507) using a multitarget fecal DNA panel (Pre-Gen Plus), compared with colonoscopy. Patients also received Hemoccult II. The fecal DNA panel was more sensitive (51.6 percent, CI: 34.8, 68.0) than nonrehydrated Hemoccult II (12.9 percent, CI: 5.1, 28.9) for CRC, but also had higher test positivity (8.2 percent vs. 5.8 percent). Neither test was sensitive, nor superior to the other, for detecting advanced adenomas (11 to 15 percent). Specificity for minor polyps was similarly high in both fecal tests (92.4 and 95.2 percent).

This trial has limitations that prevent it from providing strong evidence to support the current use of fecal DNA testing in CRC screening.[215] These limitations include questions about the study's generalizability—in light of selectively enrolling patients older than 65 years, focusing on a selected spectrum of patients and not analyzing all patients to estimate the sensitivity and specificity of this test, and excluding 20 percent of persons from the analysis—and about the its true magnitude of benefit above Hemoccult II, given the wide confidence intervals around the study's estimates of sensitivity. A major additional concern, however, is that the FDA has recently notified the

manufacturer that Pre-Gen Plus (the only commercially available fecal DNA test for CRC screening) is classified as a medical device and thus requires pre-market approval before it can be legally marketed.[216] This factor was cited in the decision by the Center for Medicare and Medicaid Services (CMS) in its recent decision to deny coverage for fecal DNA testing in CRC screening.[217] Once these issues are resolved, however, decision-makers will still need to carefully consider whether there is a mismatch between the tests for which there is clinical data supporting their test performance and those that are commercially available. The fecal DNA test evaluated in the fair-quality cohort study was a pre-commercial version (1.0) that has been replaced by a new commercial version (1.1), with other versions in the pipeline.[218] While ongoing development aims to improve various aspects of test performance—including DNA purification, DNA stabilization in the stool, and other aspects—a mismatch between available evidence of clinical accuracy and the commercially available tests is likely to continue into the future. And, although there are pending trials (see Appendix G), these reflect different versions of the test and illustrate the rapid evolution of this developing technology. Some researchers have indicated that, even when some of the pending study results become available, the fecal DNA test version evaluated will not represent the most advanced "next generation" of fecal DNA testing.[219]

A final consideration about fecal DNA testing relates to whether it is a substitute for FOBT testing every one or two years in a program of screening or should be used differently. The current clinical data supporting fecal DNA testing is limited to evaluating one-time testing (and not a program of testing), and there is no independent data on which to suggest a different rescreening interval than annually or biennially, as in FOBT screening programs. However, a recent modeling analysis for CMS on the cost-effectiveness of fecal DNA testing indicated that, even when fecal DNA was repeated only every three to five years, the costs would need to be substantially lower than at present for fecal DNA to be cost-effective compared with other currently recommended CRC screening strategies.[218]

Harms with fecal screening

We did not find any studies meeting our inclusion criteria addressing significant adverse effects of high-sensitivity guaiac FOBT, FIT, or fecal DNA tests. A recent systematic review of FOBTs and FITs found that only a few trials of FOBT have investigated the impact of being offered FOBT testing, and of positive FOBT test results, on daily life, and then only in a very small proportion of those being screened.[122] Some degree of worry can be engendered by being offered the test, but this worry is generally mild; sixty to seventy percent of those with a positive test may be worried about cancer (some call it severe worry, although most experience slight distress), and anxiety associated with false positive tests is highest before followup colonoscopy. In general, although concerns have been expressed,[220] data are quite limited to determine whether there are meaningful psychological impacts from fecal screening. However, patients with false-positive fecal test results also experience the risk of complications associated with colonoscopy. Consideration of these potential risks is warranted before substituting more sensitive FOBT or other fecal screening tests for standard guaiac FOBT that have been tested in randomized controlled trials of screening programs. If substitution gains sensitivity, but there is also an increase in false positives (due to decreased specificity),

additional colonoscopies would be expected, the potential harms of which may be significant. Ultimately, the issue of considering the incremental harms and benefits will require some degree of modeling in the absence of comparative studies reporting health outcomes. The companion decision analysis should help inform these considerations.[11] A hypothetical harm associated with fecal DNA is posed by the potentially greater significance given to false-positive and false-negative results with DNA testing, due to public opinion/belief/bias surrounding DNA testing.[215]

CRC Screening Using Direct Visualization: CT Colonography (CTC), Colonoscopy, and Flexible Sigmoidoscopy (FS)

Colonoscopy and other direct visualization techniques offer significant benefits above fecal tests in allowing greater sensitivity with a single test. In addition, colonoscopy allows treatment with polypectomy, if warranted, to occur during the screening test. Concerns about the availability of resources for screening colonoscopy, the greater potential for adverse effects, and considerations of the acceptability of a program of repeated colonoscopic screenings have driven much of the continuing search for new or alternate CRC screening methods. These include visualization methods other than colonoscopy. As such, CTC is the only newer technology (among MR colonography and enhancements in colonoscopy procedures or equipment) that has progressed enough to be potentially applicable for CRC screening in average-risk adults. However, research reports on newer technologies or on enhancements to existing technologies continue to accrue,[221] leaving the state of the science for potential CRC screening technologies subject to ongoing, potentially rapid, change.

Along with test accuracy, harms associated with these screening approaches are important considerations. In this updated review, our objective was to quantify serious adverse events for colorectal cancer screening. To evaluate harms, we included only studies with largely asymptomatic populations, usually an average-risk population, or studies conducted in a community setting. Therefore, only one study using flexible sigmoidoscopy and one study using colonoscopy[180] from the prior review are included in this updated evidence synthesis. Harms associated with CTC were not evaluated in the prior review.

CT Colonography (CTC). While there were sufficient studies to conduct a recent comprehensive meta-analysis examining the sensitivity and specificity of CTC,[116] very few of these studies (four of 33) were conducted in average-risk screening patients. This review, however, provided important indications for which CTC technical approaches affect CTC sensitivity, and the overall consistency of their results. Sensitivity was reduced 4.9 percent for every 1-mm increase in CTC slice thickness, and was higher and more consistent across studies using multidetector CT scanners (MDCT), those using concomitant 2D and 3D imaging, and those using 3D fly-through endoluminal imaging.[116]

We examined all four studies conducted in average-risk patients from the Mulhall review, but did not further consider three of them based on very small sample sizes (representing only 11 percent of all patients involved in the four studies) and use of older, less accurate scanning technologies.[148-150] We reviewed the remaining study identified for the Mulhall review,[136] along with related publications from that study,[151,152] and two

newer studies[137,138] conducted in a total of 1781 average-risk patients. Due to differences in methodologies, these data cannot be combined. Two studies provide a range of sensitivities and specificities, with imprecise estimates due to a small number of lesions and study designs primarily aimed at comparing types of technology and/or inter-reader reliability.[137,138] The other study represents the single best published estimate of the accuracy of CTC screening. In this study of 1233 average-risk patients, primary 3D endoluminal CTC had good per-patient sensitivity (93.8 percent) for large (over 10 mm) adenomas, and good sensitivity (88.7 percent) for adenomas 6 mm or larger. CTC sensitivity did not differ from sensitivity of colonoscopy for any size lesion.[136] CTC specificity for adenomas 6 mm or greater was considerably lower (79.6 percent) than CTC specificity for adenomas 10 mm or greater (96.0 percent). Based on this study alone, a referral threshold of lesions 10 mm or greater on CTC means that one of every 13 patients screened with CTC would require colonoscopy. A lower threshold for referral (lesions 6 mm or greater) would result in a much higher rate of colonoscopy referral (one out of every three screened with CTC).

Pickhardt, Kim, and colleagues have recently reported a colonoscopy referral rate of 7.9 percent of 3120 patients undergoing primary CTC screening. This rate is based on a protocol of offering referral to colonoscopy for all CTC-detected polyps 6 mm or larger in linear size, with CTC surveillance an option for those with one or two small (6 to 9 mm) polyps.[182] Out of a total of 13 percent of patients that were candidates for colonoscopy referral, based on CTC-detected 6 mm or larger polyps, 5.1 percent of patients chose CTC surveillance. Based on this study, between one in eight (if all patients offered immediate colonoscopy accepted it) and one in thirteen patients (if the same proportion elected CTC surveillance) would be referred for colonoscopy after CTC screening.

In this same study, authors also compared yields from CRC screening in average-risk adults undergoing either primary CTC screening (using contrast and primary 3D endoluminal imaging) after physician referral (n=3120), or primary colonoscopy screening after self or physician referral (n=3163) at a single institution.[182] While primary CTC and colonoscopy found a similar rate of advanced neoplasia detection (3.2 percent in CTC vs. 3.4 percent in colonoscopy), a higher rate of invasive carcinoma was detected in CTC (0.4 percent, 14 carcinomas in 12 patients), compared with colonoscopy (0.1 percent, 4 carcinomas in 4 patients). Those undergoing CTC screening had a total of 3120 CTC exams and 246 colonoscopy exams, resulting in 561 polypectomies (with no reported complications). Those undergoing colonoscopy screening had a total of 3163 colonoscopies, with 2434 polypectomies and seven (0.2 percent) colonic perforations. The primary limitation of this study is its nonrandomized design, with potential differences between those choosing the different approaches to CRC screening. Further, this study does not establish the impact on health outcomes associated with these two approaches, including the impact of allowing short-term surveillance for those with a few small polyps.

At the time of this report, results from the ACRIN National CT Colonography Trial in average-risk adults have been presented at meetings but not published in complete form.[222,223] This multisite study in 15 private practice and academic centers in the United States has complete evaluations of 2531 asymptomatic, primarily average-risk

patients undergoing CRC screening with CTC, followed by blinded colonoscopy done the same day by an undisclosed number of experienced gastroenterology staff. Fecal and fluid tagging were done on all patients. As reported by the study investigators CTC scanners across sites had a minimum of 16 detector rows, and used thin-section images with 0.6 to 1.25 mm collimation, 0.8 to 1 mm reconstruction, and low-dose protocol of 50 mAs; total dose exposure was estimated at 5 mSV per exam.[220] Fifteen study-certified readers used both primary 2D and 3D screening approaches. Certification required having read at least 500 CTC cases or attending a 1.5 day training course and passing an examination. Fecal tagging was done on all patients. Based on unpublished results from the press reports of meeting materials, the study found a total of 392 6 to 9 mm polyps in 258 patients and 155 lesions 1 cm or larger in 132 patients. Reported point estimates of the per-person sensitivity of CTC for ≥ 10 mm adenoma was 90 percent and for ≥ 6 mm adenomas was 78 percent, with a specificity of 86-88 percent. These are shown along with findings from Pickhardt et al for CTC and colonoscopy in Table 10 although available data do not allow statistical comparison. Study investigators reported that 8.3 percent (1 in 12 patients) of those undergoing CTC had polyps 6 mm or larger detected, and thus would be referred to colonoscopy; however, study authors also reported a total of 390 patients with lesions 6 mm or larger, suggesting a higher (15.4 percent, 390/2531) referral rate (1 in 6.5 patients). Results have been presented at the September 2007 ACRIN meeting and are expected to be published in the near future. These results must for now be considered preliminary, due to inconsistencies in presented results and lack of detail on study design and execution that would allow critical appraisal and interpretation. Similarly, results from the Munich Colorectal Cancer Prevention Trial of 300 average-risk patients have been presented, but have not been published. Preliminary results suggest similar or better per-patient CTC sensitivity across adenoma sizes (100 percent for 10 mm or greater, 98 percent for 6-9 mm or greater, 80 percent for adenomas 5 mm or smaller) as studies reported here, with the same per-polyp sensitivity as colonoscopy for large adenomas (96.0 percent). This study, however, found lower per-polyp sensitivity of CTC for lesions 6-9 mm (92.1 percent vs. 95.0 percent), and those 5 mm and smaller (78.9 percent vs. 89.5 percent). These results are also preliminary, due to lack of detail on study design and execution that would allow critical appraisal and interpretation.

The accuracy of CTC depends on adequate colon cleansing (and perhaps use of contrast materials for addressing residual feces and fluid), adequate distention of the colon, CT techniques and technologies, interpretation by a trained reader, and an appropriate protocol for referral for colonoscopy.[151,224,225] These are all issues that must be addressed if CTC becomes a recommended test for CRC screening in the community. Expert consensus on best practices for bowel preparation, colonic distention, patient position, use of contrast, and scan parameters for CTC have been published by the American Gastroenterological Society,[226] The European Society of Gastrointestinal and Abdominal Radiology (ESGAR),[227] and The American College of Radiology. (ACR Practice Guideline. www.acr.org). Accurate CTC interpretation was recognized to require thorough training (review of 50-75 endoscopically confirmed cases, plus additional mentored training), and experts recommend required testing to prove competence. These recommendations are reinforced by the presented (but not published) ACRIN findings, suggesting that half of the 15 radiologists failed the initial certifiying exam (after 1.5 days

of training or previous experience in over 500 cases) and required additional training before all eventually passed.[222] Experts also agree that interpretation should involve both 2D and 3D images, although primary 3D analysis is increasingly used, based on software advances allowing more time efficiency with 3D analysis. These experts believe that both primary 2D and 3D are acceptable. Comparing primary 2D and primary 3D is largely beyond the scope of this review, but includes differences in examination time, reader time, reader training and preference, and software availability. This debate is further complicated by the rapid evolution of CTC technology and techniques, with at least 9 vendors of CTC software currently in the United States.[153] The relative accuracy and availability of researched CTC technologies, compared with community CTC technologies, affects the likelihood that research findings will be translated into community practice.

Harms with CT colonography (CTC). The best estimates of adverse events from CTC screening come from three prospective cohort studies (n=4707) and the asymptomatic subgroup of a large retrospective study (n= 11,707), which did not find any evidence for clinically significant adverse events, including perforation.[136,189,190,228] These studies do not, however, address the potential risk for malignancy due to low-dose ionizing radiation.

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.[229] Data are inadequate to quantify whether risk for noncancer diseases exist for low-dose radiation exposure. Based on the current evidence, the median effective radiation dose for CTC is approximately 10mSv for dual positioning, both supine and prone. However, newer, low-dose multi-detector CT protocols, with about half the current radiation exposure, may yield similar diagnostic accuracy (or test characteristics).[230] For radiation produced in CT scanners, the effective dose equivalent (Sv) is the same as absorbed dose (Gy) (i.e., 1 mSv = 1mGy).[158] 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,[229] ionizing radiation from a single CTC exam is low. However, even low doses of ionizing radiation may convey a small excess risk of cancer.[231,232]

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.[229] Based on this report, the committee predicts that approximately one additional individual per thousand would develop cancer (solid cancer or leukemia) from an exposure to 10mSv above background using the linear no-threshold model (LNT); in comparison, 420 individuals per thousand 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.[229] 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.[233] 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). Leukemia or abdominal organ cancer risk may remain. This risk estimate is consistent with other published literature on radiation exposure risk from computed tomography.[195,232] Given the uncertainty surrounding the risk of low-dose ionizing radiation from CT exams versus benefit, this is an area of research that needs serious consideration if CT exams are to be used routinely in population-based screening programs requiring serial exams.

Extra-colonic findings on CT colonography (CTC). It is not yet clear if extra-colonic findings detected on CTC constitute a net health benefit or harm. In a recent review of studies reporting extracolonic and incidental findings on CTC, about 40 percent of patients (n=3488) were reported to have abnormalities, and many had more than one abnormality.[234] In the current literature, classification of extra-colonic findings into "high," "moderate," and "low" clinical significance is variable. "High," however, 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 future treatment (e.g., calculi, small adrenal masses). Findings of "low" clinical significance do not require further investigation or treatment.

Extra-colonic findings of "high" clinical significance are common, ranging from approximately 4.5 to 10 percent in asymptomatic populations,[136,228,235-237] up to 23 percent in symptomatic populations undergoing CTC.[228,237,238] Extra-colonic findings of "moderate" clinical significance are equally as common, ranging from 5 to 27 percent.[136,228,236-240] Because extra-colonic findings of both "high" and "moderate" clinical significance generally require medical followup,[235,236,240] the potential for significant additional morbidity and cost remains. Only a minority of these findings, representing approximately zero to 13 percent of those undergoing CTC, ultimately warrant definitive treatment (e.g., abdominal aortic aneurysm repair, resection of malignancy, chemotherapy for metastases).[228,235-238] The studies used to generate these estimates, however, vary greatly in study quality (i.e., ability to accurately assess followup) and the duration of followup, the longest of which was 2 years. Thus, none of these studies are able to articulate the true net health benefit or harm for individuals undergoing CTC due to extra-colonic findings.

Colonoscopy

Three CTC screening studies in 1781 average-risk patients reported the sensitivity of colonoscopy based on comparing initial colonoscopy findings with CTC results, after second-look colonoscopic re-examination to clarify false-negative colonoscopic findings

from false-positive CTC findings.[136-138] The proportion of missed adenomas or adenocarcinomas varied considerably, complicated by small numbers of study participants and lesions detected, and differences in the number and experience of the endoscopists in the study. Due to differences in study quality and design, data from these studies cannot be combined; the largest, good-quality study (n=1233) represents the single best estimate currently available for the sensitivity of colonoscopy when compared to a reference standard other than repeat colonoscopy.[136] In this study, in which colonoscopy was conducted by 17 experienced gastroenterologists, per-person sensitivity for adenomas 6 mm or larger was 92 percent, for adenomas 8 mm or larger was 92 percent, and for adenomas 10 mm or larger was 88 percent. One of two CRC lesions was detected by colonoscopy, while CTC detected both. The sensitivities of colonoscopy and CTC were not statistically different in this study, and also appeared comparable in the smaller studies. In the other two studies, limits in the size, design, and primary purposes limit their ability to provide informative estimates of sensitivity and specificity for polyps or for CRC. However, colonoscopy missed adenocarcinomas in two of these studies, which emphasizes that colonoscopy is clearly not 100 percent sensitive and may miss important lesions. Findings from tandem colonoscopy studies—most conducted in relatively high-risk patient samples—provide another perspective. Van Rijn et al.[241] conducted a meta-analysis of colonoscopy miss rates in 2006 using six studies of 465 patients.[241] Endoscopists missed very few large (≥ 10 mm) adenomas (2.1 percent, CI 0.3, 7.3 percent), but more smaller adenomas 5 to 10 mm size (13 percent, CI 8.0, 18 percent) and under 5 mm (26 percent, CI 27, 35 percent). These studies used experienced endoscopists and reported per-polyp (rather than per-patient) miss rates. Missed or interval CRCs have also been estimated using colonoscopies performed one to five years apart, but none of these studies met our criteria. None conducted repeat colonoscopy within 3 years of an initial screening colonoscopy conducted in average-risk asymptomatic persons. One study estimated missed colorectal tumors occurred in 3.4% of a population-based cohort (*n* = 12 487) who had previously undergone colonoscopy for any reason up to 3 years before a new diagnosis of colorectal cancer.[242] However, since these studies are commonly referred to as representing community performance for colonoscopy, they are summarized in Appendix C Table 5. Recognizing there may be suboptimal endoscopic examinations and variation in practice, experts recommend standard approaches to improve quality of colonoscopies, including specifying adequate bowel preparation and adequate time devoted to the examination, particularly during withdrawal of the colonoscope.[241,243]

Harms from Colonoscopy. From a total of 11 studies (n=55,211), we found that serious complications from colonoscopy are not uncommon—3.1 per 1000 procedures, 95 percent CI (1.7 to 5.8 per 1000 procedures). These complications include perforation, hemorrhage, diverticulitis, cardiovascular events, severe abdominal pain, and death. Few studies (three of 11) reported whether colonoscopies included polypectomies or not, which is a major flaw in the available research. In the three studies with polypectomy rates, 41 percent to 68 percent of colonscopies involved polypectomies and more than 85 percent of serious complications, perforations, or major bleeding were in colonoscopies with polypectomy. In a meta-regression, we found that study setting by country (US compared with non-US) had a statistically significant effect on rates of perforation. Therefore, we also reported stratified analyses in an attempt to derive estimates that are

more relevant for US policy-making. Total serious complications from colonoscopy in the six studies conducted in the US were slightly lower, 2.9 per 1000 procedures, 95 percent CI (1.2 to 7.6 per 1000 procedures), but not clinically different. Because of the limited number of studies, as well as the limited reporting and homogeneity of many individual study-level characteristics, our meta-regression had limited ability to detect the effect other potentially important factors—such as the rate of polypectomies, operator characteristics, or patient age and sex—have on the estimates of harms for colonoscopy.

Case reports of fatal or near-fatal outcomes in average-risk persons undergoing routine colonoscopy include splenic rupture,[244-246] retroperitoneal gas gangrene,[247,248] small bowel perforation,[249] colonic gas explosion with electrocautery,[250] and appendiceal abscess resulting in death.[251] In addition, there have been case reports of transmission of communicable diseases using unsanitized colonoscopes[252] and chemical colitis from glutaraldehyde, which is used to disinfect endoscopes.[253]

Flexible Sigmoidoscopy (FS)

Large-scale screening colonoscopy and FS cohort studies or trials report the probability of proximal colonic lesions associated with distal findings. Findings from these studies were used to calculate the sensitivity of two FS screening protocols: 1) colonoscopic referral for any distal lesion located on FS examination (e.g., FS without biopsy) and; 2) colonoscopic referral for biopsy-proven adenomas on FS examination (FS with biopsy).

Estimates of sensitivities for these two FS protocols do not appear to substantially differ, although they are not based on large numbers. The estimated sensitivity of FS without biopsy, for CRC in the entire colon, is 75 percent (based on a single study of 1994 adults, with 12 total CRCs detected),[59] while the sensitivity for advanced neoplasia in the entire colon ranged from 76.8 to 85.6 percent (from two studies in 6146 adults with 514 advanced neoplastic lesions detected).[60,146] The estimated sensitivity of FS with biopsy (assuming colonoscopy referral for advanced neoplasia, or three or more adenomas) for CRC throughout the colon ranged from 58.3 to 62.5 percent (based on two studies in 3982 adults with 20 total CRCs detected).[58,59] The sensitivity of FS with biopsy for advanced neoplasia in the entire colon ranged from 71.8 percent to 85.3 percent, based on reports of 1028 advanced neoplasias detected during 14, 938 colonoscopies in average-risk screening populations.[58-61,144-146] A single study estimated a much lower (50 percent, 36/72 lesions) sensitivity of FS with biopsy for detecting advanced neoplasia in a sample of 1463 women examined at military medical centers.[61] This study has been cited as indicating a much higher FS miss rate for proximal neoplasia in women, particularly when compared to findings in men using the same protocol.[254] Another study comparing women and men in a workplace screening program, however, suggested that FS with biopsy was equally or more sensitive in women (78 percent, 32/41 lesions), compared with men (70 percent, 98/140 lesions), for advanced neoplasia throughout the colon.[146] The limitations of sensitivity estimates based on colonoscopy findings must also be considered. These calculations are likely to be an overestimation, as they presume that polyps detected by colonoscopists would be as likely to be identified by those trained to perform FS; these simulations mostly estimate that FS exams successfully extend to the splenic flexure. Where this has not been assumed, FS sensitivity estimates are lower.[60,61]

Whether an individual FS examination reaches even the descending colon depends on the patient's size and anatomy, the quality of the bowel preparation, the patient's tolerance of discomfort, and examiner skill.[255,256]

In these screening colonoscopy cohorts, the prevalence of an isolated advanced proximal neoplasia ranged from 0.8-3.2 percent, indicating that while the distal portion of the colonoscopic exam showed no lesions, the proximal portion did. These lesions would not be detected (i.e., would result in false negative examinations) using any FS protocol. Since most studies used the splenic flexure to determine which lesions would be distal enough to be located by FS, prevalence of isolated proximal neoplasia is also likely underestimated. A single study compared using the splenic flexure to define the distal colon to using a more limited, and perhaps pragmatic, definition (i.e., the junction of the sigmoid and descending colons). This study found the prevalence of isolated proximal neoplasia increased from 2.4 percent to 3.4 percent using the more limited definition.[61] While concern has been raised about the high proportion of advanced neoplasias missed by FS (one-third to one-half) due to their proximal location, one must recall that the natural history of advanced neoplasia is unknown. Also, Farraye et al. have pointed out that the proportion of proximal lesions missed with FS could potentially be reduced by targeted screening approaches, such as selection of low-risk patients.[257] Targeted screening approaches are discussed briefly below.

Determining whether the sensitivity of FS protocols differs is an important issue, since established standards are currently lacking for which FS findings should prompt colonoscopy referral.[255] Biopsies do not appear to be routinely conducted on most polyps found during screening FS in the US.[146] Also, completed and ongoing FS trials vary in their protocols for colonoscopy referral. The small RCT of FS included in the last USPSTF review,[6] and current PLCO trial,[142] both used visual criteria without biopsy for colonoscopic referral, while the UK Flexible Sigmoidoscopy Screening Trial (UKFSST),[83] the SCORE trial,[82] and the NORCCAPS trial[81] are basing colonoscopic referral on biopsy-based criteria. Other between-trial differences, which have been recently summarized,[147] will be important to consider as these trial results become available.

While specificity could not be estimated from these simulations using screening colonoscopy trials, the PLCO trial has reported that followup colonoscopies in those with large polyps on FS detected no adenomas in 20 to 23 percent of patients, generating a specificity estimate of 77 to 80 percent.[54] This specificity estimate is likely to be an underestimate, particularly for FS with biopsy protocols, as referrals were based on any visual lesion.

Based on a single-tandem FS study,[141] and two small short-term followup (3 years) studies of those with negative FS findings, about 20 percent of all adenomas (14 percent of those ≥ 10mm) were missed on first exam. Of those screened, 0.8 percent had advanced neoplasias (none were adenocarcinomas) within reach of the FS that could have been missed on first exam. About 20 percent of all adenomas (14 percent of those larger than 10 mm) were missed on first exam.[54,143] Since these estimates are not precise due to their small numbers, their significance lies in reinforcing the importance of endoscopist skill and patient preparation for FS and colonoscopy. Even among trained and experienced FS examiners (gastroenterologists or surgeons) in the UKFSST, adenoma

detection rates varied significantly between the examiners in the proportion of patients with at least one detected adenoma.[258] Differences between thirteen examiners ranged from 8.6 to 15.9 percent, and could not be accounted for by patient sex, age, family history of CRC, or cigarette smoking. This variation has been taken to represent the range of skills among endoscopists. Thus, quality standards for those conducting FS and colonoscopy are important.

Harms of flexible sigmoidoscopy. Serious complications from FS in average-risk populations (n=126,985) are much less common than colonoscopy, 3.4 per 10,000 procedures, but estimates for FS harms encompass a much wider range, 95 percent CI (0.61 to 19 per 10,000 procedures). Serious complications include perforation, hemorrhage, diverticulitis, cardiovascular events, severe abdominal pain, and death. For the same reasons discussed in "Harms of colonoscopy" section, we reported stratified analyses by country of study setting in an attempt to derive estimates that would perhaps be most relevant. Because of the limited number of studies in the US (n=2) that reported total serious complications from FS, however, these estimates, 0.9 per 10,000 procedures, 95% CI (2.0 per million to 49.5 per 10,000 procedures), are not clinically different or more helpful than the estimates derived from all the studies.

Small polyps and implications for CRC screening

Unanswered questions remain about the natural history of adenomas under 10 mm and, therefore, about their clinical significance. Clarifying the risk associated with smaller polyps will be critical for estimating the true sensitivity and specificity of current and future CRC screening methods that directly visualize lesions for referral to colonoscopy (e.g., CTC, FS). Without the benefit of biopsy results, referral is based on polyp size. Risk from a small polyp visualized by CTC is related to whether the visualized polyp has a reasonable probability of containing advanced adenoma or carcinoma that will progress to invasive cancer before a next examination. On a FS in which no biopsy is taken, a small polyp can imply risk in two ways—it may contain advanced adenoma or in situ carcinoma, or may be a "sentinel" lesion signaling the probable presence of a high-risk adenoma or cancer elsewhere in the unexamined proximal colon. Ultimately, test performance for both CTC and FS (without biopsy) will depend on what lesion size (and type) is considered to indicate a positive test. As such, the effectiveness (and cost-effectiveness) of these screening techniques will vary accordingly.

Harms of bowel preparation for CT colonography (CTC), colonoscopy, and flexible sigmoidoscopy (FS)

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, sodium picosulphate (SPS), 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. Clinical trials comparing bowel preparations revealed variations in the prevalence of these side effects,

ranging from 15 to 95 percent.[259-266] Serious adverse events (e.g., severe dehydration, symptomatic electrolyte abnormalities) in these trials were limited to persons with major predisposing illnesses, incorrect dosing of NaP, or use of NaP in persons with pre-existing renal impairment.[264,267]

In one fair-quality systematic review, NaP appeared more easily completed than PEG, but NaP and PEG were comparable in terms of total number of minor adverse events, such that persons receiving PEG had slightly higher rates of abdominal pain, but persons with NaP had slightly higher rates of dizziness and asymptomatic electrolyte abnormalities.[260] Another recent fair-quality systematic review also found that NaP and PEG had similar tolerability and no difference in efficacy of bowel preparation. This review also found no clinically significant adverse events from these bowel preparations in the trials included in the review.[268] NaP is generally avoided, however, 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.[264]

We found no evidence of clinically significant adverse effects due to bowel preparation requiring 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,[6] and one person with severe diarrhea.[173] Case reports of serious adverse events from bowel preparation in average-risk persons undergoing colonoscopy include acute renal failure and acute phosphate nephropathy in persons who received bowel preparations with sodium phosphate,[264,269,270] one person with ischemic colitis who received bowel preparation with NaP,[264] one person with symptomatic hypokalemia with NaP,[264] and one person with a seizure secondary to hyponatremia with PEG.[271]

Emerging Issues

Special Population Issues in CRC

Race. Compared with same-sex persons in other racial/ethnic subgroups, Black men and Black women have the highest age-adjusted incidence of CRC and the highest proportion of CRC occurring in proximal locations in the colon (Table 2). When examined by subsite, Black men have the highest age-adjusted incidence rates for all subsites except the rectum and Black women have the highest age-adjusted incidence rates among women at every subsite.[272] These differences have recently been found to apply to colorectal polyps and cancers. Using data from the Clinical Outcomes Research Initiative (CORI), researchers examined screening colonoscopy results in 3195 average-risk Blacks and 43,431 average-risk Whites.[273] Blacks had fewer total polyps (35 percent vs. 38 percent with polyps), but more of these polyps were proximal to the splenic flexure (57 percent vs. 51 percent). A much higher proportion of Blacks with polyps had proximal polyps only (42 percent of Blacks compared with 30 percent of whites). In multivariate analyses controlling for age and sex, Blacks had higher odds of proximal polyps (adjusted OR 1.30, CI: 1.11, 1.52), higher odds of colonic tumors (adjusted OR 1.78, CI: 1.14, 2.77), and higher odds of proximal tumors (adjusted OR 4.37, CI: 1.16, 16.42).

Blacks have a worse CRC prognosis than Whites. In lesions across anatomic subsites, Blacks are more likely than Whites to present with advanced late-stage, rather than localized, disease.[272,274] Even after adjusting for stage at CRC diagnosis, Blacks have higher CRC mortality rates than whites.[272,275] Blacks are also more likely to be diagnosed with cancer before age 50 (10.6 percent of cancers) than Whites (5.5 percent).[276]

These data (and others) have led to calls to consider screening Blacks beginning at age 45.[277] Recent publications also suggest that colonoscopy may be the preferred screening approach for Blacks due to differences in polyp and cancer location in Blacks.[278] Blacks tend to be less likely to be current on CRC screening than Whites and are less likely to have had screening colonoscopy, although differences are statistically significant only in women.[103] Although current CRC screening uptake is also inferior in Latinos and other Nonwhites, the higher burden of disease in Blacks makes their screening issues a particular concern.

Sex. Findings from this review challenge several often-cited studies that have been interpreted to indicate that colonoscopy may be the preferred CRC screening method for all women, due to the higher proportion of advanced proximal neoplasias potentially missed by FS examination in women compared with men (64 percent vs. 34 percent).[60,61] These studies compared similar protocols using screening colonoscopy to simulate FS and its ability to detect advanced proximal neoplasia. Lieberman and colleagues screened 3121 predominantly male veterans aged 50-75 years (mean 63 years) and found a sensitivity of FS with biopsy of 81.7 percent. In contrast, the sensitivity from the main analysis reported by Schoenfeld and colleagues for FS with biopsy in 1463 women from military medical centers aged 40-70 years (mean 59 years) was 34.7 percent. When the same definition for "distal lesion" is used in both studies, the re-calculated sensitivity of flexible sigmoidoscopy for advanced proximal neoplasia is 50.0 percent in women.[61] Although the prevalence of proximal neoplasia is lower in women (4.9 percent) than men (10.5 percent), close to the same percentage of women (2.4 percent) and men (1.9 percent) would have had advanced proximal neoplasms that would be missed if screened using flexible sigmoidoscopy. The only other study in our review, by Imperiale and colleagues, reporting colonoscopy results by sex found a lower prevalence of proximal advanced neoplasia in women (1.2 percent), compared with men (3.9 percent). This study from a worksite setting also found a lower risk for isolated proximal advanced neoplasia in women (0.84 percent) than men (2.5 percent). Calculated sensitivity for flexible sigmoidoscopy (with biopsy) was similar or slightly lower in men (70 percent) compared with women (78 percent). This study's data suggest that men, rather than women, would have a greater proportion of proximal lesions missed by flexible sigmoidoscopy. When multivariate analyses of risk for advanced proximal neoplasia have been performed, older age, male sex, and distal adenomas are consistently identified as risk factors.[58,59,144] Similarly, isolated proximal neoplasia is more common in those over 60 years old, those with a family history of CRC, and smokers.[58] Differences in the prevalence of these risk factors for isolated proximal neoplasia among the study populations may explain some of the differences noted above in studies estimating the performance of FS in women.

Other issues, however, have been raised in terms of appropriate CRC screening approaches for women, including a higher risk for inadequate or limited

endoscopies.[279,280] Women have a longer colonic length (median of 155 cm compared with a median of 145 cm in men), which may contribute to greater technical difficulty and discomfort during both flexible sigmoidoscopy and colonoscopy in women.[280,281] Prior hysterectomy may be a risk factor for incomplete examination.[281,282] Women may better tolerate the use of pediatric colonoscopes for colonoscopy or upper endoscopes for flexible sigmoidoscopy.[283]

Older adults. While consideration of starting and stopping ages was beyond the formal scope of this systematic review, recent analyses have looked at factors beyond age to determine the probable benefit from CRC screening in older adults (i.e., age 75 years and older). Lin and colleagues used SEER data to model the expected life years gained among 1244 patients undergoing screening colonoscopy by comparing older adults (age 75 years and older) with younger adults (age 50-54 years).[284] While the prevalence of neoplasia increased with age, modeled mean increases in life expectancy were considerably lower in those aged 75 years and older, suggesting a reduced benefit of CRC screening in older adults. In a separate analysis of 35,755 Medicare patients, however, co-morbidities that were predictive of decreased 5-year life expectancy appear to provide more effective means of determining who could benefit from screening among adults 67 years and older than age alone.[285] Life expectancy in men and women after CRC diagnosis is significantly lower in those with three or more chronic conditions, compared with those with no chronic conditions, regardless of stage of disease or age at diagnosis. Thus, a female patient aged 81 years with no chronic conditions has a 13.8 year life expectancy and could potentially benefit from CRC screening more than a younger woman or man with three or more chronic conditions. Others who have considered in detail the complexities of inferring the evidence about CRC screening from younger to older adults also conclude that life expectancy, health status, benefits and harms of different tests, and patient preferences should all be factors when considering CRC screening in those over age 75-80 years.[286] Unfortunately, we found very little evidence to support or refute increased harms of CRC screening in older adults. Two studies[170,171] showed that persons aged 60 years and older have increased rates of major complications from colonoscopy (e.g., perforation, major bleeding, and hospitalization for diverticulitis). Many studies that reported potential harms from colonoscopy included older adults, [170-172,174,176-178,180,183] but do not provide enough information to interpret harms by age subgroups. Overall, these studies do not appear to have different proportions of harms than studies that exclude older adults.[136,181] As with expected benefits from screening, risk of harms may be more related to overall health status than to age in older adults.

Targeted (Customized) Screening Recommendations

Current CRC screening recommendations are made for all adults alike, except for differentiation based on family history and age. Those without a family history are recommended to begin CRC screening at 50 years of age, 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 in the epidemiology of adenomatous polyp and CRC development based on age, sex, and race/ethnicity.[287-289] Targeted screening recommendations could potentially address the timing of screening initiation, preferred screening method(s), or both. In

theory, targeted screening has the potential to improve CRC screening program performance and efficiency. Data evaluating the health or economic impact of targeted screening approaches, however, are quite limited.

In an effort to identify candidates at low risk for advanced proximal neoplasia who could be offered flexible sigmoidoscopy screening instead of colonoscopy, Imperiale and colleagues created and validated a novel index based on age, sex, and sigmoidoscopy findings within a split sample from a dataset of 3025 screening colonoscopy results.[146] The index resulted in scores from 0-7 points. A low score was 0 or 1 point. In the validation sample (n=1031), about half of patients had a low score. Advanced proximal neoplasia was rare (0.4 percent) in those with a low score. For women (score 0 for sex) under aged 60 (score 1 for age), only those with advanced lesions in the distal colon had a higher risk of advanced proximal lesions. The authors point out that if this index were validated in other populations, women under 60 without significant distal lesions, and others at lower risk based on age, sex, and distal findings, could be those for whom sigmoidoscopy alone is an entirely sufficient screening test.

Betes et.al. have sought to use characteristics other than family history of CRC to identify candidates at increased risk for advanced adenomas and who could potentially benefit from preferentially selecting screening colonoscopy for primary CRC screening.[144] Using a dataset of 2260 primary screening colonoscopies in average-risk patients aged 40 and older, these researchers created a scoring system based on sex, BMI, and age. Scores ranged from 0-8. The validity of the scoring system was assessed by ROC analysis, with an area under the curve of 67 percent, which indicates a somewhat useful score. Two percent or fewer patients with a lower score (0-2) had advanced adenoma anywhere in the colon. Women (score 0) under aged 60 (score 0) were considered low risk, even if they were markedly obese (BMI>35, score 2).

Screening Programs

National screening programs are being implemented in the UK, Australia, Finland, and elsewhere. In the US, many health plans are aggressively targeting colorectal cancer screening (a HEDIS quality of care measure since 2004) and the CDC is funding multiple state and community initiatives to increase CRC screening, including CRC-screening demonstration programs for low-income under- or uninsured men and women.[105] As these programs are evaluated, they could provide additional information about whether the natural variation inherent in these screening programs affects the resulting participation and, ultimately, health benefits or harms. Additionally, CDC's Community Task Force should soon publish a series of systematic reviews related to increasing screening rates for colorectal (along with breast and cervical) cancer.[290] These reports address strategies to increase community demand for preventive services, community access to recommended screening, and the use of provider reminders, incentives, and performance feedback to increase providers' actions to recommend, offer, and deliver CRC screenings.

Developing Technologies

Technological advances in new or existing CRC screening methods are occurring rapidly. This rapid development requires prudence when considering the evidence

supporting specific technologies, and will require care during the implementation process ifthese technologies are recommended for community-based screening programs.

There are ongoing developments in the use of "virtual colonoscopy", particularly CT colonography (CTC); efforts are underway to develop or validate better imaging techniques, computer-aided detection software, and cathartic-free approaches with fecal tagging.[291-294] Evaluators are considering critical issues in test interpretation that need to be understood,[295] and experts are beginning to set quality standards for screening CTCs in the community. MR colonography, which does not use radiation, has also been used for "virtual colonoscopy".[296] However, studies evaluating MR colonography for detection of colonic lesions, including polyps, have been conducted primarily in high-risk populations with a limited number of subjects.[297-304] At the time of this report, the only study in a screening population evaluated the use of dark lumen MR colonography without cathartic bowel preparation in a screening population in Germany.[221] While MR colonography was outside the scope of this report, due to the early stage of its development as a potential CRC screening tool, this study signals that MR colonography could be an important test to evaluate in the future.

Fecal testing is a very versatile field, with research ongoing in fecal markers and DNA and RNA testing.[126,157,305] For fecal DNA testing, novel approaches include amplifying DNA in stool and focused evaluations of the best individual or combinations of markers for maximizing test performance.[156] Some markers are focused on detecting adenomas,[306] as these are important for preventing CRC.[307] Hypermethylation of some tumor suppressor, or other regulatory, genes may help detect risk for adenoma recurrence,[308] suggesting a potential role in post-polypectomy surveillance, or possibly even in primary CRC screening. Development of blood assays for DNA is also underway. A number of developing technologies were not evaluated in our review—due to being early in the development process—but are being reported in the literature and may be important in future reviews of CRC screening. These include advances in colonoscopic techniques with magnification,[309-311] use of stains and dyes (chromoendoscopy),[312-315] and other optical adjuncts.[316] Some studies are investigating the use of scattering spectroscopy as an optical "biopsy" technique,[317] while others have investigated capsule endoscopy as an alternative to colonoscopy.[318] A pneumatic self-propelling, self-navigating colonoscope is still in early stages of testing.[319-321] However, newer CRC techniques may be under development for various purposes; therefore, research for the purposes of screening should be distinguished from others, e.g., CRC diagnostic evaluation, or surveillance.

Ongoing Studies

There are four ongoing RCTs evaluating the effects of various flexible sigmoidoscopy screening protocols (with and without biopsy) on CRC mortality. These are the only ongoing trials of CRC screening we have located that address health outcomes. While some have advocated strongly for a RCT evaluating screening colonoscopy,[322] we are not aware that one is currently planned or funded. A diagnostic accuracy study evaluating a multi-target DNA panel (performed in fecal or plasma samples) has been recently completed, with preliminary results presented in abstract only. The preliminary results of the multisite ACRIN study of CTC screening have also been

presented and are discussed above. Full evaluation of these results will be possible after publication.

Limitations

Our review builds on a prior systematic review and, as such, did not re-examine all of the questions previously addressed by this review. In particular, we did not address issues around test acceptability, feasibility, and compliance. Information on recommended CRC endoscopic screening methods was updated to include community performance and mortality outcomes for all recommended or newer CRC screening approaches; in particular, longer-term results from FOBT screening trials were sought. While information on improved or new CRC screening methods that were not recommended previously was considered in depth, we did not comprehensively report the state of the science for each test. Rather, we focused on determining whether adequate studies of clinical accuracy and screening benefits in average-risk asymptomatic populations exist. We summarized these studies where available. This pragmatic approach was necessary given the breadth of this review, but is also appropriate given its primary purpose of providing evidence upon which the USPSTF could base its updated CRC screening recommendation.

Due to our limited scope and timeline, we only reviewed the evidence for "serious harms" (i.e., those complications requiring unplanned medical attention in the form of hospitalizations, emergency room or physician visit, or death). For example, we did not systematically review the evidence for indirect harms (e.g., sequelae from false negative screening exams), psychological harms (e.g., "health certificate effect" from negative exams), or issues around tolerability and acceptability of each exam.

Screening for CRC is a very important public health issue that has been extensively studied over the past 30 years. Given the extensive and expanding international research literature for CRC screening, there are important issues that were beyond the scope of this review. Methods to increase the utilization of recommended CRC screening in the eligible US population were not part of this systematic review. This topic, however, is being addressed by CDC's Community Task Force and others.

Others, such as the US Multisociety Task Force, have addressed issues surrounding surveillance after positive screening, screening in high-risk groups, and rescreening. Rescreening intervals were not part of this review, but are included in the USPSTF's decision analysis, which is reported separately.[11] Given the rapid development of new technologies in CRC screening, ongoing gains in understanding the epidemiology and biology of CRC across patient subgroups, and expected results from trials elucidating various screening approaches, this topic requires continuous monitoring and frequent updating.

Future Research

Within the context of ongoing screening program implementation, well-designed cohort studies in average-risk men and women should compare the performance of novel fecal screening tests with established fecal screening tests. These studies should report test positivity, screening test accuracy, adherence with recommended colonoscopic

referral, and health outcomes. Documenting initial and repeat test adherence, other implementation issues, and costs will help further inform policy makers. Studies evaluating the test performance of multiple tests within the same individual,[160] rather than comparing different approaches in different populations,[323,324] will provide the most useful data.

Other valuable studies would include:

1. Prospective evaluations of risks associated with small and medium-sized adenomas over 1, 3, 5, and 10 years. Similarly, natural history studies of advanced neoplasia would be very useful.
2. Studies validating the availability and performance of screening CTC that meet minimal technical and proficiency standards in community settings outside specialized or academic settings. These studies should examine yield, test positivity rate, test performance, health care utilization, and reader variability and accuracy.
3. Independent validation of preliminary risk indices based on age, sex, and distal colonic findings for determining appropriate candidates for flexible sigmoidoscopy instead of colonoscopy screening, and determination of the health impact of their use.
4. Development and validation of novel risk indices that incorporate race/ethnicity as a CRC risk factor along with other strong risk factor candidates (e.g., current and/or lifetime smoking exposure).
5. Well-designed cohort studies in average-risk screening populations to evaluate the test positivity, diagnostic yield, accuracy, and efficiency of validated risk indices for determining endoscopic and other CRC screening procedures in average-risk men and women of different racial/ethnic groups (Black, White, Asian/PI, and AI/AN) at different ages.
6. Cross-sectional research on the yield of adenomas, including flat and depressed adenomas, using chromoendoscopy or other optical colonoscopic adjuncts in average-risk patients undergoing primary or secondary colonoscopic screening.
7. Well-designed observational studies with adequate followup to determine the risks versus benefits of identifying extra-colonic findings.

Conclusions

Since the previous USPSTF review, evidence has accrued about novel CRC screening methods, including FITs, CTC, and fecal DNA testing. Screening for CRC has a rapidly evolving science base, such that guidance may change as more research becomes available.

Currently, based on test performance characteristics alone, a case could be made for substituting specific FITs (Magstream and perhaps FlexSure OBT) for guaiac FOBT tests to gain sensitivity in FOBT screening programs without losing specificity. Based on these test performance criteria (gain in sensitivity without loss of specificity) alone, Hemoccult Sensa may not be a good substitute for Hemoccult II or comparable guaiac tests. However, for most fecal tests there is not evidence to support a simple substitution. In these cases, clarifying the incremental benefits and harms (and net impact) from substituting newer fecal screening tests for older guaiac tests, in the context of an FOBT screening program for CRC, were beyond the scope of this review, but are addressed in the companion decision analysis.

Clinical accuracy studies of CT colonography (CTC) may justify its consideration for population CRC screening, particularly if one accepts that important lesions for detection and referral are those 10 mm or larger. However, the apparent accuracy of CTC (compared with colonoscopy) must be balanced against what we know about potential short-term and long-term harms, particularly from low-dose ionizing radiation, or the impact of extra-colonic findings. Further, potential variability in CTC test accuracy and safety that could occur with widespread performance in the community needs to be addressed. Fecal DNA screening studies in average-risk populations are too limited to support considering this approach for population CRC screening, particularly given the ongoing and rapid evolution of these technologies.

The estimated sensitivity of flexible sigmoidoscopy, with and without biopsy, for advanced neoplasia throughout the colon ranges from 72 to 86 percent, with possibly lower (but less precise) estimates for CRC throughout the whole colon (59 to 75 percent). Imperfect sensitivity of flexible sigmoidoscopy is not new and may result from many factors, including limited examination of the colon, variable performance by examiners, lack of standardized protocols for colonoscopic referral, and differing risks for advanced proximal neoplasia among patients. More accurate considerations of the benefits of flexible sigmoidoscopy screening programs will be clear only after current RCTs are reported. Colonoscopy misses fewer large lesions than flexible sigmoidoscopy, but recent comparisons with CTC, along with other research, illustrate the importance of high quality examinations. While neither colonoscopy nor flexible sigmoidoscopy is 100 percent sensitive, they remain important means for detecting and treating CRC and its precursor lesions (adenomas). As well, colonoscopy plays an important role as part of the final pathway for other screening tests. As such, quality criteria and standards for community endoscopy for CRC screening are also important. Additionally, potential harms associated with colonoscopy are not negligible, as serious complications from screening colonoscopy in average-risk populations occur in 31 per 10,000 procedures, 95 percent CI (17 to 58 per 10,000 procedures), and are ten-fold more common than serious complications with flexible sigmoidoscopy.

More targeted CRC screening recommendations that maximize population CRC screening benefits, while minimizing associated harms, are worth investigating. Upgrading community performance of screening endoscopies through quality improvement standards and monitoring may also help reduce procedure-related harms. Similar efforts to ensure high-quality community implementation will be necessary as new tests become recognized as valid CRC screening tests.

Table 1. Crude rates of colorectal cancer by age, sex, race/ethnicity, SEER 2000-2004

	All Races	Black	NH White	Asian/PI	Hispanic	AI/AN
Males						
40-44	14.7	19.7	14.6	13.6	11.4	7.4
45-49	29.7	37.0	29.2	28.2	22.5	21.6
50-54	59.7	79.9	58.8	49.7	45.5	47.9
55-59	93.6	129.2	91.2	82.2	75.1	68.4
60-64	147.8	197.9	147.6	105.7	117.5	155.0
65-69	223.9	261.9	224.2	188.7	185.7	154.6
70-74	300.6	338.9	303.7	236.4	253.7	227.4
75-79	379.0	436.5	383.1	321.5	303.0	204.6
80-84	428.9	503.0	438.3	339.0	311.0	312.1
85+	460.5	497.0	473.4	350.9	313.7	171.5
Females						
40-44	13.6	17.1	13.0	13.5	11.1	14.8
45-49	25.3	33.6	24.2	24.4	19.0	28.8
50-54	45.6	67.5	42.7	41.1	36.1	42.3
55-59	65.2	96.8	62.4	58.0	48.3	59.0
60-64	98.1	144.4	94.7	72.5	78.2	103.4
65-69	152.4	196.1	153.3	120.3	110.4	129.0
70-74	201.7	242.0	205.2	151.5	145.7	204.0
75-79	272.5	313.0	282.0	196.6	191.7	247.6
80-84	334.5	377.8	343.8	255.4	235.5	270.4
85+	377.4	388.0	386.8	288.5	278.3	209.3

Data from SEER CanQues:
http://seer.cancer.gov/canques/incidence.html

NH = nonHispanic; PI = Pacific Islander; AI = American Indian; AN = Alaska Native

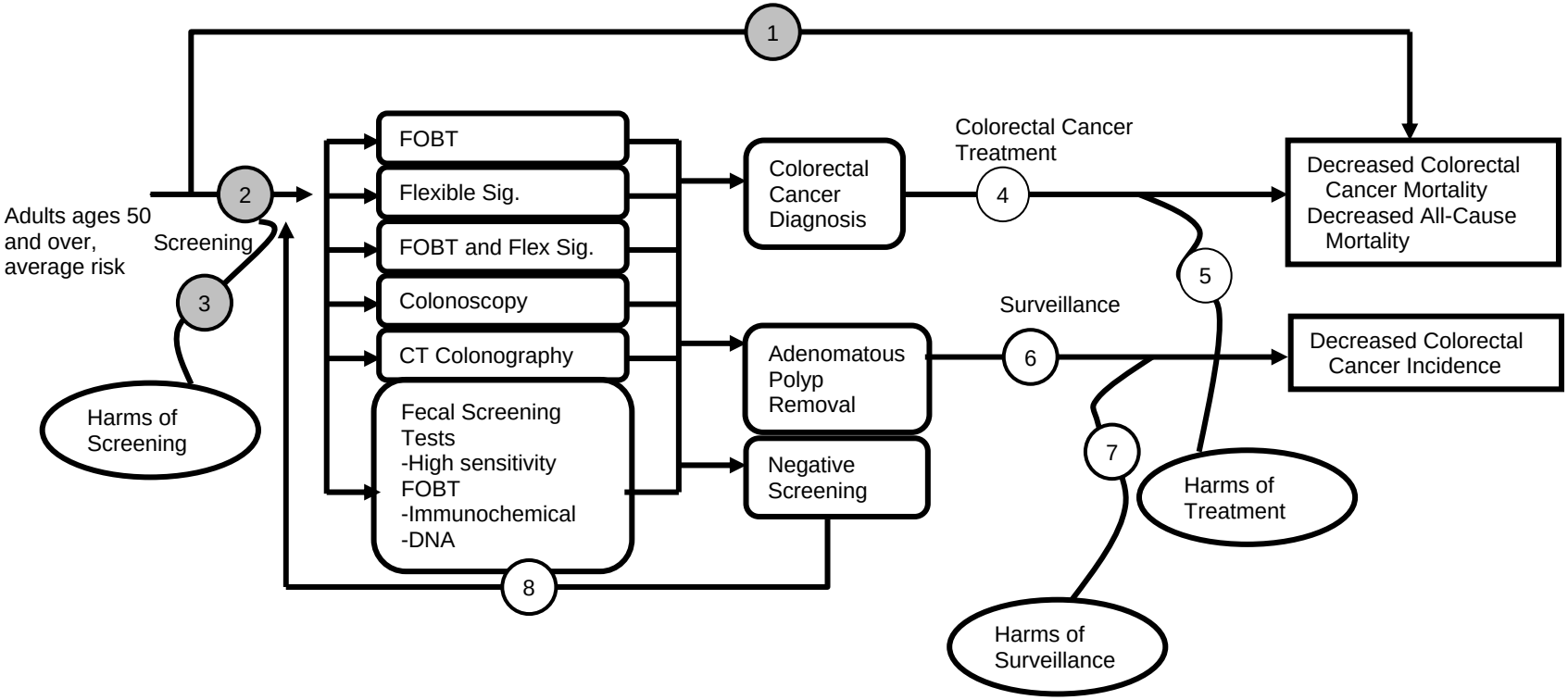
Incidence noted per 100,000; all values adjusted to US 2000 standard population

Table 2: Age-adjusted incidence of colorectal cancer by site, sex, and race/ethnicity, SEER 2000-2004

	All Races	Black	NH White	Asian/PI	Hispanic	AI/AN
Males						
All sites	60.8	72.6	61.2	49.7	47.5	42.1
Total distal	31.5	32.1	31.5	30.5	26.5	25.9
Total proximal	17.5	24.2	17.7	13.3	12.5	9.3
Ratio proximal: all	0.288	0.333	0.289	0.268	0.263	0.221
Females						
All sites	44.6	55	44.7	35.3	32.9	39.6
Total distal	20	22.1	19.8	19.2	17.3	20.2
Total proximal	14.8	18.6	14.1	10.4	9.4	9.6
Ratio proximal:all	0.332	0.338	0.315	0.295	0.286	0.242

Data from SEER CanQues: http://seer.cancer.gov/canques/incidence.html
NH = non-Hispanic; PI = Pacific Islander; AI = American Indian; AN = Alaska Native
Incidence noted per 100,000; all values adjusted to US 2000 standard population
Distal colon includes rectum and sigmoid; proximal colon includes all sites proximal to sigmoid

Figure 1. Analytic framework



KQ1: What is the effectiveness of the following screening methods (alone or in combination) in reducing *mortality* from colorectal cancer?

a. Flexible Sigmoidoscopy
b. Colonoscopy
c. CTC
d. Fecal screening tests: i. High-sensitivity guaiac fecal occult blood test; ii. Fecal immunochemical test; iii. Fecal DNA test

KQ2a: What are the sensitivity and specificity of (1) colonoscopy and (2) sigmoidoscopy when used to screen for CRC in the community practice setting?
KQ2b: What are the test performance characteristics of (1) CT-assisted colonography and (2) fecal screening tests [as listed in KQ1d] for CRC screening, as compared to a acceptable reference standard?
KQ3a: What are age-specific rates of harm from colonoscopy and sigmoidoscopy in the community practice setting?
KQ3b: What are the adverse effects of (1) CTC and (2) fecal screening tests [as listed in KQ1d]

Table 3. Key question 1 summary table

Study	Sample Demographics	CRC incidence (per 1000)	CRC mortality rate (per 1,000 persons)	RR
Annual Screening				
Minnesota (USA) Mandel 1993[5]	Sample size: S: 15,570; C: 15,394 Ages: 50-80 % female S: 52; C: 52	S: 23 persons; C: 26 persons	13 yrs NR (cumulative mortality)	0.67 (0.50-0.87)
Minnesota (USA) Mandel 1999[135] Mandel 2000[325]		S: 32 persons; C: 39 persons	18 yrs *(5 yrs; end of screening period)* NR (cumulative mortality)	0.67 (0.51-0.83)
Biennial Screening				
Nottingham (UK) Hardcastle 1996[3]	S: 76,224; C: 76,079 Ages: 50-74 % female: NR	S: 1.49 person yrs; C: 1.44 person yrs % of Dukes A: S: 20%; C: 11% P<0.001	7.8 yrs *median* S: 0.60; C: 0.70	0.85 (0.74-0.98)
Nottingham (UK) Scholefield 2002[132]		S: 1.51 person yrs; C: 1.53 person yrs % of Dukes A: NR	11.7 yrs (median) *(5 yrs after end of screening period)* S: 0.70; C: 0.81	0.87 (0.78-0.97)
Funen (Denmark) Kronborg 1996[4]	S: 30,762; C: 30,966 Ages:45-75 % female: S: 51.7; C: 53	S: 1.71 person yrs; C: 1.72 person yrs % of Dukes A: S: 22%; C: 11% P<0.01	10 yrs *(5 screening rounds)* S: 0.65; C: 0.82	0.79 (0.65-0.96)
			S: 0.73; C: 0.89*	0.82 (0.68-0.99)
Funen (Denmark) Jorgenson 2002[134]		S: 1.84 person yrs; C: 1.81 person yrs % of Dukes A: NR	13 yrs *(7 screening rounds)* S: 0.72; C: 0.88	0.82 (0.69-0.97)
			S: 0.83; C: 0.97*	0.85 (0.73-1.00)
Funen (Denmark) Kronborg 2004[131]		S: 2.06 person yrs; C: 2.02 person yrs % of Dukes A: S: 18%; C: 11%	17 yrs (*9 screening rounds)* S: 0.84; C: 1.00	0.84 (0.73-0.96)
			S: 0.99; C: 1.10*	0.89(0.78-1.01)
Minnesota (USA) Mandel 1993[5]	S: 15,587; C: 15,394 Ages: 50-80 % female S: 52.2; C: 52	S: 23 persons; C: 26 persons % of Dukes A: S: 26.6%; C: 22.3%	13 yrs NR (cumulative mortality)	0.94 (0.68-1.31)
Minnesota (USA) Mandel 1999[135] Mandel 2000[325]		S: 33 persons; C: 39 persons	18 yrs (*5 years after end of screening period)* NR (cumulative mortality)	0.79 (0.62-0.97)
Goteborg 1996 (Sweden) Towler 1998[326]	S: 34,144; C: 34,164 Ages: 60-64 % female: NR	NR	8.3 yrs (6 yrs after 2 screening rounds) NR	0.88 (0.69-1.12)
Goteborg 2005 (Sweden) Hewitson 2007[94]		NR	15.5yrs (13 years after 2 screening rounds) NR	0.84 (0.67-0.99)

* deaths from CRC "including complications from treatment".
S-screen group; C-control group

Table 4. Sensitivity of flexible sigmoidoscopy protocol* for advanced neoplasia

Study	Patient Characteristics	Overall polyp prevalence	Sensitivity of FS with biopsy for advanced neoplasia in the whole colon	Sensitivity of FS without biopsy for advanced neoplasia in the whole colon	Sensitivity of FS with biopsy for CRC in the whole colon	Sensitivity of FS without biopsy for CRC in the whole colon
Betes Ibanez 2004[144] Spain Distal definition: descending & sigmoid colon, rectum	N: 2210 Age incl: >40; Mean age: 57.9 % Ethnic Origin:NR % female: 25.4% FH: NR	Any neoplasm: 28% Adv. neoplasm: 7% CRC: 0.5%	85.3% (133/156)	NR	NR	NR
Ikeda 2000[145] Japan Distal definition: splenic flexure, descending & sigmoid colon, rectum	N: 3131 Age incl: 48-57; Mean age: 61.2 % Ethnic Origin: [Japanese] % female: 0% FH: NR	Any neoplasm:25.9% Adv. neoplasm: 2.4% CRC: 0.6%	73.7% (56/76)	NR	NR	NR
Anderson 2004[58] USA Distal definition: descending & sigmoid colon, rectum	N: 1988 Age incl: >40; Mean age: 57.2 % Ethnic Origin:1.5% NW % female: 45.6% FH: 13.6%	Any neoplasm: 21.9% Adv. neoplasm: 10.2% CRC:0.4%	73.8% (155/210)	NR	62.5% (5/8)	NR
Imperiale 2003[146] Imperiale 2000[59] USA Distal definition: descending & sigmoid colon, rectum	N: 3025 (1994 subgroup) Age incl: ≥50; Mean age: 58.9 % Ethnic Origin: 90% white % female: 42% FH: NR	Any neoplasm: NR Adv. neoplasm: 6.0% CRC: NR	Total: 71.8% (130/181) Male: 70.0% (98/140) Female: 78.0% (32/41)	76.8% (139/181)	58.3%(7/12)	75.0% (8/12)
Lieberman 2000[60] USA Distal definition: descending & sigmoid colon, rectum	N: 3121 Age incl: 50-75; Mean age: 62.9 % Ethnic Origin: 16.4% NW % female: 3.2% FH: 13.9%	Any neoplasm: 37.5% Adv. neoplasm: 10.5% CRC: 1.0%	81.7% (272/333)	85.6% (285/333)	NR	NR
Distal definition: sigmoid colon, rectum			71.2% (237/333)	78.7% (262/333)	NR	NR
Schoenfeld 2005[61] USA Distal definition: descending & sigmoid colon, rectum	N: 1463 Age incl: 40-79; Mean age: 58.9 % Ethnic Origin: 23% nonwhite % female: 100% FH: 15.7%	Any polyps: NR Any neoplasm: 20.4% Advanced neoplasm: 4.9% CRC: 0.1%	50% (36/72)	NR	NR	NR
Distal definition: sigmoid colon, rectum			34.7% (25/72)	NR	NR	NR

* This estimation of sensitivity is for flexible sigmoidoscopy *with* biopsy only

Table 5. Sensitivity and specificity of CT colonography (CTC)

	Reference standard	Sensitivity per-patient	Specificity per-patient	Total positivity Rate	Referral Rate for colonoscopy
3D measurements					
Pickhardt 2003[136] (n=1233)	Segmentally unblinded optical colonoscopy; oral contrast; fecal tagging; 1.25-2.5 mm collimation.				
adenoma ≥ 10 mm		93.8% [82.8-98.7]	96.0% [94.8-97.1]	7.5% [6.1-9.1]	1 out of every 13 screened
adenoma ≥ 8 mm		93.9% [86.3-98.0]	92.2% [90.5-93.7]	13.5% [11.7-15.6]	1 out of every 7 screened
adenoma ≥ 6 mm		88.7% [82.9-93.1]	79.6% [77.0-82.0]	29.7% [27.1-32.3]	1 out of every 3 screened
Kim 2007[137] (n=96)	Segmentally unblinded optical colonoscopy; IV contrast; no fecal tagging; 2 mm collimation.				
polyp ≥ 10 mm		100% [100-100] (calc)	100% [100-100] (calc)	9.9% [5.7-14.1] (calc)	1 out of every 10 screened
polyp ≥ 8 mm		88.5% [76.2-100] (calc)	98.5% [96.2-100] (calc)	13.5% [8.7-18.4] (calc)	1 out of every 7 screened
polyp ≥ 6 mm		75% [62.2-87.8] (calc)	94% [90.1-97.8] (calc)	21.9% [16.0-27.7] (calc)	1 out of every 5 screened
Johnson 2007[138] (n=452)	Video optical colonoscopy; no contrast; no fecal tagging; 1.25 mm collimation presented here.				
adenoma ≥ 10 mm (1.25mm slice)		73% [56.0-90.1] (calc)	98% [96.2-99.1] (calc)	3.2% [2.0-4.3] (calc)	Not calculated*
adenoma 6-9 mm (1.25mm slice)		60% [42.5-77.5] (calc)	94% [92.0-96.5] (calc)	4.6% [3.3-6.0] (calc)	Not calculated*
2D measurements					
Pickhardt 2007[151] (n=730)	Segmentally unblinded optical colonoscopy; oral contrast; fecal tagging; 1.25-2.5 mm collimation.				
polyp ≥ 10 mm		63.4% [48.7-78.2]	98.1% [97.1-99.1]	5.3% (calc)	1 out of every 19 screened
polyp ≥ 6 mm		43.0% [35.0-50.9]	95.2% [93.4-96.9]	12.6% (calc)	1 out of every 8 screened
Kim 2007[137] (n=96)	Segmentally unblinded optical colonoscopy; IV contrast; no fecal tagging; 2 mm collimation.				
polyp ≥ 10 mm		100% [100-100] (calc)	99.5% [100-100] (calc)	9.9% [5.7-14.1] (calc)	1 out of every 10 screened
polyp ≥ 8 mm		92% [82.1-102.6] (calc)	98.5% [96.2-100.2] (calc)	14.1% [9.1-19.0] (calc)	1 out of every 7 screened
polyp ≥ 6 mm		61.5% [47.0-75.8] (calc)	90% [85.0-94.7] (calc)	21.9% [16.0-27.7] (calc)	1 out of every 5 screened
Johnson 2007[138] (n=452)	Video optical colonoscopy; no contrast; no fecal tagging; 1.25 mm collimation presented here.				
adenoma ≥ 10 mm (1.25mm slice)		76% [59.3-92.7] (calc)	98% [96.8-99.4] (calc)	3.0% [1.9-4.1] (calc)	Not calculated*
adenoma 6-9 mm (1.25mm slice)		53% [35.5-71.2] (calc)	95% [93.2-97.3] (calc)	4.0% [2.7-5.2] (calc)	Not calculated*

*Polyp prevalence significantly different than those reported in similar studies.

Table 6. Fecal immunochemical test summary table*

	Gold Standard	Cut off/Other FOBT tested	Fecal sample	Test positivity rate	Sensitivity	Specificity	FDA approved	US market
Magstream								
Morikawa[163] n=21,805 Fair	Colonoscopy all patients	20 ng/ml	1-day	5.6%	CRC: 65.8% AdvNeo: 27.1% Aden ≥ 10mm: 20.0%	CRC: 94.6% AdvNeo: 95.1% Aden ≥ 10mm: NR	No	No
Launoy[166] n=7421 Fair	Registry followup-screen negative; Colonoscopy-screen positive	>20 ng/ml	2-day	5.8%	CRC: 85% AdvNeo: NR	CRC: 94% AdvNeo: NR	No	No
		>50 ng/ml		3.1%	CRC: 67.8% AdvNeo: NR	CRC: 97% AdvNeo: NR		
		>75 ng/ml		2.0%	CRC: 61% AdvNeo: NR	CRC: 98% AdvNeo: NR		
Allison[160] n=8104 Fair	Registry followup-screen negative; Colonoscopy-screen positive	HemeSelect (Magstream)	3-day	5.9%	CRC: 68.8% Polyp ≥ 10mm: 66.7%	CRC: 94.4% Polyp ≥ 10mm: 95.2%	Yes	No
		HO Sensa		13.6%	CRC: 79.4% Polyp ≥ 10mm: 68.6%	CRC: 86.7% Polyp ≥ 10mm: 87.5%	Yes	Yes
		HO Sensa/HemeSelect			CRC: 65.6% Polyp ≥ 10mm: 50.0%	CRC: 97.3% Polyp ≥ 10mm: 97.9%		
		Hemoccult II	3.0%	2.5%	CRC: 37.1% Polyp ≥ 10mm: 30.8%	CRC: 97.7% Polyp ≥ 10mm: 98.1%	Yes	Yes
OC-Hemodia								
Cheng[161] n=7411 Fair	Colonoscopy all patients		3-day	9.2%	CRC: 87.5% AdvNeo: 48.4%	CRC: 91.0% AdvNeo: 91.3%	No	No
Itoh[165] n=27,860 Fair	Registry followup-screen negative; Colonoscopy-screen positive		1-day	5.3%	CRC: 86.5%	CRC: 94.9%	No	No
Levi[327] *Family History Subset (n=80)* Fair	Colonoscopy all patients		3-day	18.8%	CRC: 66.7% AdvNeo: 55.6%	CRC: 83.1% AdvNeo: 91.9%	No	No
FlexSure OBT								
Allison†[159] n=5841 Good	Colonoscopy-screen positive or FS - screen negative	FlexSure	3-day	3.2%	CRC: 81.8% Aden ≥ 10mm: 29.5%	CRC: 96.9% Aden ≥ 10mm: 97.3%	Yes	Yes
		HOSensa		10.1%	CRC: 64.3% Aden ≥ 10mm: 41.3%	CRC: 90.1% Aden ≥ 10mm: 90.6%	Yes	Yes
		FlexSure/ HOSensa	2.1%		CRC: 64.3% Aden ≥ 10mm: 22.8%	CRC: 98.1% Aden ≥ 10mm: 98.4%		

	Gold Standard	Cut off/Other FOBT tested	Fecal sample	Test positivity rate	Sensitivity	Specificity	FDA approved	US market
Monohaem								
Nakama[169] n=4611 Fair	Colonoscopy all patients		1-day	NR	CRC: 55.6% Aden: 30.1%	CRC & Aden: 97.1%	Yes	No
			2-day	NR	CRC: 83.3% Aden: 50.7%	CRC& Aden: 96.0%		
			3-day	NR	CRC: 88.9% Aden: 54.8%	CRC & Aden: 93.9%		
Nakama*[167] n=3365 Fair	Registry followup-screen negative; Colonoscopy-screen positive	1 yr followup 2 yr followup 3 yr followup	1-day	4.7%	CRC: 90.9% CRC: 83.3% CRC: 71.4%	CRC: 95.6%	Yes	No
*Sensitivity and specificity of small adenomas or polyps of unknown size found in full evidence table. †Left-sided cancers only.								
CRC-colorectal cancer; NR-not reported; AdvNeo-advanced neoplasia; Aden-adenoma								

Figure 2. Proportion of total serious complication in colonoscopy studies

	Number of Cases	Number of Total Procedures	Proportion (95% CI)*
Kewenter, 1996	3	190	0.0158 (0.00327, 0.0454)
Robinson, 1999	7	1474	0.00475 (0.00191, 0.00976)
Thiis, 1999	1	521	0.00192 (0.0000486, 0.0106)
Nelson, 2002	18	3196	0.00563 (0.00334, 0.00889)
Segnan, 2002	2	775	0.00258 (0.000313, 0.00929)
Pickhardt, 2003	1	1233	0.00081 (0.000021, 0.00451)
Cotterill, 2005	0	324	0 (0, 0.0113)
Ko, 2006	8	502	0.0159 (0.00690, 0.0312)
Levin, 2006	44	16318	0.00270 (0.00196, 0.00362)
Rathgaber, 2006	14	12407	0.00113 (0.000617, 0.00189)
Ko, 2007	45	18271	0.00246 (0.00180, 0.00329)
Combined (excluding Ko, 2007)			**0.00319 (0.00156, 0.00654)**
All studies combined			**0.00311 (0.00168, 0.00576)**

* 95% CIs are exact confidence intervals

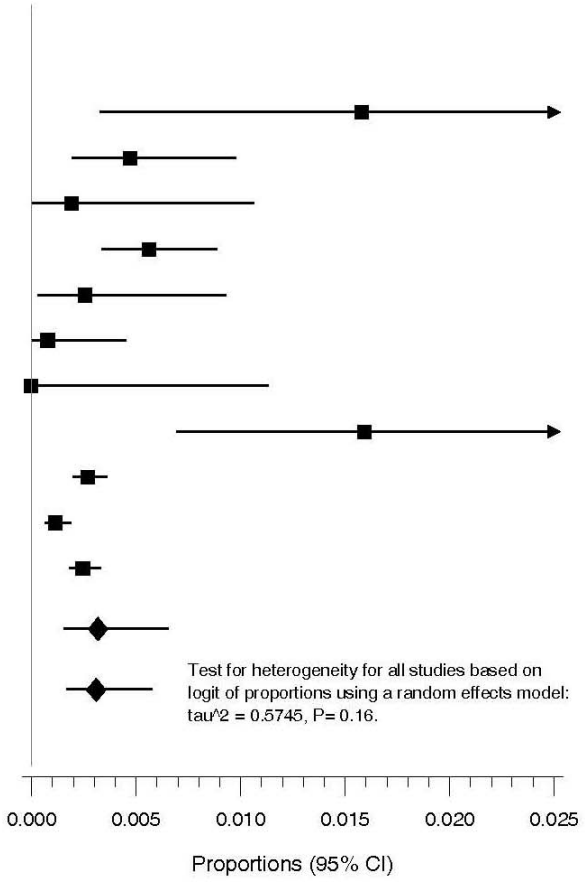


Figure 3. Proportion of total serious complication in flexible sigmoidoscopy studies.

	Number of Cases	Number of Total Procedures	Proportion (95% CI)*
Kewenter, 1996	3	2108	0.00142 (0.000294, 0.00415)
Atkin, 1998	3	1285	0.00233 (0.000482, 0.00681)
Thiis, 1999	1	446	0.00224 (0.0000568, 0.0124)
Wallace, 1999	0	3701	0 (0, 0.000996)
Levin, 2002	7	109534	0.0000639 (0.0000257, 0.000132)
Segnan, 2002	2	9911	0.000202 (0.0000244, 0.000729)
All studies combined			**0.000341 (0.0000607, 0.00192)**

* 95% CIs are exact confidence intervals

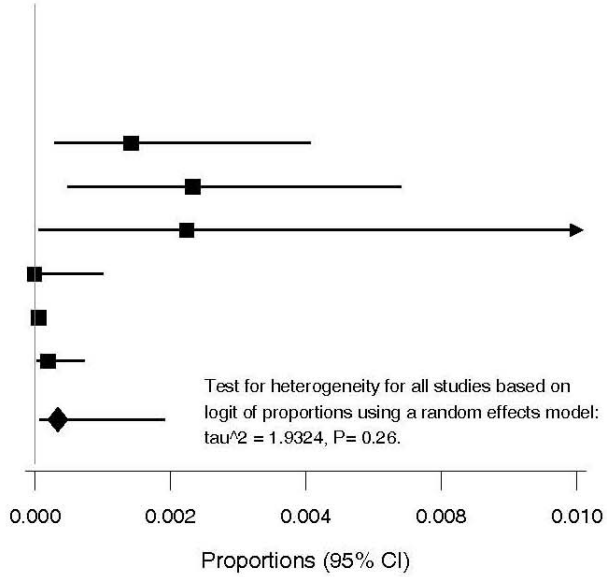


Table 7. Summary table key question 3a

Study Quality	Study Design Duration of followup	Procedure Information Operator characteristics	Patient characteristics (general, age, sex)	Adverse events	
Colonoscopy Only					
Kim 2007[182] Fair	Prospective cohort	Colonoscopies: 3163 10 gastroenterologists	98% Asymptomatic Age: 58.1 mean % female: 56%	**Death:** NR **Perf:** 7/3163 (0.2%)	**Bleed:** NR **Other Major:** NR
Ko 2007[177,183] Fair	Prospective cohort 30 days	Colonoscopies: 18271 89 gastroenterologists, with 10% trainee participation	Asymptomatic Age: 89% 50-79 years % female: 45	**Death:** 0/18271 (0%) **Perf:** 4/18271 (0.02%)	**Bleed:** 25/18271 (0.14%) **Other major:** 7/18271 (0.04%)
Levin 2006[171] Fair	Retrospective cohort 30 days	Colonoscopies: 16318 96% gastroenterologists 2% internists	Asymptomatic Mean Age: 62 % female: 40	**Death:** 1/16318 (0.006%) **Perf:** 15/16318 (0.09%)	**Bleed:** 15/16318 (0.09%) **Other major:** 14/16318 (0.09%)
Cotterill 2005[174] Fair	Prospective cohort NR	Colonoscopies: 324 2 family practitioners	Asymptomatic Age (range): 22-80 % female: 44	**Death:** NR **Perf:** 0/324 (0%)	**Bleed:** 0/324 (0%) **Other major:** NR
Rathgaber 2006[172] Fair	Retrospective cohort 30 days	Colonoscopies: 12407 8 gastroenterologists	NR but community setting Mean age: 60 % female: 52	**Death:** NR **Perf:** 2/12407 (0.016%)	**Bleed:** 11/12407 (0.09%) **Other major:** 1/12407 (0.008%)
Newcomer 1999[180] Fair	Prospective cohort 7 days	Total Colonoscopies: 270 (results for 250 reported) NR	NR but community setting Mean age: 52 % female: 43	**Death:** 0/250 (0%) **Perf:** 0/250 (0%)	**Bleed:** 0/250 (0%) **Other major:** NR
Korman 2003[170] Fair	Retrospective cohort NR	Colonoscopies: 116000 264 gastroenterologists	NR but community setting Mean age: 69 % female: 73	**Death:** NR **Perf:** 37/116000 (0.03%)	**Bleed:** NR **Other major:** NR
Nelson 2002[179] Good	Prospective cohort 30 days	Colonscopies: 3196 gastroenterologists at 13 sites	Asymptomatic Mean age: 63 % female: 3	**Death:** 1/3196 (.03%) **Perf:** 0/3196 (0%)	**Bleed:** 7/3196 (0.22%) **Other major:** 9/3196 (0.28%)
Ko 2006[176] Fair	Prospective cohort 30 days	Colonoscopies: 502 8 gastroenterologists, with 36% trainee participation	Asymptomatic Age: 91% 50-79 years % female: 50.8	**Death:** NR **Perf:** 0/502 (0%)	**Bleed:** 4/502 (0.80%) **Other major:** 4/502 (0.80%)
Robinson 1999[181] Fair	RCT for FOBT (colonoscopy if FOBT +) 30 days	Colonoscopies: 1474 NR	Asymptomatic Age range: 50-75 % female: 52	**Death:** 0/1474 (0%) **Perf:** 5/1474 (0.3%)	**Bleed:** 1/1474 (0.07%) **Other major:** 1/1474 (0.07%)
Lee 2006[178] Fair	Prospective cohort 24 hours	Colnoscopies:1000 7 gastroenterologists	Asymptomatic Mean age: 51 % female: 43	**Death:** NR **Perf:** NR	**Bleed:** NR **Other major:** NR
Pickhardt 2003[136] Fair	Prospective cohort for CTC (colonoscopy as reference) NR	Colonoscopies: 1239 14 gastroenterologists 2 colorectal surgeons	Asymptomatic Mean age: 58 % female: 41	**Death:** NR **Perf:** NR	**Bleed:** 1/1239 (0.08%) **Other major:** NR

Study Quality	Study Design Duration of followup	Procedure Information Operator characteristics	Patient characteristics (general, age, sex)	Adverse events			
FLEX SIG AND COLONOSCOPY							
Segnan 2002[82] Fair	RCT for flex sig (colonoscopy for f/u) NR	Flex Sig: 9911 Colonoscopies: 775 gastroenterologists in hospital endoscopy units	Average risk Age range: 55-64 % female: 50.0	***Flex sig*** **Death:** NR **Perf:** 1/9911(0.01%)	**Bleed:** 0/9911(0%) **Other major:** 1/9911(0.01%)	***Colonoscopy*** **Death:** NR **Perf:** 1/775 (0.13%)	**Bleed:** 1/775 (0.13%) **Other major:** NR
Thiis-Evensen 1999[6] Hoff 2001[188] Fair	RCT for flex sig (colonoscopy for f/u) 14 days	Flex Sig: 446 Colonoscopies: 521 NR	Average risk Age range: 50-59 Mean age at f/u: 67 % female: 50, at f/u: 48	***Flex sig*** **Death:** 0/446 (0%) **Perf:** 0/446 (0%)	**Bleed:** 0/446 (0%) **Other major:** 1/446 (0.22%)	***Colonoscopy*** **Death:** 0/521 (0%) **Perf:** 0/521 (0%)	**Bleed:** 0/521 (0%) **Other major:** 1/521 (0.19%)
Atkin 1998[173] Fair	RCT for flex sig (colonoscopy for f/u) 1 day	Flex Sig: 1285 Colonoscopies: 76 NR	Average risk Age range: 55-64 % female: NR	***Flex sig*** **Death:** 0/1285 (0%) **Perf:** NR	**Bleed*:** 40/1285 (3.1%) **Other major:** 3/1285 (0.23%)	***Colonoscopy*** **Death:** NR **Perf:** NR	**Bleed:** NR **Other major:** NR
Kewenter 1996[175] Fair	RCT for FOBT (endoscopy if FOBT or DCBE +) 12 days	Flex Sig: 2108 Colonoscopies: 190 NR	Asymptomatic Age range: 60-64 % female: NR	***Flex sig*** **Death:** NR **Perf:** 3/2108 (0.14%)	**Bleed:** 0/2108 (0%) **Other major:** NR	***Colonoscopy*** **Death:** NR **Perf:** 2/190 (1.05%)	**Bleed:** 1/190 (0.5%) **Other major:** NR
FLEX SIG ONLY							
Viiala 2007[187] Fair	Prospective cohort	Flex sig: 3402 Gastroenterologist, surgeons, supervised registrars, and GPs	Average risk Mean age: 60 % female: 41	**Death:** NR **Perf:** 0/3402 (0%)		**Bleed:** 0/3402 (0%) **Other major:** NR	
Levin 2002[185] Fair	Retrospective cohort 30 days	Flex Sig: 109534 Gastroenterologist, non-GI MD, or nurse.	Average risk Mean age: 61 % female:49	**Death*:** 5/109534 (0.004%) **Perf:** 2/109534 (0.002%)		**Bleed:** 2/109534 (0.002%) **Other major:** 3/109534 (0.003%)	
Jain 2002[184] Fair	Retrospective cohort NR	Flex Sig: 5017 Registered GI nurses	Average risk Age: >50 % female: NR	**Death:** 0/5017 (0%) **Perf:** 0/5017 (0%)		**Bleed:** 0/5017 (0%) **Other major:** NR	
Wallace 1999[186] Fair	Prospective cohort NR	Flex Sig: 3701 Gastroenterologists, 1 NP, 2 PAs	Average risk Mean age: 59 % female: 51	**Death:** 0/3701 (0%) **Perf:** 0/3701 (0%)		**Bleed:** 0/3701 (0%) **Other major:** 0/3701 (0%)	

Table 8. Summary table key question 3b

Study **Quality**	**Study Design** **Duration of followup**	**Procedure Information** **Operator characteristics**	**Patient characteristics**	**Adverse events**
Kim[137] 2007 Fair	Prospective Cohort F/u NR	**CTC:** 3120 5 gastrointestinal radiologists	**Age:** 57.0 mean **% female:** 56 **% symptomatic:** 2	**Total Perforations:** 0 **Other major:** 0
Pickhardt 2006[190] Fair	Retrospective cohort Variable, generally 30 days	**CTC:** 21923 Screening: 11707 Diagnostic: 10216 radiologists at 16 centers; direct MD monitoring of CTC in 45.8% of cases	**Age:** NR **% female:** NR **% symptomatic:** 47	**Total Perforations:** 2/21923 (0.009%) Screening: 0/11707 (0% Diagnostic: 2/10216 (0.02%) **Other major:** exacerbated acute renal failure: 2/21,923 (0.009%) chest pain (not MI): 1/21,923 (0.0045%)
Edwards 2004[189] Fair	Prospective cohort NR	**CTC:** 340 2 radiologists	**Age range:** 50-54; 65-69 **% female:** 49 **% symptomatic:** 0	**Total Perforations:** NR **Other major:** none
Sosna 2006[191] Fair	Retrospective cohort NR	**CTC:** 11870 Staff and resident radiologists at 5 academic centers; non-radiologist MD at 6 non-academic centers	**Mean age:** 60 **% female:** 42 **% symptomatic:** NR	**Total Perforations:** 7/11870 (0.06%) Screening: 1, unknown denominator Diagnostic: 6, unknown denominator **Other major:** NR
Pickhardt 2003[136] Fair	Prospective Cohort NR	**CTC:** 1247 6 radiologists	**Mean age**: 58 **% female:** 41 **% symptomatic:** 0	**Total Perforations:** NR **Other major:** none

Table 9. Summary evidence table

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
KQ1. What is the effectiveness of CRC screening methods (alone or in combination) in reducing mortality from colorectal cancer?							
1 meta-analysis 4 RCTs	Meta-analysis and RCTs	New CRC mortality reports from screening trials only address longer-term follow up of standard guaiac FOBT screening programs.	CRC mortality reduction estimates from biennial FOBT screening RCTs are reasonably consistent; in one trial, inclusion of CRC-related treatment deaths reduces mortality benefit to 11% which is no longer statistically significant.	Population screening trials conducted in US, UK, Sweden, and Denmark in ages 45 to 80 years. NonWhite populations not well represented in these countries.	Good	CRC, but not all-cause, mortality is reduced 13-21% (pooled estimate: RR 0.85; CI: 0.78, 0.92), generally after 8 to 13 years in biennial FOBT screening programs. Higher mortality reductions have been seen in the single annual screening trial (33%), but this trial also had higher participation rates through enlisting only volunteers. Initial participation after mailed invitation to the FOBT screening programs is high (60 to 67%) and overall participation in screening rounds is 30 to 60%. CRC incidence may be reduced with FOBT screening programs, but not until 3 to 5 years after screening programs cease.	Four FS RCTs (PLCO, SCORE, UK Flex Sig, NORCCAPS) are completed (but not published) or still underway. These trials test FS using protocols for colonoscopy referral with and without biopsy. These trials will report CRC mortality endpoints.
KQ2a. What are the sensitivity and specificity of colonoscopy and flexible sigmoidoscopy when used to screen for CRC in the community practice setting?							
Colonoscopy							
3 studies of test accuracy for colonoscopy compared with CTC; "enhanced" reference standard of second-look colonoscopy for discrepancies between CTC and colonoscopy	Cross-sectional cohort	Small number of patients studied (1781 total). Number of colonoscopists varied between studies, from five to 50, which complicates test accuracy estimates with considerations of training and experience. Estimates of colonoscopy test performance are hampered by lack of a true gold standard.	Consistent estimates are hampered by variability in CT technology (e.g., use of contrast agent vs. no contrast agent, 2D vs. 3D). All studies conducted in average-risk screening populations.	Estimates are not precise or clearly applicable to the community endoscopists.	Fair	Sensitivity of colonoscopy for CRC varied widely (20 percent to 50 percent) due in part to small numbers of cancers (7 total CRCs detected in all 3 studies). Sensitivity for large adenomas (10 mm or larger) ranged from 77 percent to 100 percent. Sensitivity for smaller polyps is harder to estimate due to inconsistent reporting, but suggests about a 10 percent miss rate.	These data are mostly useful to support the need for performance standards for community colonoscopy, particularly for screening.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
Flexible sigmoidoscopy							
3 cohort studies of FS examinations 6 cohort studies of screening colonoscopies	2 prospective cohort studies 7 cross-sectional cohort studies	Using screening colonoscopy to estimate FS results likely overestimates sensitivity because studies considered all neoplasia distal to the splenic flexure as detected by FS, but the colonoscopy bowel preparation is superior to that for FS. Endoscopist skill for colonoscopy may also vary from FS.	Six screening colonoscopy studies (n=14,938) supply data to simulate one FS screening protocol of biopsy & colonoscopy referral for adenomas of any size; Two of these screening colonoscopy studies (n=6,146) also simulate the FS screening protocol of colonoscopic referral for any lesion visualized with no biopsy done.	Estimates are taken from studies conducted in average risk screening populations.	Fair	In 3982 average-risk adults, the sensitivity of simulated FS with biopsy for CRC throughout the colon ranged from 58.3 to 62.5 percent. Among 14,938 predominantly average risk adults aged 40-79 years, estimated sensitivity of FS with biopsy for advanced neoplasia throughout the colon ranged from 70 to 86% (excluding an outlier of 50 percent in women examined in military medical centers). The sensitivity of simulated FS without biopsy for CRC was 75%, based on a single study (n =1994), and ranged from 77 to 86% for advanced neoplasia (n = 6146). Among persons with no distal adenomas on FS, isolated advanced proximal neoplasia occurred in 0.8 to 3.2%, giving a best-case estimate of the false negative rate for FS.	Simulated estimates of FS test performance characteristics with and without biopsy should be unnecessary once results are reported from four pending RCTs.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
KQ2b. What are the test performance characteristics of CT-assisted colonography and fecal screening tests (e.g., high-sensitivity guaiac fecal occult blood testing (FOBT), fecal immunochemical test, or fecal DNA tests) for CRC screening as compared to an acceptable reference standard?							
CT colonography (CTC)							
3 studies of test accuracy (supplemented by two studies re-examining the findings from the largest study)	Cross-sectional cohort studies	Differences in CTC technology and variability between readers limit studies' ability to provide precise estimates of CTC performance, particularly for lesions smaller than 10 mm in size. Health implications of uncertainties in test performance are unclear.	One large study (n=1233) using 3D flythrough endoluminal imaging represents most (69%) of patients studied, and is the only one to use contrast to allow fecal tagging and endoluminal fluid opacification. Two smaller studies (n=96 and n=452) compare 3D virtual dissection with 2D imaging.	The best data come from a single study using CT technologies and experienced readers whose generalizability to community CTC practices must be considered. Superiority of 3D compared with 2D techniques is not clear. Reader variability remains a factor.	Fair to Good	Among 1233 average risk patients, per-patient sensitivity of 3D endoluminal CTC was 93.8% for large (greater than 10 mm) adenomas and 88.7% for adenomas 6 mm or larger; sensitivity estimates were not statistically significantly different based on polyp size nor from sensitivity estimates for optical colonoscopy (OC). Specificity was significantly lower for lesions 6 mm or larger (79.6%) than for lesions 8 mm (92.2%) or 10 mm (96%) in size or larger. In two other studies (n=548) sensitivity and specificity of virtual dissection 3D CTC ranged from 73 to 100% (sensitivity) and 98 to 100% (specificity) for lesions 10 mm or greater and 60 to 75% (sensitivity) and 89 to 99% (specificity) for lesions 6 mm or greater. 3D sensitivity and specificity estimates were not clearly different from estimates for 2D imaging. Our best estimate is that between one in three and one in twelve patients would be referred for OC after CTC screening.	Reported but as-yet-unpublished results from the multisite National CT colonography trial (ACRIN) come from 15 US centers who evaluated CTC using primary 2D or 3D readings in 2531 asymptomatic persons. Reported but unpublished results from the Munich CRC Prevention trial (300 average-risk patients) also suggest excellent per-patient sensitivity for polyps of all sizes, but do not report specificity. Inconsitencies and incompleteness of presented but not published data could soon be resolved.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
Fecal tests							
High-sensitivity guaiac: 2 studies of test accuracy **Fecal Immunochemical Test (FIT)**: 9 studies of test accuracy **Fecal DNA**: 2 studies of test accuracy 11 total studies as 2 studies evaluated both FIT and high-sensitivity guaiac)	5 prospective cohort 6 cross-sectional cohort	**High-sensitivity guaiac**: Two comparative studies, one using different reference standards for different tests. **FIT**: FITs cannot be compared as a class and there are many different tests, with few studies per test. Performance for all but one FIT was reported qualitatively at a single cut-point rather than quantitatively (i.e., across multiple cut-points). Several studies used registry followup for screen-negative patients, likely overestimating sensitivity. **Fecal DNA**: One study for each of two approaches. Only Fecal DNA panel had any sensitivity for CRC and it has been replaced by upgraded tests.	**High-sensitivity guaiac**: One study provides estimates for left-sided cancers only. **FIT:** Estimates of sensitivity and specificity did show variability within each test. This may be due in part to different collection methods and reference standard applied. **Fecal DNA**: NA	**Most FIT** studies evaluated non- FDA approved tests (or those not on the US market). No eligible studies were found for most FDA-approved FIT tests (e.g., Insure/Inform, Quickvue, Hemosure) **Fecal DNA** panel was tested in a subgroup (*n* = 2507) with CRC, advanced adenomas or tumors (*n* = 436), and a randomly selected group with minor (*n* = 648) or no (*n* = 1423) detected polyps. Population was older (75% > 65 y) than usual CRC screening population; panel test evaluated has been replaced and now requires premarket review by FDA.	**High-sensitivity guaiac**: Fair **FIT**: Fair **Fecal DNA**: Fair to Poor	**High-sensitivity guaiac**: In one comparative cohort study in 8104 average-risk sceening patients, Hemoccult Sensa (13.6% test positives) was more sensitive for CRC (79.4%) than Hemoccult II (37.1%), but with lower specificity (86.7% vs 97.7%). A second study (n=5841) of left-sided CRC found Hemoccult Sensa positive in 10.1% with a sensitivity of 64.3% and specificity of 90.1%. **FIT**: Studies with a total of 86,498 average-risk patients were located that provided estimates for Magstream (and related tests), OC-Hemodia, FlexSure OBT (now Hemoccult ICT), and Monohaem. Across the tests, sensitivity for CRC ranged from 61% to 88% with specificity ranging from 91-98%. Test positive rates were generally between 2.0% and 5.9%. **Fecal DNA**: For PreGenPlus™ fecal DNA panel, sensitivity for CRC was 51.6% with a specificity of 94.4%. Test positives were 8.2%. In comparison, Hemoccult II sensitivity for CRC was 12.9% and specificity was 94.3%, with 5.8% test positives. Among all participants (*n* = 5486), more (11.7%) did not adhere to fecal DNA tests than to Hemoccult II (7.8%).	Sensitivity of non-rehydrated Hemoccult II for CRC ranged from 25 to 38 percent (with one outlier study of 60 percent) and specificity was 98-99 percent in a recent systematic review. Results are pending from NCT00025025 (Colorectal Cancer Screening: Fecal Blood vs. DNA. David Ahlquist MD, Mayo Clinic Cancer Center, protocol chair). A randomized multicenter study of 2000 patients (65-80 years of age) undergoing FOB testing, a newer generation multi-target DNA-based panel testing of blood and of stool, and colonoscopy.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
KQ3a. What are the age-specific rates of harm from colonoscopy and flexible sigmoidoscopy in the community practice setting?							
Colonoscopy							
16 cohort studies	3 retrospective cohort; 13 prospective cohort (6 nested within trials)	Not all studies were conducted in a community setting. However those conducted in research or academic settings were conducted in asymptomatic populations. Variation in duration of followup and methods for determining adverse events.	No significant statistical heterogeneity in pooling estimates of serious adverse events. Limited meta-regression showed that only study setting by country was significantly associated with complications from perforations. However, stratified analyses by country of setting did not produce clinically significantly different estimates harms (total, perforation, bleeding).	All studies conducted either among asymptomatic persons or in a community setting, or both.	Fair	In 11 studies (n=55,211), serious complications occurred in 3.1 per 1000 procedures (CI: 1.7, 5.8). In the six US studies, serious complications occurred in 2.9 per 1000 procedures (CI: 1.2, 7.6). In 13 studies (n=173,391), perforations occurred in 5.6 per 10,000 procedures (CI: 2.2, 14.5). In the eight US studies, perforations occurred in 3.8 per 10,000 procedures (CI: 1.4, 10.4). In 12 studies (n=55,461), major bleeding occurred in 12 per 10,000 procedures (CI: 8.9, 16). In the seven US studies, major bleeding occurred in 12.3 per 10,000 procedures (CI: 7.8, 19.3). Unable to obtain reliable pooled estimates for the proportion of other types of complications, including death, due to sparse data.	Only one study (Newcomer 1999) was included in the 2002 review. One study (Ko 2007) is currently only available in abstract form, additional details were provided by the author.
Flexible sigmoidoscopy							
8 cohort studies	2 retrospective cohort 6 prospective cohort (2 nested within trials)	Five studies not conducted in the US and endoscopist characteristics not reported in 3 of the 5 studies. Variation in duration of followup and methods for determining adverse events.	No significant statistical heterogeneity in pooling estimates of serious adverse events. Limited meta-regression showed that only study setting by country was significantly associated with total serious complications. However, stratified analyses by country of setting did not produce clinically significantly different estimates harms.	All studies conducted among asymptomatic, average-risk persons.	Fair	In 6 studies (n=126,985), serious complications occurred in 3.4 per 10,000 procedures (CI: 0.6,19). In the two US studies, serious complications occurred in 0.9 per 10,000 procedures (CI: 2 per million, 50 per 10,000). In 7 studies (n=134,119), perforations occurred in 4.6 per 100,000 procedures (CI: 0.4, 59). In the three US studies, perforations occurred in 0.2 per 10,000 procedures (CI: 1 per million, 3.5 per 10,000). Unable to obtain reliable pooled estimates for the proportion of other types of complications due to sparse data.	Only one study (Atkin 1998) was included in the 2002 review.

No. of studies	Design	Limitations	Consistency	Applicability	Overall Internal Validity	Summary of Findings	Comment
KQ 3b. What are the adverse effects of CT colonography (CTC) and/or fecal screening tests (high-sensitivity fecal occult blood tests, fecal immunochemical, and fecal DNA)?							
CT colonography (CTC)							
5 cohort studies	3 prospective cohort 2 retrospective cohort	Unclear clinical significance of perforations visualized on CT. No direct evidence of harms from low-dose ionizing radiation from CT studies.	Three prospective studies included predominantly asymptomatic, average- risk populations. Two large retrospective studies included both symptomatic and asymptomatic persons. Risk of perforations from CTC appears higher in symptomatic persons.	Evidence for harms from CTC among asymptomatic persons not in community settings	Fair	In 3 prospective studies (n=4707) and the asymptomatic subgroup of one large retrospective study (n=11,707), there were no serious complications, including perforation. In the other large retrospective study (n=11,870), with both symptomatic and asymptomatic patients, there were 7 total perforations. However, only one perforation occurred in the asymptomatic population (the number of screening CTC procedures is not reported).	One study (Pickhardt 2006) is only available in abstract form, additional details were provided by the author. Indirect evidence of risk of malignancy from low-dose ionizing radiation is included in the discussion.
Fecal tests							
No studies							

Table 10. Reported accuracy of CT Colonography

	Colonoscopy	CT Colonography		
	Pickhardt 2003	Pickhardt 2003	Kim 2007	ACRIN 2007 (unpublished)
Patients (n)	1233	1233	3120	2531
Sensitivity (per patient), [95% CI]				
Adenoma ≥ 10 mm	87.5, [74.8, 95.3]	93.8, [82.8, 98.7]	n/a	90, [nr]
Adenoma ≥ 6 mm	92.3, [87.1, 95.8]	88.7, [82.9, 93.1]	n/a	78, [nr]
Specificity (per patient), [95% CI]				
Lesions ≥ 10 mm	n/a	96.0, [94.8, 97.1]	n/a	86, [nr]
Lesions ≥ 6 mm	n/a	79.6, [77.0, 82.0]	n/a	88, [nr]
Referral to OC				
Lesions ≥ 10 mm	n/a	1 in 13	nr	nr
Lesions ≥ 6 mm	n/a	1 in 3	1 in 8-13*	1 in 6-12**

n/a- not applicable, nr- not reported

* higher estimate because only a few of those persons with lesions ≥ 6mm choose CTC surveillance over immediate colonoscopy followup

** variable estimates based on discrepancies in presented data on proportion with lesions ≥ 6mm

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Appendix A. Detailed Methods

Update Key Questions and Analytic Framework

Under the guidance of the USPSTF, we developed an analytic framework and five key questions (Figure 1), which received final approval from USPSTF liaisons. This report's scope differs from the 2002 USPSTF evidence report in several important ways:

1. We did not update the direct evidence that standard FOBT screening is effective, except in addressing longer-term follow-up results from the original trials included in the 2002 report, because this evidence was foundational for the last recommendation.
2. We did not update evidence on CRC screening methods not recommended after the last review (e.g., digital rectal exam) or omitted from this review by the USPSTF due to poor test performance characteristics (e.g., DCBE). A single study (n=580) from the previous 2002 evidence report found that DCBE as a surveillance method after adenomatous polypectomy (with comparison to colonoscopy as the gold standard) showed a sensitivity of only 48 percent (CI: 24, 67) for polyps larger than 10 mm. A more recent study in a high-risk screening and diagnostic evaluation population comparing DCBE to both optical and CT colonoscopy showed similarly low sensitivity estimates for large polyps.[115] Given its confirmed low sensitivity for the targets of screening (lesions 10 mm or larger), DCBE as a primary CRC screening test was removed from the review.
3. Systematic review of screening test adherence, acceptability, and feasibility was not part of this report. Similarly, the USPSTF judged that a thorough review of cost effectiveness analyses was beyond the scope of our review, particularly since the USPSTF was conducting a simultaneous decision analysis. This separate decision analysis also removed the systematic review of evidence on screening intervals and on ages to start and stop screening from our formal systematic review.

KQ1 examined direct evidence that screening programs for colorectal cancer in primary care comparable patients reduce morbidity and/or mortality. KQ2A examined the effectiveness of colonoscopy and/or sigmoidoscopy in the community practice setting for CRC screening. KQ2B examined the efficacy of CT colonography and fecal screening tests including high-sensitivity guaiac FOBT, immunochemical FOBT, and fecal DNA tests for CRC screening. KQ3A examined the adverse effects of colonoscopy or sigmoidoscopy, in the community practice setting, used for CRC screening. KQ3B examined the adverse effects of CT colonography and fecal screening tests for CRC screening.

Literature Search Strategy

We initially searched for synthesized literature and guidelines published since the previous USPSTF report in PubMed, Database of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment Database (HTA), and the Cochrane Database of Systematic Reviews (CDSR). We also searched the National Guideline Clearinghouse, Institute of Medicine, and National Institute for Clinical Evidence websites for relevant reports.

For all key questions, we used already synthesized literature to the extent possible, supplementing with primary literature searches bridging from the search windows of relevant systematic reviews and meta-analyses. We developed literature search strategies and terms for each KQ (see Appendix A Table 1), with search dates guided by existing systematic reviews (including the 2002 UPSPTF report) and the development of screening technology.

We conducted five separate literature searches in both Medline and Cochrane Central Register of Controlled Trials (CCRCT). Search one was for KQ1, search two was for KQ2A, search three was for KQ2B, search four was for KQ3A and KQ3B, and search five was a more complex search of harms for KQ3A and KQ3B. Although the searches were specifically designed for a particular key question, all abstracts were reviewed for inclusion in all key questions. All searches went through January 2008.

For KQ1 (mortality outcomes of screening), we found no systematic reviews conforming to our inclusion and exclusion criteria more recent than the 2002 USPSTF review. Therefore, we searched for newly published primary literature from January, 2000 through January, 2008.

For KQ2a (accuracy of flexible sigmoidoscopy and colonoscopy), we found no systematic reviews conforming to our inclusion and exclusion criteria more recent than the 2002 USPSTF review and therefore searched from January, 2000 through January, 2008 for primary literature.

KQ2b (test performance characteristics of newer screening tests) covered three tests: CT colonography, fecal immunochemical tests (FIT), and fecal DNA tests. Three separate approaches were used for the three different tests. For CT colonography, a good-quality review published in 2005[116] used acceptable methods and reported their methods and the data necessary for us to use as a foundation for further searching. This review was compared with five other recently published reviews of CT colonography (Hayes report (searched through Dec 2005));[117-121] and we reviewed for inclusion any articles we found that were not reported in Mullhall et al's review. The most recent search date among the 6 reviews[116-121] was December 2005. Therefore we searched from January, 2006 through August, 2007 for primary literature.

Although we found several reviews of FIT, none clearly met our standards for methods and reporting and we therefore used these reviews only as sources of articles and conducted our own searches beginning in 1990, when the early primary literature was being published on FIT. A good-quality TEC assessment[124] was used as the basis for fecal DNA test literature, which searched through June, 2006. Using this review as our foundation, we search from January, 2006 through January, 2008.

For KQ3a and KQ3b (harms of screening tests) we found no synthesized evidence more recent than the 2002 USPSTF review that could be used as a foundation for the current review and therefore searched Medline and CCRCT from January, 2000 through January, 2008. We developed two different search strategies: one comprehensive, broad strategy that yielded many irrelevant abstracts, and one more focused strategy with fewer irrelevant abstracts. Although our pilot-testing of the more focused strategy suggested that it was sufficiently comprehensive, we nevertheless coded all the abstracts from the broader strategy for January 2006 – January 2008.

Study Selection

Two investigators reviewed all 3948 abstracts and 488 full-text articles. Abstracts and articles were evaluated against a set of inclusion/exclusion criteria for each key question (see Appendix A Table 2) and required the agreement of 2 reviewers. Eligible studies reported on the performance of colorectal cancer screening tests (sensitivity and specificity) or health outcomes. We excluded studies that did not address average-risk populations for colorectal cancer screening, unless an average-risk subgroup was reported. Studies including persons with a family history of CRC were considered acceptable, unless the familial history included heritable syndromes such as FAP (Familial Adenomatous Polyposis), HNPCC (Hereditary Non-polyposis Colorectal Cancer, or Lynch Syndrome), Gardner syndrome (FPC, Familial Polyposis Coli), Turcot syndrome, and Peutz-Jeghers syndrome. Since the applicability of the diagnostic accuracy of screening tests in persons undergoing 'surveillance' is uncertain, we limited our inclusion to studies with surveillance populations of less than 50%. However, symptomatic persons, persons with iron deficiency anemia, and persons with positive FOBT, were not considered acceptable populations for extrapolation of diagnostic accuracy studies. Therefore, we limited our inclusion to studies with these populations to less than 10 percent. We excluded case--control studies of screening accuracy because these may overestimate sensitivity as a design-related source of bias,[154] as recently demonstrated for FOBTs.[122] To avoid biases related to reference standards, we excluded studies of test accuracy that incompletely applied a valid reference standard or used an inadequate reference standard.[328] For CT colonography, we

considered only technologies that were compared against colonoscopy in average-risk populations, used a multidetector scanner,[116] and reported per-patient sensitivity and specificity.

Quality Assessment and Data Abstraction

Two investigators critically appraised and quality-rated all eligible studies by using design-specific quality criteria based on the USPSTF methods (Appendix A Table 3), supplemented by NICE and Oxman criteria for systematic reviews,[127,128] and QUADAS criteria for diagnostic accuracy studies.[329] Only good-quality systematic reviews were used as sources for primary articles, and all poor-quality studies were excluded from the review. One investigator abstracted key elements of all included studies into standardized evidence tables. A second reviewer verified these data. Disagreements about data abstraction or quality appraisal were resolved by consensus.

Literature Synthesis

No studies were found for KQ1 and therefore no data synthesis was required. Results of KQ2b and KQ3b were judged to be too heterogeneous in terms of populations, settings, and study designs for meta-analysis and were therefore qualitatively synthesized.

Although we had some concerns about the level of heterogeneity in the populations of the KQ2a studies, we nevertheless explored the statistical heterogeneity of the KQ2a studies for adenoma miss rates and polyp miss rates using Stata v9.2 “meta” command. Not surprisingly, Q statistics indicated significant statistical heterogeneity as well ($Q=22.6$, $p<.001$ for adenoma miss rates, $Q=37.8$, $p<.001$ for polyp miss rates) and meta-analysis results are not presented for KQ2a. Data were too limited to explore heterogeneity through statistical means.

Due to study design and limitations in reporting for two of the studies evaluating CTC test performance, we calculated point estimates for per person sensitivity and specificity and their respective confidence intervals. The major limitation in calculating point estimates in these two studies, which evaluated the test performance of CTC between different radiologists using both 2D and 3D technology, is the double counting of lesions as independent, even though the radiologists were reading the same set of lesions (e.g., three radiologists reading three separate exams are pooled as if it was one radiologist reading nine exams). However, despite this limitation, the calculated point estimates and confidence intervals were not different from the range of estimates per reader presented in the original articles. We used the following formula to calculate confidence intervals (for p= proportion):

$$\hat{p} - 1.96\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} \le p \le \hat{p} + 1.96\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$$

Because of the stringency of our inclusion criteria for key question 3a, which focused on estimates of harms in the community practice setting, the studies we included were thought to be clinically homogenous enough to allow pooling of complication rates. Meta-analysis was performed for KQ3a to estimate combined complication rates for serious bleeding, perforation, and any serious complications related to colonoscopy, and for any serious complications related to sigmoidoscopy. Several studies reported that their patients experienced no adverse events, and therefore we used a logistic random effects model[129,130] to include studies without any adverse events and estimate the combined complication rates. The model was described briefly as follows.

Suppose that there are $i = 1, \ldots, n$ studies and number of complications and total procedures are x_i and n_i for study i. Denote that the complication rate from each study is p_i, then we have

$$x_i \sim \text{binomial}(n_i, p_i) \qquad (1)$$

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \mu_i \qquad (2)$$

$$\mu_i \sim N(0, \tau^2) \qquad (3)$$

where μ_i is the random effects across studies and τ^2 estimates the heterogeneity among studies on the logit scale. The combined complication rate, p_{com}, would be estimated by

$$p_{com} = \frac{\exp(\beta_0)}{1+\exp(\beta_0)} \qquad (4)$$

This model allows inclusion of studies with no adverse events and the random effects incorporates variation among studies into the combined estimate. A p-value less than 0.05 for τ^2 is considered as statistically significant for heterogeneity.

Exploratory meta-regressions were conducted using logistic random effects models to examine the association of important study level characteristics: study design, study setting by country, and population characteristics including age range, and indication for endoscopy with complication rate. To do this, we only need to add one more term to equation (2) of the logistic random effects model:

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 z_i + \mu_i \qquad (5)$$

where z_i represents any study level characteristics from study *i* and the association of this study characteristic with complication rate is investigated through β_1.

The analysis was performed using the NLMIXED procedure in SAS v9.1 (see below for SAS code).

SAS Code for the Meta-Analysis of Serious Complications. The following SAS code shows how to calculate the combined rate of total serious complications and examines the impact of Community_setting (1 = Yes, 0 = No) on total serious complication rate using a logistic random-effects model with PROC NLMIXED.

```
data totalSC;
input Study$        n_proc   n_serious_tot       Community_setting;
   /* Community_setting = 1 if the study was conducted in a community setting;
   0, otherwise */
datalines;
Kewenter_1996              190              3          0
Robinson_1999              1474             7          1
Thiis_1999                 521              1          0
Nelson_2002                3196             18         0
Segnan_2002                775              2          0
Pickhardt_2003             1233             1          0
Cotterill_2005             324              0          1
Ko_2006                    502              8          0
Levin_2006                 16318            44         1
Rathgaber_2006             12407            14         1
ko_2007                    18271            45         1
;

/** To obtain a combined rate of total serious complication rate */

proc nlmixed data = totalSC;
 parms beta0 = -7.0 s2u = 0.5; /* Specify the initial value */
 eta = beta0 + u;
   /* Specify the model on logit scale where
   beta0 will be used to estimate combined complication rate, and
   u is the random-effects term across studies */

 expeta = exp(eta);
 p = expeta/(1+expeta);
 model n_serious_tot ~ binomial(n_proc,p);
    /* Specify the distribution for the number of complications */

 random u ~ normal(0,s2u) subject=study;
    /* Specify the distribution of random effects */

 estimate              "Complication Rate" exp(beta0)/(1+exp(beta0));
   /* Obtain the combined complication rate using beta0 */
run;


/** To examine the impact of community setting on the total serious complication rate */
```

```
proc nlmixed data = totalSC;
 parms beta0 = -7.0 s2u = 0.5 beta1 = 0.5; /* Specify the initial values */
 eta = beta0 + beta1 * Community_setting + u;
   /* Impact of community setting is investigated by beta1*/

 expeta = exp(eta);
 p = expeta/(1+expeta);
 model n_serious_tot ~ binomial(n_proc,p);
    /* Specify the distribution for the number of complications */

 random u ~ normal(0,s2u) subject=study;
    /* Specify the distribution of random effects */
run;
```

External review process

The USPSTF appointed four liaisons to guide the scope and reporting of this review. The work plan was not reviewed by outside experts. A draft of the evidence synthesis was reviewed by eight experts, including experts in the fields of gastroenterology and radiology, and several experts who have written systematic evidence reviews on one or more aspects of colorectal cancer screening.

USPSTF Involvement

The authors worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework questions and resolve issues around scope, and final evidence synthesis. 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, reviewed the draft report, and assisted in external review of the draft evidence synthesis.

Appendix A Table 1. Search strategies

Systematic Evidence Review Search
PubMed, DARE, Cochrane Database, IOM, HTA search to identify systematic reviews

#41 Search #22 OR #40
#40 Search #38 AND systematic[sb] Limits: English, Publication Date from 1999 to 2007
#39 Search #38 AND systematic[sb]
#38 Search #37 AND (publisher[sb] OR in process[sb])
#37 Search #33 OR #34 OR #35 OR #36
#36 Search sigmoidoscop*[tiab]
#35 Search colonograph*[tiab]
#34 Search colonoscop*[tiab]
#33 Search #32 AND screen*[tiab]
#32 Search #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#31 Search "colonic cancer"[tiab]
#30 Search "colonic neoplasms"[tiab]
#29 Search "colonic neoplasia"[tiab]
#28 Search "colon neoplasia"[tiab] 1
#27 Search "colorectal neoplasia"[tiab]
#26 Search "colon neoplasms"[tiab] 1
#25 Search "colorectal neoplasms"[tiab]
#24 Search "colon cancer"[tiab]
#23 Search "colorectal cancer"[tiab]
#22 Search #20 AND systematic[sb] Limits: English, Publication Date from 1999 to 2007
#21 Search #20 AND systematic[sb]
#20 Search #14 OR #19
#19 Search "Colonoscopy"[MeSH:NoExp] OR "Sigmoidoscopy"[MeSH] OR "Colonography, Computed Tomographic"[MeSH]
#14 Search #11 AND #13
#13 Search "Mass Screening"[MeSH:NoExp] OR screen*[tiab]
#11 Search #1 OR #6 OR #10
#10 Search "Intestinal Polyps"[MeSH:NoExp] OR "Colonic Polyps"[MeSH]
#6 Search "Rectal Neoplasms"[MeSH:NoExp] OR "Anus Neoplasms"[MeSH:NoExp] OR "Anal Gland Neoplasms"[MeSH]
#1 Search "Colorectal Neoplasms"[MeSH:NoExp] OR "Colonic Neoplasms"[MeSH:NoExp] OR "Sigmoid Neoplasms"[MeSH]

Key Questions 1
Database: Ovid MEDLINE(R) <1966 to January 2008>
Search Strategy:
---
1 Colonoscopy/
2 colonoscop$.ti,ab.
3 Sigmoidoscopy/
4 sigmoidoscop$.ti,ab.
5 Colonography, Computed Tomographic/
6 colonograph$.ti,ab.
7 Occult Blood/
8 fobt$.ti,ab.
9 ifobt$.ti,ab.
10 fecal occult blood.ti,ab.
11 faecal occult blood.ti,ab.
12 ((fecal or faecal) and immunochemical).ti,ab.
13 ((fecal or faecal) and dna).ti,ab.
14 instant-view.ti,ab.
15 immoCARE.ti,ab.
16 FlexSure OBT.ti,ab.
17 HemeSelect.ti,ab.
18 MonoHaem.ti,ab.
19 Hemoccult.ti,ab.
20 ColoScreen.ti,ab.
21 Seracult.ti,ab.
22 HM-Jack.ti,ab.

Appendix A Table 1. Search strategies

23 OcculTech.ti,ab.
24 PreGen-Plus.ti,ab.
25 QuickVue.ti,ab.
26 HemoQuant.ti,ab.
27 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 Mass Screening/
29 screen$.ti,ab.
30 28 or 29
31 27 and 30
32 limit 31 to (clinical trial or controlled clinical trial or randomized controlled trial)
33 clinical trials/ or controlled clinical trials/ or randomized controlled trials/
34 double-blind method/ or random allocation/ or single-blind method/
35 random$.ti,ab.
36 33 or 34 or 35
37 31 and 36
38 Colorectal Neoplasms/
39 Colonic Neoplasms/
40 Sigmoid Neoplasms/
41 Rectal Neoplasms/
42 Anus Neoplasms/
43 Anal Gland Neoplasms/
44 Intestinal Polyps/
45 Colonic Polyps/
46 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47 46 and 28
48 46 and screen$.ti.
49 47 or 48
50 limit 49 to (clinical trial or controlled clinical trial or randomized controlled trial)
51 49 and 36
52 Mortality/
53 mortality.fs.
54 Survival Rate/
55 survival analysis/
56 Life Expectancy/
57 "Cause of Death"/
58 mortality.ti,ab.
59 death.ti,ab.
60 deaths.ti,ab.
61 survival.ti,ab.
62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63 31 or 49
64 62 and 63
65 32 or 37 or 50 or 51 or 64
66 limit 65 to humans [Limit not valid; records were retained]
67 limit 65 to animals
68 67 not 66
69 65 not 68
70 limit 69 to english language
71 limit 70 to yr="2000 - 2008"

Database: EBM Review : Cochrane Central Registries of Controlled Trials <1985 to 4th quarter 2007>
Search Strategy:
---
1 colonoscop$.ti,ab,hw. (789)
2 sigmoidoscop$.ti,ab,hw. (362)
3 colonograph$.ti,ab,hw. (26)
4 occult blood.hw. (260)
5 fecal occult blood.ti,ab. (97)
6 faecal occult blood.ti,ab. (75)
7 ((fecal or faecal) and immunochemical).ti,ab. (9)
8 ((fecal or faecal) and dna).ti,ab. (15)

Appendix A Table 1. Search strategies

9 (fobt$ or ifobt$).ti,ab. (38)
10 (instant-view or immoCARE or FlexSure OBT).ti,ab. (4)
11 (HemeSelect or MonoHaem or Hemoccult).ti,ab. (63)
12 (ColoScreen or Seracult or HM-Jack or OcculTech or PreGen-Plus).ti,ab. (2)
13 (quickvue or hemoquant).ti,ab. (10)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1322)
15 screening.hw. (2409)
16 screen$.ti,ab. (7222)
17 15 or 16 (8051)
18 14 and 17 (300)
19 (colon$ and (cancer or neoplas$)).hw. (1679)
20 (colorectal and (cancer or neoplas$)).hw. (1416)
21 (rectal and (cancer or neoplas$)).hw. (806)
22 (colon$ and (cancer or neoplas$)).ti. (476)
23 (colorectal and (cancer or neoplas$)).ti. (1285)
24 (rectal and (cancer or neoplas$)).ti. (322)
25 19 or 20 or 21 or 22 or 23 or 24 (3896)
26 25 and 15 (232)
27 25 and screen$.ti. (236)
28 18 or 26 or 27 (371)
29 limit 28 to yr="2000- 2008" (158)

Key Question 2A
Database: Ovid MEDLINE(R) <1996 to January 2008>
Search Strategy: Part 1
---
1 Sigmoidoscopy/
2 Colonoscopy/
3 1 or 2
4 "Sensitivity and Specificity"/
5 "Predictive Value of Tests"/
6 ROC Curve/
7 False Negative Reactions/
8 False Positive Reactions/
9 Diagnostic Errors/
10 "Reproducibility of Results"/
11 Reference Values/
12 Reference Standards/
13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 3 and 13
15 Colonoscopy/st [Standards]
16 Sigmoidoscopy/st [Standards]
17 14 or 15 or 16
18 limit 17 to english language
19 limit 18 to yr="2000 - 2008"
20 colonoscop$.ti,ab.
21 sigmoidoscop$.ti,ab.
22 1 or 2 or 20 or 21
23 specificit$.ti,ab.
24 sensitiv$.ti,ab.
25 predictive value.ti,ab.
26 accurac$.ti,ab.
27 miss rate$.ti,ab.
28 detection rate$.ti,ab.
29 diagnostic yield$.ti,ab.
30 likelihood ratio$.ti,ab.
31 diagnostic odds ratio$.ti,ab.
32 odds ratio/ and di.fs.
33 13 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 22 and 33
35 15 or 16 or 34

Appendix A Table 1. Search strategies

36 limit 35 to english language
37 limit 36 to yr="2000 - 2008"
38 Mass Screening/
39 screen$.ti,ab.
40 38 or 39
41 37 and 40
42 200608$.ed.
43 200608$.up.
44 42 or 43
45 41 and 44
46 19 not 41
47 45 or 46

Database: Ovid MEDLINE(R) <1996 to January 2008>
Search Strategy: Part 2
---

1 Sigmoidoscopy/
2 Colonoscopy/
3 1 or 2
4 "Sensitivity and Specificity"/
5 "Predictive Value of Tests"/
6 ROC Curve/
7 False Negative Reactions/
8 False Positive Reactions/
9 Diagnostic Errors/
10 "Reproducibility of Results"/
11 Reference Values/
12 Reference Standards/
13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 3 and 13
15 Colonoscopy/st [Standards]
16 Sigmoidoscopy/st [Standards]
17 14 or 15 or 16
18 limit 17 to english language
19 limit 18 to yr="2000 - 2008"
20 colonoscop$.ti,ab.
21 sigmoidoscop$.ti,ab.
22 1 or 2 or 20 or 21
23 specificit$.ti,ab.
24 sensitiv$.ti,ab.
25 predictive value.ti,ab.
26 accurac$.ti,ab.
27 miss rate$.ti,ab.
28 detection rate$.ti,ab.
29 diagnostic yield$.ti,ab.
30 likelihood ratio$.ti,ab.
31 diagnostic odds ratio$.ti,ab.
32 odds ratio/ and di.fs.
33 13 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 22 and 33
35 15 or 16 or 34
36 limit 35 to english language
37 limit 36 to yr="2000 - 2006"
38 Mass Screening/
39 screen$.ti,ab.
40 38 or 39
41 37 and 40

Appendix A Table 1. Search strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th quarter 2007>
Search Strategy:

1 colonoscop$.hw.
2 sigmoidoscop$.hw.
3 1 or 2
4 sensitivity.hw.
5 specificity.hw.
6 predictive value.hw.
7 (roc or receiver operat$).hw.
8 false negative.hw.
9 false positive.hw.
10 diagnostic error$.hw.
11 reproducibility.hw.
12 reference value$.hw.
13 reference standards.hw.
14 diagnostic accuracy.hw.
15 diagnostic value.hw.
16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 3 and 16
18 colonoscop$.ti,ab.
19 sigmoidoscop$.ti,ab.
20 1 or 2 or 18 or 19
21 specificit$.ti,ab.
22 sensitiv$.ti,ab.
23 predictive value.ti,ab.
24 accurac$.ti,ab.
25 miss rate$.ti,ab.
26 detection rate$.ti,ab.
27 diagnostic yield$.ti,ab.
28 likelihood ratio$.ti,ab.
29 diagnostic odds ratio$.ti,ab.
30 (odds ratio and diagnosis).hw.
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 20 and 31
33 screening.hw.
34 screen$.ti,ab.
35 33 or 34
36 32 and 35
37 17 or 36
38 limit 37 to yr="2000 - 2008"

Key Question 2B
Database: Ovid MEDLINE(R) <1950 to January 2008>
---

1 Colonography, Computed Tomographic/
2 colonograph$.ti,ab.
3 occult blood.ti,ab,hw.
4 guaiac.ti,ab,hw.
5 fobt$.ti,ab,hw.
6 fecal.ti,ab,hw.
7 faecal.ti,ab,hw.
8 feces.ti,ab,hw.
9 3 or 4 or 5 or 6 or 7 or 8
10 dna.ti,ab,hw.
11 9 and 10
12 pregen plus.ti,ab.
13 1 or 2 or 11 or 12
14 limit 13 to yr="2006 - 2008"
15 ifobt.ti,ab.
16 i fobt.ti,ab.
17 instant-view.ti,ab.

Appendix A Table 1. Search strategies

18 immocare.ti,ab.
19 flexsure obt.ti,ab.
20 hemeselect.ti,ab.
21 monohaem.ti,ab.
22 hemosure.ti,ab.
23 hemoccult ict.ti,ab.
24 hm-jack.ti,ab.
25 occultech.ti,ab.
26 quickvue.ti,ab.
27 hemoquant.ti,ab.
28 immunochemi$.ti,ab,hw.
29 9 and 28
30 insure.ti,ab.
31 9 and 30
32 hemoccult sensa.ti,ab.
33 hemoccultsensa.ti,ab.
34 coloscreen es.ti,ab.
35 coloscreenes.ti,ab.
36 seracult plus.ti,ab.
37 seracultplus.ti,ab.
38 3 or 4 or 5
39 high sensitivity.ti,ab.
40 38 and 39
41 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 29 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 40
42 limit 41 to yr="1990 - 2008"
43 "Sensitivity and Specificity"/
44 "Predictive Value of Tests"/
45 ROC Curve/
46 False Negative Reactions/
47 False Positive Reactions/
48 Diagnostic Errors/
49 "Reproducibility of Results"/
50 Reference Values/
51 Reference Standards/
52 Observer Variation/
53 Quality Control/
54 Quality Assurance, Health Care/
55 standards.fs.
56 specificit$.ti,ab.
57 sensitiv$.ti,ab.
58 predictive value.ti,ab.
59 accurac$.ti,ab.
60 false positive$.ti,ab.
61 false negative$.ti,ab.
62 miss rate$.ti,ab.
63 error rate$.ti,ab.
64 detection rate$.ti,ab.
65 diagnostic yield$.ti,ab.
66 likelihood ratio$.ti,ab.
67 odds ratio/ and di.fs.
68 diagnostic odds ratio$.ti,ab.
69 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70 14 or 42
71 69 and 70
72 limit 71 to english language
73 remove duplicates from 72

Appendix A Table 1. Search strategies

Key Question 3A & 3B
Database: Ovid MEDLINE(R) <1996 to January 2008>
Search Strategy: Harms Simple

1 Colonoscopy/ae [Adverse Effects]
2 Colonoscopy/mo [Mortality]
3 Sigmoidoscopy/ae [Adverse Effects]
4 Sigmoidoscopy/mo
5 Colonography, Computed Tomographic/ae [Adverse Effects]
6 Colonography, Computed Tomographic/mo [Mortality]
7 virtual colonoscop$.ti,ab.
8 CT colonograph$.ti,ab.
9 computed tomographic colonograph$.ti,ab.
10 7 or 8 or 9
11 limit 10 to yr="2000 - 2001"
12 (adverse effects or mortality).fs.
13 11 and 12
14 colonoscop$.ti.
15 sigmoidoscop$.ti.
16 colonograph$.ti.
17 14 or 15 or 16
18 complication$.ti.
19 adverse$.ti.
20 harm$.ti.
21 18 or 19 or 20
22 17 and 21
23 1 or 2 or 3 or 4 or 5 or 6 or 13 or 22
24 limit 23 to english language
25 limit 24 to humans
26 limit 24 to animals
27 26 not 25
28 24 not 27
29 limit 28 to yr="2000 - 2008"

Database: Ovid MEDLINE(R) <1996 to January 2008>
Search Strategy: Harms Complex
---

1 colonoscopy/
2 colonoscop$.ti.
3 sigmoidoscopy/
4 sigmoidoscop$.ti.
5 polypectom$.ti.
6 Colonic Polyps/su [Surgery]
7 Intestinal Polyps/su [Surgery]
8 Adenomatous Polyps/su [Surgery]
9 Colonography, Computed Tomographic/
10 colonograph$.ti.
11 (colon cancer and screening).ti,ab.
12 (colorectal cancer and screening).ti,ab.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 harm.ti,ab.
15 harms.ti,ab.
16 harmed.ti,ab.
17 harmful$.ti,ab.
18 adverse effects.fs.
19 complication$.ti,ab.
20 side effect$.ti,ab.
21 adverse effect$.ti,ab.
22 adverse event$.ti,ab.
23 adverse reaction$.ti,ab.
24 death/
25 death$.ti,ab.

Appendix A Table 1. Search strategies

26 mortality.fs.
27 mortalit$.ti,ab.
28 or/14-27
29 13 and 28
30 pain/
31 pain.ti,ab.
32 painful.ti,ab.
33 discomfort.ti,ab.
34 cramps.ti,ab.
35 bloating.ti,ab.
36 chills.ti,ab.
37 dizziness.ti,ab.
38 weakness.ti,ab.
39 nausea/
40 nausea$.ti,ab.
41 vomiting/
42 vomiting.ti,ab.
43 bleeding.ti,ab.
44 Hemorrhage/
45 Gastrointestinal Hemorrhage/
46 Postoperative Hemorrhage/
47 hemorrhag$.ti,ab.
48 haemorrhag$.ti,ab.
49 perforat$.ti,ab.
50 Intestinal Perforation/
51 Intraoperative Complications/
52 Postoperative Complications/
53 or/30-52
54 13 and 53
55 ((anesthe$ or anaesthe$) and react$).ti,ab.
56 (coloring agents/ or tattoo$.ti,ab. or dye.ti,ab.) and react$.ti,ab.
57 Water-Electrolyte Imbalance/
58 electrolyte imbalance$.ti,ab.
59 electrolyte disturbance$.ti,ab.
60 Electrolyte disorder$.ti,ab.
61 electrolyte level$.ti,ab.
62 electrolyte abnormalit$.ti,ab.
63 Dehydration/
64 dehydrat$.ti,ab.
65 Hyponatremia/
66 Hyponatremia.ti,ab.
67 Hyponatraemia.ti,ab.
68 chemical colitis.ti,ab.
69 Colitis/ci [Chemically Induced]
70 or/55-69
71 13 and 70
72 emergency room.ti,ab.
73 emergency department.ti,ab.
74 Emergency Service, Hospital/
75 emergencies/
76 Hospitalization/
77 hospitaliz$.ti,ab.
78 hospitalise$.ti,ab.
79 hospitalisa$.ti,ab.
80 hospital admission$.ti,ab.
81 or/72-80
82 13 and 81
83 false positive$.ti,ab.
84 false negative$.ti,ab.
85 False Negative Reactions/
86 False Positive Reactions/
87 Diagnostic Errors/

Appendix A Table 1. Search strategies

88 overdiagnos$.ti,ab.
89 or/83-88
90 13 and 89
91 tolerability.ti,ab.
92 tolerable.ti,ab.
93 tolerate$.ti,ab.
94 tolerance.ti,ab.
95 intolera$.ti,ab.
96 Patient Acceptance of Health Care/
97 acceptance.ti,ab.
98 acceptability.ti,ab.
99 Patient Satisfaction/
100 Patient Compliance/
101 incomplete.ti,ab.
102 completion rate$.ti,ab.
103 failure rate$.ti,ab.
104 or/91-103
105 13 and 104
106 29 or 54 or 71 or 82 or 90 or 105
107 limit 106 to english language
108 limit 107 to humans
109 limit 107 to animals
110 109 not 108
111 107 not 110
112 Occult Blood/
113 fobt$.ti,ab.
114 ifobt$.ti,ab.
115 fecal occult blood.ti,ab.
116 faecal occult blood.ti,ab.
117 ((fecal or faecal) and immunochemical).ti,ab.
118 ((fecal or faecal) and dna).ti,ab.
119 hemoccult.ti,ab.
120 stool screening.ti,ab.
121 stool test$.ti,ab.
122 stool based test$.ti,ab.
123 Feces/
124 120 or 121 or 122 or 123
125 colorectal neoplasms/
126 colonic neoplasms/
127 sigmoid neoplasms/
128 rectal neoplasms/
129 anus neoplasms/
130 anal gland neoplasms/
131 Adenomatous Polyps/
132 intestinal polyps/
133 colonic polyps/
134 colorectal cancer.ti,ab.
135 colorectal neoplas$.ti,ab.
136 colon cancer.ti,ab.
137 colon neoplas$.ti,ab.
138 or/125-137
139 124 and 138
140 or/112-119
141 139 or 140
142 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 89 or 104
143 141 and 142
144 limit 143 to english language
145 limit 144 to humans
146 limit 144 to animals
147 146 not 145
148 144 not 147
149 111 or 148

Appendix A Table 1. Search strategies

150 limit 149 to yr="2000 - 2007"
151 Colonoscopy/ae [Adverse Effects]
152 Colonoscopy/mo [Mortality]
153 Sigmoidoscopy/ae [Adverse Effects]
154 Sigmoidoscopy/mo
155 Colonography, Computed Tomographic/ae [Adverse Effects]
156 Colonography, Computed Tomographic/mo [Mortality]
157 virtual colonoscop$.ti,ab.
158 CT colonograph$.ti,ab.
159 computed tomographic colonograph$.ti,ab.
160 157 or 158 or 159
161 limit 160 to yr="2000 - 2001"
162 (adverse effects or mortality).fs.
163 161 and 162
164 colonoscop$.ti.
165 sigmoidoscop$.ti.
166 colonograph$.ti.
167 164 or 165 or 166
168 complication$.ti.
169 adverse$.ti.
170 harm$.ti.
171 168 or 169 or 170
172 167 and 171
173 151 or 152 or 153 or 154 or 155 or 156 or 163 or 172
174 limit 173 to english language
175 limit 174 to humans
176 limit 174 to animals
177 176 not 175
178 174 not 177
179 limit 178 to yr="2000 - 2008"
180 150 not 179
181 limit 180 to yr="2006 - 2008"

Database: EBM Reviews Cochrane Central Registry of Controlled Trials <4th quarter 2007>
Search Strategy:
---

1 colonoscop$.ti,hw.
2 sigmoidoscop$.ti,hw.
3 colonograph$.ti,hw.
4 1 or 2 or 3 (899)
5 complication$.ti,hw.
6 adverse$.ti,hw.
7 harm$.ti,hw.
8 mortalit$.ti,hw.
9 side effect.ti,hw.
10 5 or 6 or 7 or 8 or 9
11 4 and 10
12 limit 11 to yr="2000 - 2007"

Appendix A Table 2. Inclusion/Exclusion Criteria

Key Question	Population	Study Design	Setting	Outcomes	Other
KQ 1 Impact of screening on mortality	Age ≥ 40 y; average risk Recruited from primary care or primary care–comparable population	Systematic evidence review; RCT; cluster RCT; or well-designed CCT, cohort, and case–control studies	Primary care or other setting with primary care–comparable population	Mortality (all-cause or CRC-specific)	For guaiac FOBT, only updates for the trials included in the previous review were considered.
KQ 2a Accuracy of flexible sigmoidoscopy and colonoscopy (community setting)	Age ≥ 40 y; average risk Recruited from primary care or primary care–comparable population	Systematic evidence review; RCT; cohort studies; systematically selected case series; screening registry	Community primary care or other setting with primary care–comparable population	Sensitivity and specificity (per person) or miss rates (per polyp); yield for CRC, advanced neoplasia, or adenomas by size	Colonoscopy as reference standard; full spectrum of disease represented; indeterminate results not excluded
KQ 2b Accuracy of newer screening tests (CTC, high-sensitivity FOBT, FIT, fecal DNA)	Age ≥ 40 y; average risk Recruited from primary care or primary care–comparable population	Systematic evidence review; RCT; diagnostic cohort studies; systematically selected case series; screening registry	Any	Sensitivity and specificity (per person) or miss rates (per polyp); yield for CRC, advanced neoplasia, or adenomas by size	Colonoscopy (or registry follow-up) as reference standard; full spectrum of disease represented; indeterminate results not excluded
KQ 3a Harms of flexible sigmoidoscopy and colonoscopy (community setting)	Age ≥ 40 y; average risk Recruited from primary care or primary care–comparable population	Systematic evidence review; RCT/CCT; registries; large-database observational studies, cohort studies; cross-sectional studies; systematically selected case series	Community primary care or other setting with primary care–comparable population	Adverse events requiring hospitalization, including perforation, major bleeding, severe abdominal symptoms, cardiovascular events, and/or resulting in death	Harms due to bowel preparation and sedation considered separate from serious adverse events
KQ 3b Harms of newer screening tests (CTC, high-sensitivity FOBT, FIT, fecal DNA)	Age ≥ 40 y; average risk	Systematic evidence review; RCT/CCT; registries; large-database observational studies, cohort studies; cross-sectional studies; systematically selected case series	Any	Adverse events requiring hospitalization, including perforation, major bleeding, severe abdominal symptoms, cardiovascular events, and/or resulting in death	Potential harms due to radiation and extracolonic findings considered separate from serious adverse events

*CCT = controlled clinical trial; CRC = colorectal cancer; CT = computed tomography; FIT = fecal immunochemical test; FOBT = fecal occult blood test; KQ = key question; RCT = randomized, controlled trial.

Appendix A Table 3. Quality rating criteria

Design	United States Preventive Services Task Force quality rating criteria[114]	National Institute for Health and Clinical Excellence methodology checklists
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• The study addresses an appropriate and clearly focused question • A description of the methodology used is included • The literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable
Case-control studies	• Accurate ascertainment of cases • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• The study addresses an appropriate and clearly focused question • The cases and controls are taken from comparable populations • The same exclusion criteria are used for both cases and controls • What percentage of each group (cases and controls) participated in the study? • Comparison is made between participants and non-participants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • Is it clearly established that controls are non-cases? • Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment • Exposure status is measured in a standard, valid and reliable way • The main potential confounders are identified and taken into account in the design and analysis • Have confidence intervals been provided?
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups. • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • The treatment and control groups are similar at the start of the trial • The only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid and reliable way • What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? • All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • Where the study is carried out at more than one site, results are comparable for all sites

Appendix A Table 3. Quality rating criteria

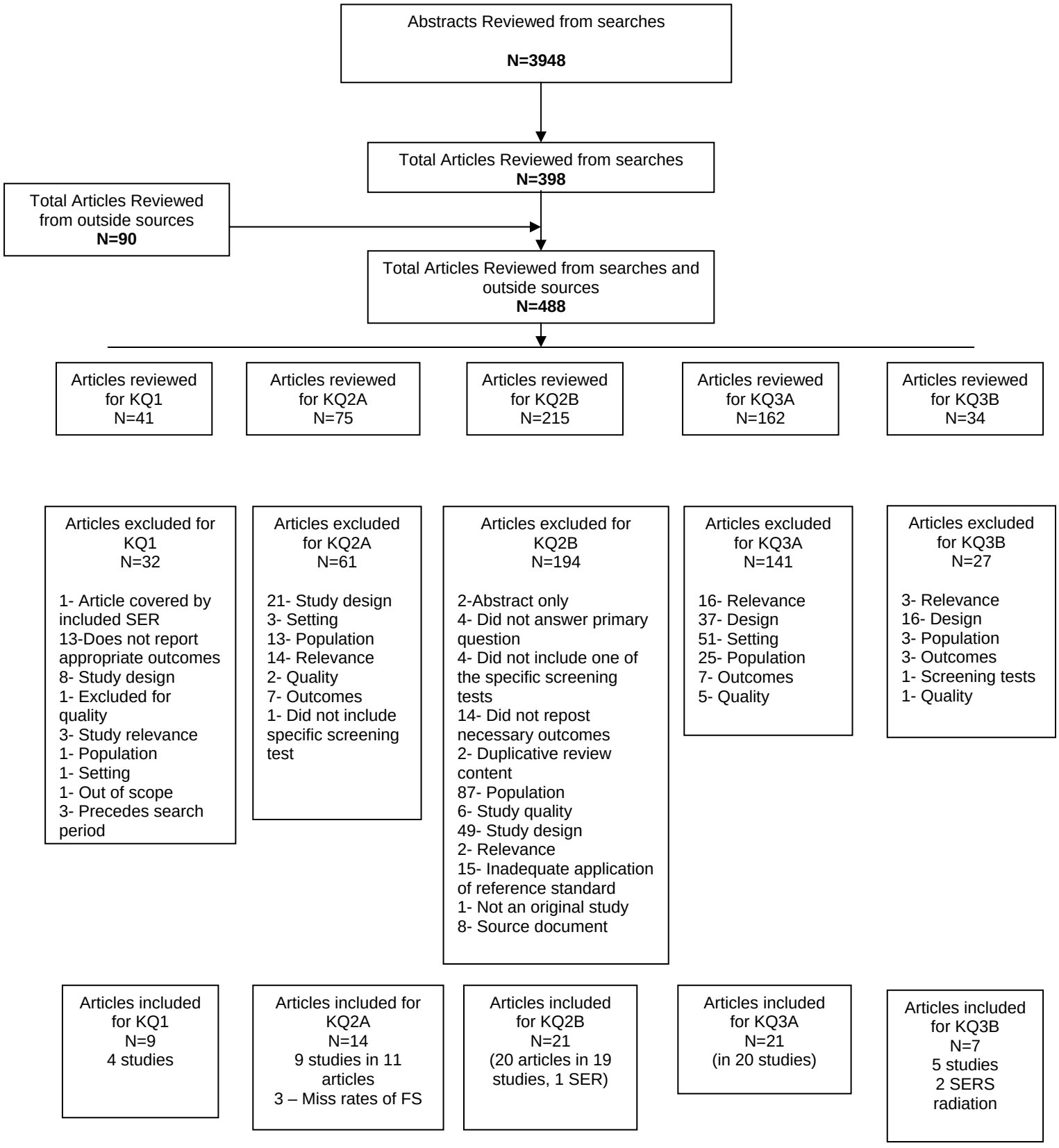
Design	United States Preventive Services Task Force quality rating criteria[114]	National Institute for Health and Clinical Excellence methodology checklists
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? • Comparison is made between full participants and those lost to follow-up, by exposure status • The outcomes are clearly defined • The assessment of outcome is made blind to exposure status • Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • The measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Exposure level or prognostic factor is assessed more than once • The main potential confounders are identified and taken into account in the design and analysis • Have confidence intervals been provided?
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• The nature of the test being studied is clearly specified • The test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • The test and gold standard are measured independently (blind) of each other • The test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported

Appendix A Table 3. Quality rating criteria

Hierarchy of research design

I	Properly conducted randomized controlled trial (RCT)
II-1:	Well-designed controlled trial without randomization
II-2:	Well-designed cohort or case-control analytic study
II-3:	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III:	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Figure 1. Literature retrieval process: Search results and article flow by Key Question*



Note: Articles may have been included for more than 1 key question.

Appendix B. Key Question 1 study details.

There are four large trials examining long-term outcomes for a group of people randomized to FOBT screening (Hemoccult II) biennially (every 2 years), compared to a control group who received no screening. Two of the trials used nonrehydrated slides (Nottingham, Funen), and two used rehydrated slides (Minnesota, Goteborg). While the latter technique increased sensitivity, it also reduced specificity.

The Nottingham trial had a statistically significant CRC mortality reduction of 15 percent for the screening group, relative to the control group, at the end of the screening period (7.8 years).[3] The CRC-related mortality rate difference between screening and control groups continued 3.9 years after the screening program had stopped (total followup of 11.7 years), with a statistically significant relative mortality reduction of 13 percent.[132] It is notable that this mortality reduction was achieved using a higher threshold for test positives (4 of 6 squares) and employing a Hemoccult retesting strategy for some test-positives (see Appendix B Table 1). This approach differs from trials in which persons with one of six test squares was considered screen-positive (see Appendix B Table 1).

The Funen trial is the only trial that has continued its screening program over the entire followup period. Three reports from this trial published in 1996,[4] 2002,[134] and 2004[131] indicate a statistically significant relative mortality reduction for CRC-related deaths after five, seven, and nine rounds of screening (corresponding to 10, 13 and 17 years of followup). At 10-years followup this relative CRC-related mortality reduction was 21 percent, at 13 years the reduction was 18 percent, and at 17 years the reduction was 16 percent. When comparing the CRC mortality rates that include deaths related to CRC treatment, however, the relative CRC mortality reduction is no longer statistically significant at 13 and 17 years. It is not clear from the published methods what categories of death would have been considered treatment-related, as opposed to CRC-related, making this distinction difficult to interpret. While the individuals judging cause of death were blinded to group assignment, there is insufficient information to completely interpret the elimination of CRC mortality benefit due to analyzing deaths in this manner.

In the Goteborg trial, no statistically significant reduction in the relative risk of colorectal cancer mortality was found (RR 0.88; CI: 0.69,1.12) after 8.3 years of followup.[326] After 15 years of followup, more than 13 years after the screening program stopped, a CRC-related mortality reduction of 16 percent was statistically significant (RR 0.84; CI 0.67,0.99).[94] Given that the Goteborg trial enrolled only 60 to 64 year olds, held only two rounds of FOBT screening in total, and offered positive tests further workup without using colonoscopy, a 16 percent reduction in CRC deaths 13 years later is difficult to explain.

The Minnesota trial examined both annual and biennial screening. The biennial screening group did not have a statistically significant relative CRC mortality reduction, compared to the control group, after 13 years of followup (RR 0.94; CI: 0.68,1.31).[5] This reduction did reach significance after 18 years of followup, which was 5 years after the screening program had stopped (RR 0.79; CI:0.62, 0.97).[135] After 13 years of annual screening, the relative CRC-related mortality reduction was 33 percent. [5] This reduction remained constant after 18 years of followup (5 years after the screening program had ceased).[135] It is unclear, however, whether the higher mortality impact of this study is due to annual screening or due to the use of rehydrated slides (yielding a 9.8 percent positivity rate, as compared to a 2.4 percent positivity rate for nonrehydrated). This could have led to a high proportion of patients receiving colonoscopy, and subsequent high rates of CRC and adenoma detection.

Appendix B Table 1. Key question 1 evidence table.

Study	Sample Demographics	FOBT prep FOBT development	Follow-up of positive FOBT	CRC incidence (per 1000)	CRC Cumulative mortality (per 1,000 persons)	Relative Risk
Annual Screening						
Minnesota (USA) Mandel 1993[5]	**Sample size:** **S:** 15,570 **C:** 15,394 **Proportion completing screening:** *>1 screen:* 90.2% *All rounds of screening:* 46.2% **Ages:** 50-80	Dietary and medication restrictions Rehydrated	**Definition of positive test:** ≥1/6 positive squares **Follow-up of positive test:** 1. Colonoscopy (if incomplete, DCBE) 2. History and physical exam 3. Routine lab tests 4. X-rays of upper GI and chest 5. EKG **Proportion of positive tests receiving colonoscopy** 13 yrs: 80.9% 17 yrs: 83% (colonoscopy OR DCBE + FS)	**S:** 23 persons **C:** 26 persons	**13 yrs** S: 5.88 C: 8.83	0.67 (0.50-0.87)
Minnesota (USA) Mandel 1999[135]				**S:** 32 person years **C:** 39 person years	**18 yrs** *(5 yrs after end of screening period)* S: 9.46 C: 14.09	0.67 (0.51-0.83)
Biennial Screening						
Nottingham (UK) Hardcastle 1996[3]	**S:** 76,224 **C:** 76,079 Proportion completing screening: *>1 screen:* 59.6% *All rounds of screening:* 38.2% **Ages:** 50-74	No dietary or medication restrictions Nonrehydrated	**Definition of positive initial test:** • ≥5/6 positive squares OR • ≤4/6 positive squares followed by ≥1/12 positive squares on repeat FOBT (with dietary restrictions) OR • ≤4/6 positive squares followed by all negative squares on repeat FOBT (with dietary restrictions) followed 3 months later by ≥1/6 positive squares on repeat FOBT (with dietary restrictions) **Follow-up of positive test:** Colonoscopy **Proportion of positive tests receiving colonoscopy** 7.8 yrs: 87% (c) 11.7 yrs: 73%	**S:** 1.49 person years **C:** 1.44 person years **% of Dukes A:** **S:** 20% **C:** 11% p<0.001	**7.8 yrs** median S: 0.60 C: 0.70	0.85 (0.74-0.98)
Nottingham (UK) Scholefield 2002[132]				**S:** 1.51 person years **C:** 1.53 person years **% of Dukes A:** NR	**11.7 yrs** (median) (5 yrs after end of screening period) S: 0.70 C: 0.81	0.87 (0.78-0.97)
Funen (Denmark) Kronborg 1996[4]	**S:** 30,762 **C:** 30,966 **Proportion completing screening:** <u>1996</u> *>1 screen:* 67.2% *All rounds of screening:* 46.2% <u>2002</u> All rounds of screening: 35.9% <u>2004</u>	Dietary and medication restrictions Nonrehydrated	**Definition of positive test:** ≥1/6 positive squares **Follow-up:** 1. Colonoscopy (if incomplete, DCBE) 2. History and physical exam **Proportion of positive tests receiving colonoscopy** 10 yrs: >85% 13 yrs: 94.1% 17 yrs: 93.2%	**S:** 1.71 person years **C:** 1.72 person years **% of Dukes A:** **S:** 22% **C:** 11% p<0.01	**10 yrs** (5 screening rounds) S: 0.65 C: 0.82	0.79 (0.65-0.96)
					S: 0.73* C: 0.89*	0.82* (0.68-0.99)
Funen (Denmark) Jorgenson 2002[134]				**S:** 1.84 person years **C:** 1.81 person years **% of Dukes A:** NR	**13 yrs** (7 screening rounds) S: 0.72 C: 0.88	0.82 (0.69-0.97)
					S: 0.83* C: 0.97*	0.85 * (0.73-1.00)

Study	Sample Demographics	FOBT prep FOBT development	Follow-up of positive FOBT	CRC incidence (per 1000)	CRC Cumulative mortality (per 1,000 persons)	Relative Risk
Funen (Denmark) Kronborg 2004[131,134]	**All rounds of screening**: 30.4% **Ages:** 45-75			**S:** 2.06 person years **C:** 2.02 person years **% of Dukes A**: **S:** 18% **C:** 11%	**17 yrs** (9 screening rounds) S: 0.84 C: 1.00	0.84 (0.73-0.96)
					S: 0.99* C: 1.10*	0.89* (0.78-1.01)
Minnesota (USA) Mandel 1993[5]	**S:** 15,587 **C:** 15,394 **Proportion completing screening:** >1 screen: 89.9% **All rounds of screening:** 59.7% **Ages:** 50-80	Dietary and medication restrictions Rehydrated	**Definition of positive test:** ≥1/6 positive squares **Follow-up of positive test:** 1. Colonoscopy (if incomplete, DCBE) 2. History and physical exam 3. Routine lab tests 4. X-rays of upper GI and chest 5. EKG **Proportion of positive tests receiving colonoscopy** 13 yrs: 81.7% 17 yrs: 84% (colonoscopy OR DCBE + FS)	**S:** 23 person **C:** 26 person **% of Dukes A:** **S:** 26.6% **C:** 22.3%	**13 yrs** NR (cum. incidence)	0.94 (0.68-1.31)
Minnesota (USA) Mandel 1999[135]				**S:** 33 per 1,000 p **C:** 39 per 1,000 p	**18 yrs** (5 years after end of screening period) NR (cum. incidence)	0.79 (0.62-0.97)
Goteborg 1996 (Sweden) Towler 1998[326]	**S:** 34,144 **C:** 34,164 **1st screening:** 63% **2nd screening:** 60% **Ages:** 60-64	Dietary and medication restrictions Rehydrated (majority)	**Definition of positive test:** 1/6 positive **Follow up of positive test:** Proctoscopy rectosigmoidoscopy DCBE **Proportion of positive tests receiving full work-up** 1st round: 85% 2nd round: 88%	NR	**8.3 yrs** (6 yrs after 2 screening rounds) NR	0.88 (0.69-1.12)
Goteborg 2005 (Sweden) Hewitson 2007[94]				NR	**15.5 yrs** (13 years after 2 screening rounds) NR	0.84 (0.67-0.99)

* Includes deaths from CRC treatment

Appendix B Table 2. Relationship of findings in the distal and the proximal colon.

Study	Participants	Patient Characteristics	Overall Prevalence of Proximal Neoplasia				Prevalence of Proximal Neoplasia by FS Findings			
			Proximal Adenoma	Advanced Proximal Adenoma	P-CRC	PAN	No Lesions	Distal Polyps or Adenomas		
								Small	Medium	Large
O'Brien 2003[330]	5,291 FS 606 w/ ≥ 1 adenoma: (12%) 550 w/ colonoscopy	**Age:** 63.4 ± 0.6 yrs **% Ethnic Origin:** NR **% Symptomatic:** NR **% Female:** 32 **Avg. Risk Status:** NR **SES:** NR **# polyps:** NR	34% (186/550)	8% (41/550)	0.7% (4/550)	NR	NR	**Proximal Adenoma**		
								Single Adenoma <6mm 27% (23, 33%)	***Single 6-10mm or multiple < 11mm*** 36% (29, 44%)	***Adv. AD 45%*** (38, 53%)
								Advanced Proximal Adenoma		
								Single Adenomas <6mm 5% (3, 9%)	***Single 6-10mm or multiple < 11mm*** 8% (5, 13%)	***Adv. AD*** 12% (38, 53%)
Schoen 2006[54]	64,658 FS 15,150 (23.4%) w/ any polyp or mass. 10,875 w/ CRC within 1 year	**Age:** 55-59yr: 30.2% 60-64yr: 31.7% 65-69yr: 24.7% 70-74yr: 13.4% **% Ethnic Origin:** %white: 91.5 % AA: 4.4 %Other: 4.0 **% Symptomatic:** NR **% Female:** 39.6 **Avg. Risk Status:** 11.9% (1296) w/ first degree relative. 4.5% (487) missing fam history **SES:** College Grad: 34.3% Post HS: 34.6% HS or less: 30.8% **# polyps:** NR	NR	Can't calculate prevalence due to non-report of whole colon lesions distal in those with lesions greater than 10mm		NR	NR	**Advanced Proximal Adenoma**		
								<5mm polyp ***Male*** 4.3% (135/3155) ***Female*** 2.3% (53/2274)	**5-9mm polyp** ***Male*** 4.2% (91/2183) ***Female*** 3.0% (43/1426)	
								CRC		
								<5mm polyp ***Male*** 0.3% (8/3155) ***Female*** 0.2% (5/2274)	**5-9mm polyp** ***Male*** 0.2% (5/2183) ***Female*** 0.2% (3/1426)	

PAN: Proximal Advanced Neoplasia: Advanced Proximal Adenoma + CRC
APA: Advanced Proximal Adenoma
Advanced Neoplasm: Any large adenoma ≥ 10mm and/or any size with villous histopathology and/or any size with severe dysplasia (including carcinoma); Diminutive Adenoma: ≤ 5mm (or per study)
Small Adenoma: 6-9mm (or per study)
Large Adenoma: ≥ 10mm
Adv AD: Advanced Adenoma: Advanced Neoplasm
Invasive Cancer: cell invades beyond muscularis mucosa

Appendix B Table 3. Key question 1 excluded studies.

Reference	Reason for exclusion
Anderson WF, Guyton KZ, Hiatt RA et al. Colorectal cancer screening for persons at average risk. *J Natl Cancer Inst* 2002; 94(15):1126-1133.	Excluded for study design
Andreoni B, Crosta C, Lotti M et al. Flexible sigmoidoscopy as a colorectal cancer screening test in the general population: recruitment phase results of a randomized controlled trial in Lombardia, Italy. *Chir Ital* 2000; 52(3):257-262.	Does not report appropriate outcomes
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):137-144.	Does not report appropriate outcomes
Banerjee S, Van Dam J. CT colonography for colon cancer screening. *Gastrointest Endosc* 2006; 63(1):121-133.	Does not report appropriate outcomes
Blue Cross Blue Shield Association. CT colonography ('virtual colonoscopy') for colon cancer screening. 2004. Chicago IL: Blue Cross Blue Shield Association (BCBS).	Does not report appropriate outcomes
Blue Cross Blue Shield Association. Immunochemical versus guaiac fecal occult blood tests. 2004. Chicago IL: Blue Cross Blue Shield Association (BCBS).	Does not report appropriate outcomes
Conlisk E. Colorectal cancer in North Carolina. Risk factors, screening behaviors, incidence, stage at diagnosis, and mortality. *N C Med J* 2001; 62(5):298-303.	Excluded for study design
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; 126(7):1674-1680.	Out of scope
Gupta AK, Melton LJ, III, Petersen GM et al. Changing trends in the incidence, stage, survival, and screen-detection of colorectal cancer: a population-based study. *Clinical Gastroenterology & Hepatology* 2005; 3(2):150-158.	Excluded for study design
Hamashima C, Sobue T, Muramatsu Y et al. Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program. *Jpn J Clin Oncol* 2006; 36(5):301-308.	Does not report appropriate outcomes
Hoff G, Grotmol T, Bretthauer M et al. Flexible sigmoidoscopy screening: a randomised controlled study of the population in the south of Norway. The Norwegian colorectal cancer prevention study (NORCCAP). - *Int J Cancer* 2002; Issue Suppl 13:93, 2002.	Does not report appropriate outcomes
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; 10(2):131-137.	Does not report appropriate outcomes
Lewis PR, Dixon AJ, Newberry GL. Survival of patients with colorectal cancer detected by a community screening program. *Med J Aust* 2000; 172(10):516-518.	Excluded population
Malila N, Anttila A, Hakama M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. *J Med Screen* 2005; 12(1):28-32.	Does not report appropriate outcomes
McCallion K, Mitchell RM, Wilson RH et al. Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening. *Gut 48(4):522-5,* 2001.	Does not report appropriate outcomes
McLeod R, with the Canadian Task Force on Preventive Health Care. Screening strategies for colorectal cancer: systematic review and recommendations. 2001. London, Ontario: Canadian Task Force on Preventive Health Care (CTFPHC).	Precedes search period

Appendix B Table 3. Key question 1 excluded studies.

Medical Services Advisory Committee. Faecal occult blood testing for population health screening. 2004. Canberra: Medical Services Advisory Committee (MSAC).	Does not report appropriate outcomes
Nelson D. Colonoscopy and polypectomy. *Hematology - Oncology Clinics of North America 16(4):867 -74 ,* 2002.	Excluded for study design
Newcomb PA, Norfleet RG, Storer BE et al. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992; 84(20):1572-1575.	Article covered by an included ser
Niv Y. Screening the average risk population for colorectal cancer: the Israeli experience 1985-97. *Colorectal Disease* 2003; 5(4):358-361.	Excluded for study relevance
Rennert G. Fecal occult blood screening--trial evidence, practice and beyond. *Recent Results Cancer Res* 2003; 163:248-253.	Excluded for study design
Rex DK. Rationale for colonoscopy screening and estimated effectiveness in clinical practice. *Gastrointestinal Endoscopy Clinics of North America 12(1):65-75,* 2002.	Excluded for study design
Saito H, Soma Y, Koeda J et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. *International Journal of Cancer 61(4):465 -9,* 1995.	Precedes search period
Saito H, Soma Y, Nakajima M et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep* 2000; 7(4):815-819.	Excluded for study quality
Sano Y, Fujii T, Oda Y et al. A multicenter randomized controlled trial designed to evaluate follow-up surveillance strategies for colorectal cancer: the Japan Polyp Study. - *Digestive Endoscopy* 2004; 16(4):376-378.	Does not report appropriate outcomes
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 Clinic Proceedings 74 (12):1207 -13,* 1999.	Precedes search period
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; 94(23):1763-1772.	Does not report appropriate outcomes
Sharma VK, Vasudeva R, Howden CW. Colorectal cancer screening and surveillance practices by primary care physicians: results of a national survey. *Am J Gastroenterol* 2000; 95(6):1551-1556.	Excluded for study relevance
Steele RJ, Parker R, Patnick J et al. A demonstration pilot trial for colorectal cancer screening in the United Kingdom: a new concept in the introduction of healthcare strategies. *J Med Screen* 2001; 8(4):197-202.	Excluded for study relevance
Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review. *JAMA 289(10):1288-96,* 2003.	Excluded for study design
Zappa M, Castiglione G, Grazzini G et al. "Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data." by Moayyedi P and Achkar E. *American Journal of Gastroenterology 101(10):2433 ; author reply 2433 -4,* 2006.	Excluded for study design
Zheng S, Chen K, Liu X et al. Cluster randomization trial of sequence mass screening for colorectal cancer. *Diseases of the Colon & Rectum* 2003; 46(1):51-58.	Not applicable setting

Appendix C. Study Details KQ2a. Flexible sigmoidoscopy

Flexible Sigmoidoscopy

Estimated adenoma and carcinoma miss rates for flexible sigmoidoscopy within the distal colon. In a good-quality prospective cohort study by Schoen et al.,{Schoen, 2003 1414 /id} investigators performed repeat flexible sigmoidoscopy (FS) on 9,317 patients with a previously negative FS three years earlier. Subjects were among those aged 55-74 recruited for a large multicenter cancer screening trial, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. The 9,317 patients comprised 80.4 percent of the original sample with a negative initial flexible sigmoidoscopy. All patients were asymptomatic and were examined for CRC screening, although 10.1 percent of patients had a single first degree relative with a history of CRC; 86.7 percent of patients were Caucasian and 38.4 percent were female, with a mean age of 65.7 years. Diagnostic followup was completed in 951 (73.6 percent) of the 1,292 individuals with an abnormal finding at the year-three screening sigmoidoscopy. The prevalence of distal advanced adenoma or cancer at 3 years followup was found to be 78 out of 9,317 persons, resulting in an approximate miss rate for advanced neoplasia in the distal colon of 0.8 percent of persons with an initial negative FS. A depth of penetration of greater than 60 cm in more than 63 percent of initial FS examinations suggests that the quality of initial examinations was high overall.

Burke et al.[143] also examined the prevalence of distal adenomas and cancers in an asymptomatic screening cohort using a subgroup that agreed to followup FS exam 3 years after the negative FS examinations. Nine hundred and fifteen asymptomatic patients agreed to undergo the second FS. The authors did not report what proportion of the initial examinees declined the second test. Attending gastroenterologists at the Cleveland Clinic conducted all of the examinations. The status of family history was not reported. The median depth of examination for the first examination was 35 cm and 45 cm for the second examination. The mean age of patients was 54 years, and 36 percent of patients were female. After 3 years of follow-up, 8 of the 915 patients (0.87 percent) had an advanced neoplasia on exam, including 1 patient with invasive carcinoma. All of the advanced neoplastic lesions were in locations within reach of the initial flexible sigmoidoscopy exam, so the less-than-optimal initial examinations did not impact the overall miss rates in this study.

A fair-quality tandem FS study by Schoenfeld et al.[141] examined the comparative miss rates for adenomatous polyps for three trained nurse endoscopists, compared with six trained physician endoscopists, among all patients attending for screening FS within a five-month period. Three hundred and

thirteen patients were enrolled to receive their first FS by either a nurse or physician, with a tandem, same-day follow-up FS by the other type of clinician, who was masked as to the first FS findings. Patients were 34 percent female and had a mean age of 60 years. Risk status and other sociodemographic characteristics were not reported. A total of 43 people (13.7 percent) had at least one adenoma identified on baseline FS and 6 people with no adenoma on first FS had one or more adenomas found on second FS. The proportion of patients who had adenomas identified only on the second exam was 3 percent (4/126) for the physicians and 3 percent (2/123) for the nurses. The adenoma miss rate for physicians was 20 percent (6/30), and for nurses was 21 percent (3/14). Neither physicians nor nurses missed any adenoma greater than one centimeter diameter. Average insertion depth for the sigmoidoscope was further for physicians, as compared to nurses (mean depth 61 cm vs. 55 cm, $p< 0.05$) and there were no complications reported. Insertion to 35 cm or less was associated with missing descending colon polyps. The study's major limitation was the high attrition rate of 20 percent (64/313), primarily due to voluntary withdrawal after the first exam and secondarily to incomplete endoscopy from excess retained stool. As well, the use of magnesium citrate, an oral laxative, for bowel preparation is more than the enemas usually used for flexible sigmoidoscopy. Above-average bowel cleansing in this study suggests this is an underestimation of true community miss rates.

Sensitivity of FS protocols for advanced neoplasia or CRC, based on distal findings: Screening colonoscopy studies. To estimate the diagnostic utility of distal colonic polyps, Betes et .al.[144] retrospectively reviewed results in 2210 average-risk patients (mean age 57.9 years, 25 percent female, all without a family or personal history of CRC) who participated in a university-based colonoscopy screening program in Spain from 1988 through 1998. In all those screened, there were 56 proximal advanced neoplasms (PAN) (2.5 percent). This number, and subsequent evaluations, is affected when the definition of distal includes the rectum, descending, and sigmoid colons. Most (73.1 percent) persons screened (1616/2210) had no findings, or only hyperplastic polyps or benign polyps, in the distal colon; 5.4 percent had advanced neoplasia (n=119); 15.0 percent had nonadvanced adenomas (n=331); and several (6.5 percent) had diminutive polyps (n=144) in the distal colon. While the prevalence of PAN in those with no distal findings was low (1.4 percent; 22/1616), 39.3 percent of all PAN lesions were in those with no distal lesions. Prevalence of PAN was highest (16.0 percent) in those with distal advanced neoplasia (n=119), less common (4.3 percent) in those with non-advanced distal adenomas (n=331), and rare (0.7 percent) in those with diminuitive polyps. Sensitivity of the FS with biopsy protocol was calculated to be 85.3% for advanced neoplasia in the whole colon. Data for calculating other sensitivity estimates was not available.

Ikeda and colleagues[145] retrospectively evaluated screening colonoscopies in 3131 Japanese average risk, asymptomatic men conducted as part of a pre-retirement health evaluation program—after excluding those with hyperplastic polyps alone (n=197). Among the 3131 participants, 812 men (26 percent) had a total of 1231 neoplastic lesions (18 CRC, 1213 adenomas). Almost half (44 percent) of adenomas were proximal. The distal colon was again defined as including the rectum, sigmoid and descending colon. Among all 3131 men with colonoscopy, the prevalence of small proximal tubular adenomas was 12.0 percent, of advanced proximal neoplasia was 0.9 percent, and of CRC was 0.1 percent. In those with no distal lesions, 10.7 percent had small proximal tubular adenomas, while 0.8 percent had advanced small proximal tubular adenomas. Prevalence of proximal adenomas was similar in those with small distal adenomas (less than 10 mm) compared with advanced distal neoplasia. Risk of PAN was much higher (6.0 percent), however, in those with advanced neoplasia compared with small adenomas (1.3 percent). Sensitivity of the FS with biopsy protocol was calculated to be 73.7% for advanced neoplasia in the whole colon. Data for calculating other sensitivity estimates was not available.

Anderson et al.[58] conducted a retrospective review of 1,988 charts from screening colonoscopies in average-risk patients referred to a university screening clinic in Stony Brook, New York. The authors evaluated the association of isolated proximal neoplasia in this cohort with other demographic factors recorded in their charts, including age, BMI, gender, family history of colorectal cancer, smoking status, education, aspirin use, ethnicity, alcohol use, exercise habits, and fruit/vegetable intake. Patients with gastrointestinal symptoms, prior history of colonic disease, or an endoscopic exam during the previous 10 years were excluded from the study. Overall prevalence of advanced neoplasia in the colon was 10.2 percent. The prevalence of isolated PAN was 3.2 percent, given the definition of the distal colon as including the descending and sigmoid colon and rectum. The odds of having any colorectal neoplasia for those over age of 60 were more than twice that of those 60 and younger (OR 2.34; 1.79, 3.05; P<0.001). The prevalence of isolated PAN also increased with age: 0.9 percent for age <49, 2.0 percent for those age 50 to 59 years, 4.1 percent for those age 60 to 69 years, and 5.4 percent for those age >70 years. The odds of having any colorectal neoplasia for current smokers were nearly twice the odds for those who had never smoked (OR 1.89; 1.42, 2.52; P<0.001). Family history and gender were also associated with a statistically significant increased risk of colorectal neoplasia. Sensitivity of the FS with biopsy protocol was 73.8% for advanced neoplasia and 62.5% for CRC in the whole colon.

Imperiale et.al.[146] conducted a similar retrospective analysis of 3025 screening colonoscopies in average-risk, asymptomatic, primarily (90 percent) white, middle-to-upper SES adults over aged years (1753

in men and 1272 in women) who were part of a workplace-based screening program. These data provide detailed information on risk for PAN by age and sex. Overall, 2.7 percent of all those screened had PAN, with higher percentages in men (3.9 percent) than women (1.2 percent). Risk increased with 5-year age increments (from 0.8 percent in persons 50 to 54 years to 5.6 percent in those 65 years and older). Due to a threefold greater risk of PAN in men than women, the absolute risk of PAN by age varied between men and women. For women under age 65, the absolute risk of PAN did not exceed 1.0 percent, while the absolute risk of PAN was 3.5 percent or greater in men beginning at age 55 years. Risk for PAN was above 5.0 percent in men and women with any distal adenomas (regardless of size or histology). Sensitivity for FS with biopsy protocol was 71.8% for advanced neoplasia in the whole colon. Sensitivity of the FS without biopsy protocol was slightly higher, 76.8% for advanced neoplasia in the whole colon. A study[59] of the earliest members of the same cohort reported histology and size of polyps on screening colonoscopy in 1994 patients. The sensitivity of the FS with biopsy protocol for CRC in the whole colon 58.3% (7/12), and of the FS without biopsy protocol was 75.0% (8/12) for CRC in the whole colon.

Lieberman et al.[60] conducted a prospective study of screening colonoscopy in 3,121 asymptomatic veteran males, aged 50-75 years and primarily white (83.6 percent). Patients were recruited from 13 Veterans Affairs medical centers from major cities in the United States and were asymptomatic, with no major comorbidities, no history of colorectal disease, and no previous colon examination within the preceding 10 years. Of the study population, 13.9% had a family history of colorectal cancer in at least one first-degree relative. Overall, 10.5 percent of patients had advanced neoplasms in the colon. The patients with distal hyperplastic polyps did not have a higher risk of advanced proximal neoplasia than the patients without any distal polyps. The prevalence of PAN was greater for those with distal non-advanced adenomas (6.8 percent), and greater yet for those with distal advanced adenomas (11.4 percent). The prevalence of PAN increased with age ($P<0.001$), from 2 percent for patients 50 to 59 years old, to 4.9 percent for those 60 to 69 years old, to 5.9 percent for those 70 to 75 years old. The overall prevalence of PAN was higher (5.4 percent) when the distal colon was designated as including only the rectum and sigmoid colon (and not the descending colon, as above—3.9 percent). Two sets of estimates of sensitivity were available and were based on differing definitions of the distal colon. With the distal colon including the descending colon (Definition 1), sensitivity estimates were higher than for the inclusion of the rectum and sigmoid colon only (Definition 2). For the more inclusive definition of the distal colon, Definition 1 (which mirrors the results of the above studies), sensitivity of the FS with biopsy protocol was 81.7% for advanced neoplasia in the whole colon. Sensitivity of the FS without biopsy protocol is slightly higher, 85.6% for advanced neoplasia in the whole colon. For the less inclusive (and more conservative) definition of the distal colon, Definition 2,

sensitivity of the FS with biopsy protocol was 71.2% for advanced neoplasia in the whole colon. Sensitivity of the FS without biopsy protocol is slightly higher, 78.7% for advanced neoplasia in the whole colon.

Schoenfeld et al.[61] conducted a prospective study of screening colonoscopy in veteran women as a comparative study to that conducted by Lieberman et al. Colonoscopy was completed in 1,463 women aged 40-79 years, 15.7 percent of whom had a family history of CRC in a first-degree relative. Patients with gastrointestinal symptoms, a history of colon disease, a previous flexible sigmoidoscopy within 5 years, a previous colonoscopy within 10 years, or a positive FOBT test within 1 year were excluded. The prevalence of advanced neoplasms in the colon overall was 4.9 percent. This prevalence varied significantly by age: 3.3 percent in those 50 to 59 years of age, 5.5 percent in those 60 to 69 years of age, and 11.7 percent of women who were 70 to 79 years of age. The prevalence of isolated proximal advanced neoplasia was 3.2 percent. The sensitivity of distal colon findings for advanced neoplasia is much lower than for other studies at 34.7 percent. As in Lieberman's study, the authors provide two sets of sensitivity estimates based on different definitions of the distal colon. For the more inclusive definition of the distal colon, Definition 1 (which mirrors the results of the other studies), sensitivity of the FS with biopsy protocol is 50.0% for advanced neoplasia in the whole colon. For the less inclusive (and more conservative) definition of the distal colon, Definition 2, sensitivity of the FS with biopsy protocol is 34.7% for advanced neoplasia in the whole colon.

Appendix C Table 1. KQ2A sensitivity of colonoscopy evidence table

Study	Setting Targeted Population	Reference/Gold Standard	Inclusion / Exclusion Criteria	Patient Characteristics
Pickhardt 2003[136] Good	3 US medical centers Recruited consecutive patients who were primarily referred for screening colonoscopy	OC with segmental unblinding to CTC; applied to 100% of patients. Seventeen experienced colonoscopists (14 gastroenterologists, 3 colorectal surgeons) Six experienced radiologists (minimum 25 CTC readings, two of the six had >100 CTC readings)	**Inclusion:** Asymptomatic adults age 50 to 79 years of average risk, age 40 to 79 years with family history, referred for CRC screening **Exclusion:** Positive FOBT result or iron deficiency anemia within the past 6 months; rectal bleeding or hematochezia or unintentional weight loss within the past 12 months; colonoscopy within the past 10 years; barium enema within the past 5 years; personal history of adenomatous polyps, CRC or IBD; family history of FAP or nonpolyposis cancer syndromes; rejection for colonoscopy for any reason; medical condition that precludes use of sodium phosphate prep; pregnancy	**N:** 1233 (1253 enrolled) **Age, mean:** 57.8 yrs **Female**: 41% **Ethnicity**: NR **SES:** NR **% with Risk Factors**: 2.6% with family history of CRC
Kim 2007[137] Fair	Korea Retrospective analysis to compare 2D and 3D interpretation of CTC	OC with segmental unblinding to CTC; applied to 100% of patients Five experienced gastroenterologists(7-15 years experience) Two experienced radiologists (100 CTC readings)	**Inclusion:** NR **Exclusion:** Prior colorectal surgery; IBD; iron deficiency anemia or positive FOBT results within the past 6 months; age <40 years; history FAP; history of polypectomy within past year	**N:** 96 **Age, mean**: 54.8 yrs **Female**: 42% **Ethnicity:** 100% Asian (assumed) **SES:** NR
Johnson 2007[138] Fair	Mayo Clinic, MN Prospective analysis to compare 2D and 3D interpretation of CTC	Videotaped OC with selective repeat colonoscopy (n=6) if comparison with CTC had lesions ≥ 10mm after re-review by radiologists and determined to have a high likelihood of being a true neoplasm Staff gastroenterologists, or were supervised by one of approximately 50 experienced staff gastroenterologists and colorectal surgeons Three experience radiologists (>1000 CTC reads)	**Inclusion:** Asymptomatic, ≥40 years old, scheduled to undergo screening colonoscopy **Exclusion:** Melena, hematochezia, IBD, familial polyposis, or symptomatic	**N:** 452 **Age, mean**: 65 yrs **Female:** 44% **Ethnicity**: White 85% Asian 12% Hispanic 3% African American 1% Native American 0.2% **SES**: NR

Appendix C Table 1. KQ2A sensitivity of colonoscopy evidence table

Study	Prevalence and Yield of Polyps	Sensitivity and miss rates of colonoscopy	Applicability	Comments
Pickhardt 2003[136] Good	***Polyps (all)*** # total polyps: 1310 # polyps ≥6 mm: 344 # polyps ≥10 mm: 82 ***Polyps (adenomatous)*** # total polyps: 554 # polyps ≥6 mm: 210 # polyps ≥10 mm: 51	**Sensitivity per polyp (adenomatous), [95%CI]:** ≥ 6 mm: 90.0% (189/210) , [85.1, 93.7] ≥ 8 mm: 89.5% (85/95), [81.5, 94.8] ≥10 mm: 88.2% (45/51), [76.1, 95.6] **Miss rate per polyp (adenomatous) (c):** ≥ 6 mm: 10.0% (21/210) ≥ 8 mm: 10.5% (10/95) ≥10 mm: 11.8% (6/51) **Sensitivity for adenoma per person, [95%CI]:** ≥ 6 mm: 92.3% (155/168) , [87.1, 95.8] ≥ 8 mm: 91.5% (75/82), [83.2, 96.5] ≥10 mm: 87.5% (42/48), [74.8, 95.3] **Miss rate for adenoma per person (c):** ≥ 6 mm: 7.7% (13/168) ≥ 8 mm: 8.5% (7/82) ≥ 10 mm: 12.5% (6/48)	Colonoscopists may be more experienced than in the community setting	20 patients excluded (8 had incomplete colonoscopy, 6 had inadequate prep, 6 had failure of CTC system) Standard bowel prep, and fecal tagging with oral contrast for CTC, type of sedation NR Only 2 CRC detected, one of the two was missed by colonoscopy
Kim 2007[137] Fair	***Polyps (all)*** # total polyps: 134 # polyps ≥6 mm: 35 # polyps ≥10 mm: 12 ***Polyps (adenomatous)*** # total polyps: 61 # polyps ≥6 mm: 22 # polyps ≥10 mm: 8	**Sensitivity per polyp (adenomatous), [95%CI]:** ≥ 6 mm: 93.4% (57/61), [NR] ≥ 8 mm: NR ≥10 mm: NR **Miss rate per polyp (adenomatous) (c):** ≥ 6 mm: 6.6% (4/61) **Sensitivity and miss rate per person: NR**	Full patient descriptions not available- although some high risk populations were clearly excluded. Generalizability to the US population is unknown.	Standard bowel prep, no fecal tagging, conscious sedation with midazolam No CRC detected
Johnson 2007[138] Fair	***Polyps (all)*** # total polyps: NR # polyps ≥6 mm: 93 # polyps ≥10 mm: 43 ***Polyps (neoplastic)*** # total polyps: NR # polyps ≥6 mm: 64 # polyps ≥10 mm: 26	**Sensitivity per neoplastic polyp, [95%CI]:** ≥ 6 mm: NR ≥ 8 mm: NR ≥10 mm: 76.9% (20/26), [NR] **Miss rate per neoplastic polyp (c):** ≥10 mm: 23.1% (6/26) **Sensitivity and miss rate per person: NR**	Asymptomatic population but did include persons with previous colonic resection	Six patients with incomplete colonoscopy Variable bowel prep (at the discretion of referring physician), no fecal tagging with oral contrast, type of sedation NR Did not use segmental unblinding Only five CRC detected, 4 of the 5 CRC missed by colonoscopy

Appendix C Table 2. Key question 2A excluded studies

Reference	Reason for exclusion
Allison JE. Colon Cancer Screening Guidelines 2005: the fecal occult blood test option has become a better FIT. *Gastroenterology.* 2005;129:745-748.	Excluded study design
Avidan B, Sonnenberg A, Schnell TG, Leya J, Metz A, Sontag SJ. New occurrence and recurrence of neoplasms within 5 years of a screening colonoscopy. *American Journal of Gastroenterology 97(6):1524*	Excluded for incorrect population
Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med.* 2006;355:2533-2541.	Excluded study design
Bianco MA, Rotondano G, Marmo R et al. Predictive value of magnification chromoendoscopy for diagnosing invasive neoplasia in nonpolypoid colorectal lesions and stratifying patients for endoscopic resection or surgery. *Endoscopy 38(5):470 -6.* 2006.	Excluded for study relevance
Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology.* 2007;132:96-102.	Excluded for study design
Chen SC, Rex DK. Endoscopist Can Be More Powerful than Age and Male Gender in Predicting Adenoma Detection at Colonoscopy. *Am J Gastroenterol.* 2007.	Excluded study design
Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. *Gut.* 2001;48:812-815.	Excluded for study relevance
Deenadayalu VP, Chadalawada V, Rex DK. 170 degrees wide-angle colonoscope: effect on efficiency and miss rates. *Am J Gastroenterol.* 2004;99:2138-2142.	Excluded population
Doria-Rose VP, Levin TR, Selby JV, Newcomb PA, Richert-Boe KE, Weiss NS. The incidence of colorectal cancer following a negative screening sigmoidoscopy: implications for screening interval.[see comment]. *Gastroenterology.* 2004;127:714-722.	Did not report relevant outcomes
Halligan S, Atkin W. Unbiased studies are needed before virtual colonoscopy can be dismissed. *Lancet.* 2005;365:275-276.	Excluded study design
Harewood GC. What is the most sensitive screening method for the detection of colon cancer? *Nature Clinical Practice Gastroenterology & Hepatology 2(3):134-5.* 2005.	Excluded study design
Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. *Am J Gastroenterol.* 2004;99:519-522.	Excluded population
Hixson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. *Gastrointest Endosc.* 1991;37:125-127.	Excluded for incorrect population
Hixson LJ, Fennerty MB, Sampliner RE, McGee D, Garewal H. Prospective study of the frequency and size distribution of polyps missed by colonoscopy. *J Natl Cancer Inst.* 1990;82:1769-1772.	Excluded setting
Ho, C., Jacobs, P., Sandha, G., Noorani, H. Z., and Skidmore, B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectiveness. 2006. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA).	Did not report necessary outcomes
Hoff G, Thiis-Evensen E, Grotmol T, Sauar J, Vatn MH, Moen IE. 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;10:131-137.	Excluded for study relevance

Appendix C Table 2. Key question 2A excluded studies

Reference	Reason for exclusion
Hosokawa O, Shirasaki S, Kaizaki Y, Hayashi H, Douden K, Hattori M. Invasive colorectal cancer detected up to 3 years after a colonoscopy negative for cancer. *Endoscopy.* 2003;35:506-510.	Excluded study design
Hurlstone DP, Sanders DS. Recent advances in chromoscopic colonoscopy and endomicroscopy. *Current Gastroenterology Reports 8(5):409 -15.* 2006.	Excluded for study design
Kato S, Fujii T, Koba I et al. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? *Endoscopy.* 2001;33:306-310.	Excluded for study relevance
Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA. Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control.* 1998;9:455-462.	Excluded for study relevance
Kiesslich R, von BM, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. *Endoscopy.* 2001;33:1001-1006.	Excluded for study relevance
Leaper M, Johnston MJ, Barclay M, Dobbs BR, Frizelle FA. Reasons for failure to diagnose colorectal carcinoma at colonoscopy. *Endoscopy.* 2004;36:499-503.	Excluded for study design
Levin TR, Farraye FA, Schoen RE et al. Quality in the technical performance of screening flexible sigmoidoscopy: recommendations of an international multi-society task group. *Gut.* 2005;54:807-813.	Excluded study design
Levin TR, Palitz A, Grossman S et al. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. *JAMA.* 1999;281:1611-1617.	Excluded study design
Levin TR. What does sigmoidoscopy really miss? *American Journal of Gastroenterology 98(10):2326 -7.* 2003.	Excluded study design
Lewis JD, Ng K, Hung KE et al. Detection of proximal adenomatous polyps with screening sigmoidoscopy: a systematic review and meta-analysis of screening colonoscopy. *Archives of Internal Medicine 163(4):413-20.* 2003.	Excluded study design
Lieberman DA, Weiss DG, Harford WV et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology.* 2007;133:1077-1085.	Did not report relevant outcomes
Lieberman DA, Weiss DG, Veterans Affairs Cooperative Study Group. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *New England Journal of Medicine 345(8):555-60.* 2001.	Excluded setting
Luchtefeld MA, Kim DG. Colonoscopy in the office setting is safe, and financially sound ... for now. *Diseases of the Colon & Rectum 49 (3):377 -81 ; discussion 381 -2.* 2006.	Excluded for study relevance
Matsushita M, Takakuwa H, Matsubayashi Y, Nishio A, Ikehara S, Okazaki K. Appendix is a priming site in the development of ulcerative colitis. *World Journal of Gastroenterology.* 2005;11:4869-4874.	Excluded setting
McCallion K, Mitchell RM, Wilson RH et al. Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening. *Gut 48(4):522-5.* 2001.	Excluded study design
Menardo G. Sensitivity of diagnostic examinations for colorectal polyps. *Techniques in Coloproctology 8 Suppl 2:s273 -5.* 2004.	Excluded study design

Appendix C Table 2. Key question 2A excluded studies

Reference	Reason for exclusion
Muller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. *Arch Intern Med.* 1995;155:1741-1748.	Did not report necessary outcomes
Neugut AI, Jacobson JS, Ahsan H et al. Incidence and recurrence rates of colorectal adenomas: a prospective study. *Gastroenterology.* 1995;108:402-408.	Excluded for study quality
Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst.* 1992;84:1572-1575.	Excluded for study relevance
Nicholson FB, Korman MG, Stern AI, Hansky J. Distribution of colorectal adenomas: implications for bowel cancer screening. *Med J Aust.* 2000;172:428-430.	Excluded population
Phillips KA, Liang SY, Ladabaum U et al. Trends in colonoscopy for colorectal cancer screening. *Med Care.* 2007;45:160-167.	Excluded for study relevance
Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Annals of Internal Medicine 141(5):352-9.* 2004.	Excluded study design
Postic G, Lewin D, Bickerstaff C, Wallace MB. Colonoscopic miss rates determined by direct comparison of colonoscopy with colon resection specimens. *Am J Gastroenterol.* 2002;97:3182-3185	Excluded for study quality
Rasmussen M, Kronborg O, Fenger C, Jorgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study. *Scandinavian Journal of Gastroenterology 34(1):73-8.* 1999.	Excluded for study relevance
Rex DK, Chadalawada V, Helper DJ. Wide angle colonoscopy with a prototype instrument: impact on miss rates and efficiency as determined by back-to-back colonoscopies. *Am J Gastroenterol.* 2003;98:2000-2005.	Did not include one of the specific screening tests
Rex DK, Cummings OW, Helper DJ et al. 5-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons [see comment]. *Gastroenterology.* 1996;111:1178-1181	Excluded for study design
Rex DK, Cutler CS, Lemmel GT et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology.* 1997;112:24-28.	Excluded population
Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. *Gastroenterology.* 1997;112:17-23.	Excluded population
Rex DK. Colonoscopic withdrawal technique is associated with adenoma miss rates. *Gastrointest Endosc.* 2000;51:33-36.	Excluded for study relevance
Rex DK. Colonoscopy practice variation. *Gastrointest Endosc.* 2003;58:639-640.	Excluded population
Rex DK. Maximizing detection of adenomas and cancers during colonoscopy. *American Journal of Gastroenterology 101(12):2866 -77.* 2006.	Excluded study design
Rockey DC, Paulson E, Niedzwiecki D et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet.* 2005;365:305-311.	Excluded population

Appendix C Table 2. Key question 2A excluded studies

Reference	Reason for exclusion
Sawhney MS, Farrar WD, Gudiseva S et al. Microsatellite instability in interval colon cancers. *Gastroenterology 131 (6):1700-5.* 2006.	Excluded for study design
Schoen RE, Weissfeld JL, Pinsky PF, Riley T. Yield of advanced adenoma and cancer based on polyp size detected at screening flexible sigmoidoscopy. *Gastroenterology 131 (6):1683 -9.* 2006.	Excluded for study relevance
Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med.* 1992;326:653-657.	Did not report necessary outcomes
Senore C, Segnan N, Bonelli L et al. Predicting proximal advanced neoplasms at screening sigmoidoscopy. *Diseases of the Colon & Rectum 47(8):1331-40.* 2004.	Excluded population
Shapero TF, Hoover J, Paszat LF et al. Colorectal cancer screening with nurse-performed flexible sigmoidoscopy: results from a Canadian community-based program. *Gastrointest Endosc.* 2006.	Excluded study design
Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA 295(20):2366 -73.* 2006.	Excluded population
Sonwalkar S, Rotimi O, Rembacken BJ. Characterization of colonic polyps at conventional (nonmagnifying) colonoscopy after spraying with 0.2 % indigo carmine dye. *Endoscopy.* 2006;38:1218-1223.	Excluded for study relevance
Stergiou N, Frenz MB, Menke D, Riphaus A, Wehrmann T. Reduction of miss rates of colonic adenomas by zoom chromoendoscopy. *International Journal of Colorectal Disease 21(6):560 -5.* 2006.	Excluded for incorrect population
Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol.* 1999;34:414-420.	Excluded for study relevance
Thomas-Gibson S, Thapar C, Shah SG, Saunders BP. Colonoscopy at a combined district general hospital and specialist endoscopy unit: lessons from 505 consecutive examinations. *J R Soc Med.* 2002;95:194-197.	Did not report necessary outcomes
Thomson J, Phull P. Audit of bowel preparation with Picolax (sodium picosulfate plus magnesium citrate) for colonoscopy. *Int J Clin Pract.* 2006;60:602-603.	Did not report necessary outcomes
van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol.* 2006;101:343-350.	Excluded population
Winawer SJ, Zauber AG, O'Brien MJ et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med.* 1993;328:901-906.	Excluded study design

Appendix C Table 3. Studies estimating sensitivity of flexible sigmoidoscopy.

Study	Patient characteristics	Overall polyp prevalence	Prevalence of patients with proximal neoplasia	Prevalence of patients with proximal advanced neoplasia by FS findings		
				Among all with no distal lesions	Among all with distal polyps or adenomas	
					Non-advanced adenoma	Advanced adenoma
Betes Ibanez 2004[144] Spain Distal definition: descending & sigmoid colon, rectum	N: 2,210 Age incl: >40; Mean age: 57.9 % Ethnicity: NR % Female: 25.4 % FH: 0	Any polyps: 7.3% Any neoplasm: 28% Adv. neoplasm: 7% CRC: 0.5%	PA: NR APA: NR P-CRC: NR PAN: 2.5% (56/2110)	1.3% (23/1836)	4.2% (14/331)	16% (19/119)
Ikeda 2000[145] Japan Distal definition: splenic flexure, descending & sigmoid colon, rectum	N: 3,131 Age incl: 48-57; Mean age: 61.2 % Ethnicity: [Japanese] % Female: 0 % FH: NR	Any polyps: NR Any neoplasm: 25.9% Adv. neoplasm: 2.4% CRC: 0.6%	PA: 12% (376/3131) APA: NR P-CRC: 0.1% PAN: 0.9% (29/3131)	0.8% (20/2620)	1.3% (6/461)	6.0% (3/50)
Anderson 2004[58] USA Distal definition: descending & sigmoid colon, rectum	N: 1,988 Age incl: >40; Mean age: 57.2 % Ethnicity: 1.5 nonwhite % Female: 45.6 % FH: 13.6	Any polyps: NR Any neoplasm: 21.9% Adv. neoplasm: 10.2% CRC: 0.4%	PA: NR APA: NR P-CRC: NR PAN: NR	3.2% (55/1697)	NR	NR
Imperiale 2003[146] Imperiale 2000[59] USA Distal definition: descending & sigmoid colon, rectum	N: 3,025 (1994 subgroup) Age incl: ≥50; Mean age: 58.9 % Ethnicity: 90 white % Female: 42 % FH: NR	Any polyps: NR Any neoplasm: NR Adv. neoplasm: 6.0% CRC: NR	PA: NR APA: NR P-CRC: NR PAN: Male: 3.9% (68/1753) Female: 1.2% (15/1272)	Total: 1.8% Male: 2.5% (33/1309) Female: 0.84% (9/1075)	Total: 7.9% Male: 8.7% (14/161) Female: 5.9% (4/68)	Total: 12.5% Male: 14.3% (12/84) Female: 7.1% (2/28)
Lieberman 2000[60] USA Distal definition: descending & sigmoid colon, rectum	N: 3,121 Age incl: 50-75; Mean age: 62.9 % Ethnicity: 16.4 nonwhite % Female: 3.2 % FH: 13.9	Any polyps: 53.8% Any neoplasm: 37.5% Adv. neoplasm: 10.5% CRC: 1.0%	PA: NR APA: NR P-CRC: NR PAN: 4.1% (128/3121)	2.7% (48/1765)	6.8% (38/561)	11.4% (24/210)
Distal definition: sigmoid colon, rectum						
Schoenfeld 2005[61] USA Distal definition: descending & sigmoid colon, rectum	N: 1,463 Age incl: 40-79; Mean age: 58.9 % Ethnicity: 23 nonwhite % Female: 100 % FH: 15.7	Any polyps: NR Any neoplasm: 20.4% Advanced neoplasm: 4.9% CRC: 0.1%	PA: NR APA: 3.4% (50/1462) P-CRC: NR PAN: 3.4% (50/1462)	2.4% (36/1324)	2.2% (3/138)	
Distal definition: sigmoid colon, rectum				3.4% (47/1367)	4.1% (3/73)	0% (0/22)

Abbreviations: FH = family history; NR = not reported; CRC = colorectal cancer; PA = proximal adenoma; APA = advanced proximal adenoma; P-CRC = proximal invasive colorectal cancer; PAN = proximal adenomatous neoplasia

Appendix C Table 3. Studies estimating sensitivity of flexible sigmoidoscopy.

Study	Sensitivity of FS with biopsy for advanced neoplasia in the whole colon	Sensitivity of FS without biopsy for advanced neoplasia in the whole colon	Sensitivity of FS with biopsy for CRC in the whole colon	Sensitivity of FS without biopsy for CRC in the whole colon
Betes Ibanez 2004[144] Spain Distal definition: descending & sigmoid colon, rectum	85.3% (133/156)	NR	NR	NR
Ikeda 2000[145] Japan Distal definition: splenic flexure, descending & sigmoid colon, rectum	73.7% (56/76)	NR	NR	NR
Anderson 2004[58] USA Distal definition: descending & sigmoid colon, rectum	73.8% (155/210)	NR	62.5% (5/8)	NR
Imperiale 2003[146] Imperiale 2000[59] USA Distal definition: descending & sigmoid colon, rectum	Total: 71.8% (130/181) Male: 70.0% (98/140) Female: 78.0% (32/41)	76.8% (139/181)	58.3% (7/12)	75.0% (8/12)
Lieberman 2000[60] USA Distal definition: descending & sigmoid colon, rectum	81.7% (272/333)	85.6% (285/333)	NR	NR
Distal definition: sigmoid colon, rectum	71.2% (237/333)	78.7% (262/333)	NR	NR
Schoenfeld 2005[61] USA Distal definition: descending & sigmoid colon, rectum	50% (36/72)	NR	NR	NR
Distal definition: sigmoid colon, rectum	34.7% (25/72)	NR	NR	NR

Appendix C Table 4. KQ2A Miss rates of flexible sigmoidoscopy

Study	Setting Targeted Population	Reference Standard Operator Characteristics	Inclusion / Exclusion Criteria	Patient Characteristics
Schoenfeld 1999[141]	Bethesda, MD: Hospital All pts attending for FS in 5-month period	FS; applied to 100% of pts *Nurse endoscopist*: (2+ years as gastro nurse; 100+ supervised FS; 50 independent procedures *Gastroenterologists*: 1-4 years exp; 1000+ endoscopies; one colorectal surgeon > 4 yrs experience and > 200 endoscopic procedures Pts randomized to either gastroenterologist or nurse endoscopist for first exam	**Inclusion:** Attended clinic for screening FS within 5-month period **Exclusion:** Too much stool retained for FS; medical condition made back to back FS harmful; inappropriate referral for screening (64 refused 2nd FS)	**N:** 313 enrolled; 249 completed both FS ***Gastro*** (n: 162) **Age:** 61± 10 yr **% Female:** 33 ***Nurse*** (n: 151) Age: 59± 10 yr **% Female:** 34 All NS
Burke 2006[143]	Cleveland Clinic Subjects chosen from a cohort of pts undergoing FS for CRC screening between 1987 and 2002, as those with an initial negative FS	Repeat FS 3-5 years later Staff gastroenterologists	**Inclusion:** Asymptomatic pts; No other concurrent method of screening; all examinations had adequate preparation; had a normal baseline FS; had a followup examination 3 yrs (+/-6 months) or 5 yrs (+/- 6 months) later. Only subjects with two FS examinations were included in the cohort.	**N:** 2,146 **Age (mean):** 54 yr **% Female:** 36 **% Ethnicity:** NR **SES:** NR **% with Risk Factors:** NR
Schoen 2003[142]	PLCO trial, multicenter American screening study Sample taken from the (randomized) intervention arm of a large multicenter screening study.	Repeat FS, sometimes with colonoscopic re-examination 3 years later Trained nurses or certified physicians	**Inclusion:** Age 55-74 years; no current treatment for cancer except basal cell or squamous cell skin cancer; no known prior cancer of the colon, rectum, prostate, lung or ovaries; no surgical removal of the colon, lung, ovary or prostate; no participation in another cancer screening or cancer prevention trial; no finasteride use (in men) or no tamoxifen use (in women) in the past 6 months; provision of informed consent; no more than 1 prostate-specific antigen test in the past 3 years (for men randomized after April 1995); and no colonoscopy, sigmoidoscopy, or barium enema in the past 3 years (for individuals randomized after April 1995).	**N:** 9,317 **Age (mean):** 65.7 yr **% Female:** 38.4 **% Ethnicity:** ***White, NH:*** 86.7 ***Hispanic:*** 1.1 ***Black, NH:*** 3.8 ***Asian:*** 7.5 ***Other:*** 0.9 **% SES:** ***High school grad or less***: 27 ***High school grad, less than college grad:*** 31.7 ***College grad:*** 19.5 ***Postgrad training:*** 21.8 **% with risk factors:** 10.1 reported a FH of CRC in a first degree relative

Appendix C Table 4. KQ2A Miss rates of flexible sigmoidoscopy

Study	Prevalence and Yield of Polyps	Miss Rates (Any polyp, Adenomas, high-risk adenomas, CRC)	Screening Test Adequacy	Comments
Schoenfeld 1999[141]	***Gastro:*** n=162 # pts with adenomas: 26 (16%) # pts with anatomic polyps: 70 (43%) # pts with multiple anatomic polyps: 55 (17%) ***Nurse:*** n=151 # pts w/ adenomas: 17 (11%) # pts w/ anatomic polyps: 68 (45%) # pts w/ multiple anatomic polyps: 33 (22%) All NS	***Person Miss Rate: (Gastro; Nurse)*** pts w/ anatomic polyp: 51% (64/126); 47% (58/123) pts w/ polyp 1st FS: 40% (50/126); 41% (51/123) pts w/ polyp 2nd FS: 23% (29/126); 14% (17/123) pts w/ no polyp 1st FS found on 2nd FS: 12% (14/126); 6% (7/123) pts w/ no adenoma on 1st found on 2nd FS: 3% (4/126); 2% (2/123) All NS ***Adenoma miss rates: N: 249*** **Gastro** (n: 126) missed/total polyps; **Nurse** (n: 123) missed/total polyps 1-5 mm 2/15; 3/8 6-9 mm 2/5; 0/2 ≥10 mm 2/10; 0/4 ***Polyp miss rates:*** **Gastro** / **Nurse** All polyps 29% (41/139); 17%(22/128); p=0.02 Hyperplastic 32% (35/109); 17% (19/114); p=0.01 Adenoma 20% (6/30); 21% (3/14); NS	**% refused 2nd exam:** 20	pg 316, if the sigmoidscope was only inserted 35 cm during 1st FS then descending colon polyps were frequently missed. The 1st FS inserted the scope at least 50 cm in (223/249) 90% of pts. In these pts only 3 additional polyps were found when the sigmoidscope was inserted further during the 2nd FS. Depth of FS was limited to 35 cm in (11/249) 4.4% of pts. Of these pts 27% had additional polyps
Burke 2006[143]	N/A (initial exam negative)	3.2% of 915 subjects had neoplasia detected on 3-yr follow-up FS. Of the total lesions, approximately 60% were tubular adenomas, and 40% were tubulovillous or more advanced. 1 carcinoma was found in 915 subjects at 3 yr follow-up. 93% of the neoplasms in the 3-yr subjects were in the area of the colorectum that had been previously examined		Unclear what number of pts with an initial negative screening FS were lost to followup. Also not stated what proportion in cohort were excluded due to poor bowel preparation
Schoen 2003[142]	N/A (initial exam negative)	**Distal colon** / **Prox Colon** **Nonadvanced adenoma** 214; 124 **Advanced adenoma** 72; 39 **Cancer** 6; 1 **Total** 292; 164 Prevalence of distal advanced adenoma or cancer at 3 years followup is 78/9,317 = 0.8%Prevalence of proximal advanced adenoma or cancer at 3 years followup is 40/9,317 = 0.4% Prevalence of any distal adenoma or cancer at 3 years is 292/9,317 = 3.1%	9,317 of 11,583 indv. (80.4%) without a polypoid mass or lesion on initial FS returned for repeat screening 3 yr later. Of the 9,317 indv, 8,025 (86.1%) had nonsuspicious findings. Of the 1,292 with abnormal, suspicious findings, 951 (73.6%) had diagnostic followup (341 did not). Of the 951 with diagnostic followup, 847 had colonoscopy (89.1%) and 104 had FS (10.9%).	Only those with abnormal findings on FS had a followup colonoscopy

Appendix C Table 5. Missed and interval cancers estimated on follow-up colonoscopy or retrospectively from diagnosed CRC.

Author, year	Cohort characteristics	Follow-up	Proportion with CRC on follow-up	Study limitations
Prospective studies of screening colonoscopy				
Imperiale, 2008[331]	1,256 of 2,436 persons with a negative screening colonoscopy who had a repeat screening colonoscopy 5 years later	Repeat colonoscopy 5 years later	0 of 1256 were diagnosed with CRC within the next 5 years	Low follow-up of original cohort, sensitivity analysis done for adenomas and advanced neoplasia, but not CRC Time interval of follow-up may not correspond to "missed" cancer Unclear generalizablity of endoscopists to community setting
Lieberman, 2007[332]	298 of 501 patients selected from a pool of 1,950 that had an initially negative screening colonoscopy and repeat colonoscopy in 5.5 years • 23.8% of 298 patients had a family history of CRC	Repeat colonoscopy 5.5 years later	1 of 298 was diagnosed with CRC within 5 years 1/298 = 0.3% interval incidence of CRC	Low follow-up of original cohort Time interval of follow-up may not correspond to "missed" cancer
Rex, 1996[333]	154 of 368 patients with a negative initial screening colonoscopy who had a repeat colonoscopy 5.5 years later	Repeat colonoscopy at a mean of 5.5 years later	0 of 154 were diagnosed with CRC	Low follow-up of original cohort Time interval of follow-up may not correspond to "missed" cancer
Prospective studies of diagnostic colonoscopy				
Hosokawa, 2003[334]	List of 7,365 patients who had a colonoscopy (and no CRC found) during a 5 year period in a community hospital in Japan, who had: • No adenomas or • Adenomas without high-grade dysplasia <u>Reasons for colonoscopy:</u> Surveillance: 32.7% +FOBT/DCBE: 30% Screening: 6.5% Signs/symptom disease: 13.2% IBD surveillance: 1.9% Other/not stated: 16%	Matched with entries on the local government-based Cancer registry at 3 yrs	15 of those diagnosed with CRC during the next 3 years (248) had a negative colonoscopy 15 / 7,365 = 0.2% interval incidence of CRC	High proportion of initial cohort had colonoscopy for reasons other than screening No clear differentiation between those without any adenomas on colonoscopy and those with low-grade adenomas
Neugut, 1995[335]	99 of 508 patients who had an initially negative	A second colonoscopy	0 of 99 were diagnosed with	High proportion of initial cohort had

Appendix C Table 5. Missed and interval cancers estimated on follow-up colonoscopy or retrospectively from diagnosed CRC.

Author, year	Cohort characteristics	Follow-up	Proportion with CRC on follow-up	Study limitations
	colonoscopy, and had a repeat colonoscopy within the next 3 years • 59.6% symptomatic • 37.4% had family history of CRC	within 3 years	CRC	colonoscopy for reasons other than screening Low follow-up of original cohort
Avidan, 2002[336]	391 patients at the Hines VA Hospital, with negative screening colonoscopy followed by a second 1-5 years later. • 44.8% had ≥ 1 first degree relatives with CRC. • 98.5% male	Repeat colonoscopy 1-5 years later	2 of 391 were diagnosed with CRC within the next 5 years 2 / 391 = 0.5% interval incidence of CRC	High proportion of patients with a family history of CRC Size of original cohort (those with a first colonoscopy only) not stated. Time interval of follow-up may not correspond to "missed" cancer
Retrospective studies of screening or diagnostic colonoscopy				
Bressler, 2007[242]	12,487 patients with a diagnosis of CRC, 430 of whom had received a colonoscopy within 36 months prior to CRC diagnosis	Those with a screening colonoscopy 6-36 months prior to CRC diagnosis were defined as missed or interval CRC.	430 / 12,487 =3.4% with a diagnosis of CRC had a 'missed' or 'interval' cancer	Unknown proportion of initial cohort had colonoscopy for reasons other than screening
Sawhney, 2006[337]	993 patients with a diagnosis of CRC, 51 had received a complete colonoscopy within 5 years prior to CRC diagnosis 98% Male	Those with a colonoscopy within 5 yrs of CRC diagnosis were defined as missed or interval cancer.	51 / 993 = 5.1% with a diagnosis of CRC had a 'missed' or 'interval' cancer	Unknown proportion of initial cohort had colonoscopy for reasons other than screening Time interval of follow-up may not correspond to "missed" cancer
Rex, 1997[338]	941 patients with a diagnosis of CRC, 47 had received a complete colonoscopy within 3 years prior to CRC diagnosis • 66 of 941 patients had colonoscopy for screening	Those with a colonoscopy within 3 yrs of CRC diagnosis were defined as missed or interval cancer.	47 / 941 = 5.0% with a diagnosis of CRC had a 'missed' or 'interval' cancer	High proportion of initial cohort had colonoscopy for reasons other than screening
Farrar, 2006[339]	830 patients with a diagnosis of CRC, 45 had received a complete colonoscopy within 5	Those with a colonoscopy within 5 yrs of CRC	45 / 830 = 5.4% with a diagnosis of CRC had a 'missed' or	Time interval of follow-up may not correspond to "missed" cancer

Appendix C Table 5. Missed and interval cancers estimated on follow-up colonoscopy or retrospectively from diagnosed CRC.

Author, year	Cohort characteristics	Follow-up	Proportion with CRC on follow-up	Study limitations
	years prior to CRC diagnosis	diagnosis were defined as missed or interval cancer.	'interval' cancer	Unknown proportion of initial cohort had colonoscopy for reasons other than screening

Appendix D. Study Details KQ2B. CT Colonography, Fecal Occult Blood Tests, and Fecal DNA.

CT Colonography

Three smaller studies only briefly mentioned in the text of the report are described here. A fair-to-poor quality study of 68 average-risk male veterans used some newer aspects of CT technology that are more sensitive (multidetector scanning) when combined with less sensitive aspects (2D imaging with 3D confirmation only as needed).[149] They found polyps (any histological type) in 57 percent of 68 male veterans. Per-polyp sensitivity for all polyps tended to be lower in smaller polyps (6-9 mm), compared with larger ones (10 mm or greater), although estimates were unstable due to small numbers and per patient sensitivity was not reported. Per-patient specificity was 89.7 percent (CI: 72.7, 97.8) for polyps of all sizes, and better for polyps 10 mm or greater (98.5 percent: CI 91.7, 99.9). CTC lesions not found on OC were assumed to be false positives due to fecal material.

Two small studies provide additional limited evidence on the test-performance characteristics of CTC. One study of fair-to-poor quality study examined 46 Veterans at an Indianapolis VA Hospital system and compared results from spiral CT to those from same-day colonoscopy.[150] Subjects were intentionally selected from a population of older men (98 percent male, mean age of 67.7 years) to increase polyp prevalence. Images were examined from 2D axial CT as well as interactive multiplanar images and 3D CTC (consisting of surface and volume-rendered images). CTC examinations employed older, single-detector technology without contrast. Three-dimensional imaging proved superior to 2D for polyp detection, although the difference was statistically significant only for lesions ranging from 6 to 9 mm. The sensitivity of three-dimensional exam met or, more commonly, exceeded that of 2D for all sizes of lesion. The per-patient sensitivity for adenomas of at least 1 cm was calculated at 89 percent. Flat adenomas in the proximal colon were notably missed by CTC. Oversight of large, flat adenomas was attributed to residual stool and water in the region or to bowel segment collapse, strengthening the case for special attention to adequate bowel preparation being central to the identification of nonpolypoid lesions.

A second study of fair-quality enrolled 42 patients in New York City enrolled subjects more representative of the general screening population, including asymptomatic middle-aged adults (mean age 56 years) of either gender (42 percent female, 58 percent male), 29 percent of whom reported a family history of CRC.[148] Two methods of examination included: initial review of axial 2D images with 3D reexamination only of focal areas suspicious for abnormality (Method 1). Initial review of 2D images followed by complete examination with simultaneous 3D fly-through CTC (surface-rendered images) and multiplanar

reformatted images regardless of initial findings (Method 2). Examinations employed older single detector technology without contrast. Within this population, the prevalence of polyps was 31 percent (13/42) by traditional colonoscopy. Missed polyps on CTC (10 of 16) included two at 2 mm, five at 3 mm, one at 4 mm, and two at 6 mm. Sixty-seven percent of polyps measuring at least 6 mm were captured by CTC, as were 100 percent of polyps measuring at least 7 mm. Both CTC methods had similar per-polyp sensitivity (38 percent) and NPV (Method 1: 73 percent; Method 2: 72 percent), while the more targeted Method 1 outperformed Method 2 in per-polyp specificity and PPV (100 percent versus 96 percent and 100 percent versus 86 percent, respectively). Axial 2D CTC was found to be comparable to 3D CTC for detection of polyps, and the more complete and time-intensive Method 2 offered no justifiable advantage over the focal review conducted in Method 1.

Fecal Occult Blood Tests

High-sensitivity guaiac tests. Two studies conducted in the same managed care organization evaluated the performance of Hemoccult Sensa in average-risk patients.[159,160] The first fair-quality study provided comparative single-test performance information for Hemoccult Sensa compared with nonrehydrated Hemoccult II[160] in 8104 multi-ethnic (46.5 percent nonwhite) adults aged 50 or older. Participants underwent simultaneous testing with Hemoccult Sensa, nonrehydrated Hemoccult II, and HemeSelect, followed by FS and/or colonoscopy for any positive FOBT result. All participants were followed for two years through complete medical record review, supplemented by tumor registry and pathology laboratory result reviews. This is an adequate surrogate reference standard for CRC only (not polyps). Test completion rates were similar for both tests (91.4 to 93.5 percent). The percentage of positive tests was much higher for Hemoccult Sensa (13.6 percent) compared with Hemoccult II (2.5 percent). Sensitivity of Hemoccult Sensa for CRC was significantly better than nonrehydrated Hemoccult II (79.4 vs. 37.1 percent), although PPV was poorer (Hemoccult Sensa 2.5 percent compared with 6.6 percent for Hemoccult II). Specificity of Hemoccult Sensa for CRC was likewise significantly inferior to Hemoccult II (86.7 percent vs. 97.7 percent). While this is a well-performed study, these results are limited by the design constraints of being performed in the "real-world." As such, while comparative test performance results are available, these were not comparably determined. Only 36 percent of those with positive Hemoccult Sensa tests had colonoscopy (the remainder receiving FS with followup Hemoccult II testing over the next year as an alternative "gold standard," a change in study protocol implemented mid-way due to very high test positivity of Hemoccult Sensa). Those with positive results on the other FOBT tests had a colonoscopy rate of 78 percent-85 percent. Thus, the

sensitivity is likely to be over-estimated for Hemoccult Sensa compared with Hemoccult II and with HemeSelect, and the specificity is likely to be underestimated. What is clear is that the percentage with positive test results is about twice as high (13.6 percent), compared with 2.5 percent for Hemoccult II.

The second and more recent study was a good-quality study in which all patients (n=5841: 26 percent nonwhite; 53 percent female; 11 percent aged 70 years and older) received followup endoscopy.[159] Patients screening positive were advised to undergo colonoscopy and those screening negative underwent a flexible sigmoidoscopy exam. All patients were followed through medical records review for an additional 2 yrs. The study compared Hemoccult Sensa alone or in combination with a FIT (FlexSure OBT) to evaluate the test characteristics for identifying left-sided cancers and adenomas. Hemoccult Sensa had the highest test positivity rate (10 percent) with possible lower sensitivity for left-sided CRC than FIT alone (64.3 percent sensitivity compared with 81.8 percent, estimates not statistically different) and clearly lower specificity for left-sided CRC (90.1 percent compared with 96.9 percent). A combination Hemoccult Sensa/FlexSure screening approach, where the FIT was developed only if the guaiac-based test was positive, had identical sensitivity and better specificity than Hemoccult Sensa alone (98.1 percent compared with 90.1 percent). Absolute sensitivity or specificity for whole-colon CRC cannot be inferred from these estimates, although the authors' provision of estimates for left-sided lesions are reliable.

Immunochemical tests. *Magstream and related tests (HemeSelect) (3 studies).* Morikawa recently reported a retrospective analysis of 21,805 asymptomatic adults participating in a Japanese comprehensive health examination program (including colonoscopy) from 1983 to 2002. The study also tested a single stool collection with Magstream 1000 system (a nonFDA approved FIT with an automated reader using a test related to HemeSelect).[163] Most (72 percent) participants were male, with ages ranging from 21 to 90 years, and a mean age of 48.2 (+/- 9) years; 18.8 percent were under age 40 years. Invasive cancers were present in 79 patients (0.4 percent), high-grade dysplastic lesions in 119 (0.5 percent) and large adenomas (10 mm or greater) in 529 (2.4 percent). The overall test-positive rate was 5.6 percent using the standard cut-point of 20 ng/ml for hemoglobin. Sensitivity for invasive cancer was 65.8 percent and specificity was 94.6 percent. Sensitivity for any advanced neoplasia was 27.1 percent (compared with 10.4 percent for any neoplasia which also included 10 mm or larger adenoma). Specificity was about the same (95.1 percent to 95.5 percent) for both of these categories. Given the accumulation of cases over 10 years in a health examination program, it is not clear whether the same FIT was used during this entire time period.

Launoy and colleagues evaluated quantitative screening test results using the Magstream 1000 system in 7421 average-risk French patients aged 50-74 (57 percent female). Physicians invited their

patients to participant in a 2-day fecal sampling for a CRC screening program during a regular office visit between January 2001 and December 2003.[166] Two higher cut-points (>50 ng/ml and >75 ng/ml) were evaluated in addition to the usual cut-point (>20 ng/ml hemoglobin). In all participants, 28 CRC were detected, 22 at colonoscopy, 2 in test-positive patients who did not undergo colonoscopy, and four during 2-year followup of screen-negative participants; 181 adenomas were detected in 366 people undergoing colonoscopy (102 adenomas larger than 10 mm). Test positivity for Magstream was 5.8 percent (cut-point >20 ng/ml), 3.1 percent (cut-point >50 ng/ml), or 2.0 percent (cut-point >75ng/ml). At 2 years, sensitivity for CRC was 85 percent, specificity was 94 percent and PPV was six percent. At higher cut-points (50 or 75 ng/ml), sensitivity for CRC was substantially lower (68 and 61 percent respectively), with three to four percent improvement in specificity to 97 to 98 percent and similar improvement in PPV (nine to 13 percent).

In the same large managed care study that evaluated Hemoccult Sensa,[160] HemeSelect tests were also evaluated. A major issue with HemeSelect was the relatively poor test completion rates (62 percent of HemeSelect tests had adequate samples for test completion compared with 91-93 percent of Hemoccult II or Hemoccult Sensa tests). The sensitivity of HemeSelect for CRC was not statistically significantly better than for non-rehydrated Hemoccult II, although specificity was lower (94.4 vs. 97.7).

Monohaem FIT (2 studies). Nakama et.al. calculated the sensitivity and specificity of the Monohaem FIT using samples from three consecutive days, without dietary or medication restrictions, prior to colonoscopy in 4611 Japanese persons aged 40 years and older who were participating in a colorectal cancer checkup.[169] Although patients were reported as asymptomatic, nothing further was reported about their risk status (e.g., sex, age distribution, or family history). Eighteen patients had CRC (0.4 percent) and 73 had an adenoma or other colorectal disease (1.6 percent). Overall test-positive rate was not reported. Sensitivity for cancer and adenomas increased significantly with a 2- or 3-day collection sample compared with a single day sample. Similarly, specificity also decreased with greater days of sample collection. With 2 days of samples (optimal approach), sensitivity for cancer was 83.3 percent and for adenomas was 50.7 percent, and specificity was 96.0 percent.

In a separate study in rural Japan, Nakama screened 3365 mainly asymptomatic males and females 40 years and older using a single stool sample for Monohaem screening.[167] Test positive adults (4.7 percent) received colonoscopy while test negatives were followed through a cancer registry for up to three years. In all participants, there were 14 cases of CRC; 43 polyps were detected in the 157 persons undergoing colonoscopy. Sensitivity of Monohaem for CRC decreased with followup from 91 percent in the first year to 71 percent in the third year, due to the identification of false-negative cancers, specificity was 95.6 percent.

OC-Hemodia (4 studies). Separate investigative teams reported on the sensitivity and specificity of OC-Hemodia (using an unspecified number of collection days) in 7411 asymptomatic Taiwanese men and women participating in a health checkup (that included colonoscopy) between 1997 and 2000.[161,168] One study[168]appears to be a sub-study (n=1387) of those that received esophagogastroscopy and colonoscopy from the same screening population as the other study[161] and is not discussed further. The prevalence of cancer was 0.2 percent (16 cancers), advanced neoplasia was 1.3 percent (93 lesions), and polyps was 9.7 percent (719 polyps). The overall test-positive rate was 9.2 percent. Sensitivity for cancer was 87.5 percent, specificity for cancer was 91.0 percent. Sensitivity was lower for any advanced neoplasm (including CRC) at 48.2 percent. OC-Hemodia is not FDA approved or apparently available in the U.S. market.

A study in 27,860 Japanese workers participating in a corporate screening program evaluated OC-Hemodia by sending screen positive patients only to have a colonoscopic exam and following the screen negative patients through insurance claim data for 2 yrs.[165] The study employed a 2-day sampling approach that resulted in a test positive rate of 5.3 percent and estimated sensitivity for CRC to be 86.5% and specificity to be 94.9%.

A third study conducted in Israel performed colonoscopy on all participants regardless of FIT results, but only a small subgroup (n=80) were considered average-risk.[162] Sensitivity was estimated to be 66.7 percent (CI: 13.3, 120) and specificity was 83.1 percent (CI: 74.7, 91.5). These numbers are imprecise due to the small number of participants within this subgroup.

FlexSure OBT (now Hemoccult ICT) (1 study). A single good-quality prospective study in 5841 screening patients aged 50 and older (26 percent nonWhite, 53 percent female, 11 percent aged 70 years and older) evaluated FlexSure OBT (now Hemoccult ICT) and sequential screening using Hemoccult Sensa followed by FlexSure OBT for positives only in a real-world managed care setting in the US.[159] FOBT-positives were sent for colonoscopy and FOBT-negatives were referred for FS (with about 80 percent completion of endoscopy), with 2-year followup for CRC detection as well. Fourteen cancers were detected along with 128 large adenomas. Test positivity was slightly higher for FlexSure (3.2 percent) than the combination (2.1 percent); both were much lower than Hemoccult Sensa alone (10.1 percent). FlexSure had similar (or perhaps better) sensitivity for distal CRC (82 percent) and for large distal adenomas (30 percent) than either other screening approach (power for differences was limited due to small numbers). The combination test had the best specificity for either outcome, with FIT a close second (96.9 percent and 98.1 percent for CRC, respectively). Absolute sensitivity or specificity for whole-colon CRC can not be inferred from these estimates. These estimates for left-sided lesions, however, are reliable.

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Setting	Reference Standard Operator Characteristics CT test characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics
Pickhardt 2003[136] Good	Military Medical Centers in Bethesda, MD; Washington, DC; San Diego, CA Recruited consecutive patients who were primarily referred for screening colonoscopy	OC with segmental unblinding Same day CTC and OC. Performed by 1/17 experienced colonoscopists 1 of 6 board-certified radiologists prospectively reviewed the CT data. All had completed training and read at least 25 studies. Two had interpreted more than 100. Flythrough 3D with 2D correlation of any abnormality; 1.25-2.5 mm collimation; 1 mm reconstruction interval; Multidetector; Oral contrast; Viatronix V3D 1.2	**Inclusion**: Adults 50-79 yrs of average risk; 40-79 yrs with family history of CRC **Exclusion**: positive guaiac-based stool test within 6 mo of referral; iron-deficiency anemia within 6 mo; rectal bleeding or hematochezia within 12 mo; unintentional weight loss > 10 lbs within 12 mo; optical colonoscopy within 10 yrs; BE within 5 yrs; history of adenomatous polyps, CRC or IBD; history of familial adenomatous polyposis or hereditary non polyposis cancer syndromes; rejection for optical colonoscopy; medical condition that precludes use of sodium phosphate prep; pregnancy.	**N**: 1233 **Mean age**: 57.8 yrs **Female**: 41% **Race/Ethnicity**: NR **SES**: NR **Average risk:** 97.4% (1201/1233) **Family history:** 2.6% (32/1233)
Pickhardt 2004[152]	**Flat lesions**: Secondary analysis of Pickhardt 2003 data			
Pickhardt 2007[151]	Re-analysis of 730 cases utilizing 2D analysis by more experienced CTC readers than in the original trial. Compared against original 1233 cases in primary 3D review.			

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Prevalence and Yield of Polyps	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Applicability	Comments
Pickhardt 2003[136] Good	**Prevalence** **≥ 10 mm:** 3.9% **≥ 8 mm:** 6.7% **≥ 6 mm:** 13.6% **Yield** **Any size polyp:** Adenomatous 554 Nonadenomatous 756 **≤ 5 mm:** Adenomatous 344 Nonadenomatous 622 **6-9 mm:** Adenomatous 159 Nonadenomatous 103 **≥ 10 mm:** Adenomatous 51 Nonadenomatous 31	**Of adenomas per patient** ≥ 6: 88.7 (82.9, 93.1) ≥ 7: 90.9 (83.9, 95.6) ≥ 8: 93.9 (86.3, 98.0) ≥ 9: 93.0 (83.0, 98.1) ≥ 10: 93.8 (82.8, 98.7) **Of adenomas per polyp** ≥ 6: 85.7 (80.2, 90.1) ≥ 7: 89.5 (83.0, 94.1) ≥ 8: 92.6 (85.4, 97.0) ≥ 9: 91.8 (81.2, 97.3) ≥ 10: 92.2 (81.1, 97.8)	**Of adenomas per patient** ≥ 6: 79.6 (77.0, 82.0) ≥ 7: 87.4 (85.3, 89.2) ≥ 8: 92.2 (90.5, 93.7) ≥ 9: 94.9 (93.5, 96.1) ≥ 10: 96.0 (94.8, 97.1)	**PPV** Of adenomas per patient ≥ 6: 40.7% ≥ 7: 41.3% ≥ 8: 46.1% ≥ 9: 46.9% ≥ 10: 48.9% (Calculated) **NPV** Of adenomas per patient ≥ 6: 97.8% ≥ 7: 99.0% ≥ 8: 99.5% ≥ 9: 99.6% ≥ 10: 99.7% (Calculated)	Uses rigorous methods that are unlikely to be found in general practice (type of bowel prep, stool tagging, electronic fluid cleansing). Screening conducted at military medical centers. Large sample size that includes 41% women. Ethnic diversity unknown.	Incomplete optical colonoscopy: 0.6% (8/1253) Inadequate preparation: 0.5% (6/1253) Failure of CT colographic system: 0.5% (6/1253)
Pickhardt 2004[152]	**Prevalence of flat polyps** Persons: 4.2% (52/1233) **Yield of flat lesions** 59 of 344 total polyps identified (17.2%) **Adenomatous flat lesions** 29/59 (49.2%) **Adenomatous flat lesions of all adenomas identified** 29/210 (13.8%)	**To detect adenomatous flat lesions** 82.8% (vs 86.2% non-flat adenomas, p=0.58 for difference)				
Pickhardt 2007[151]		**By-patient** **Adenoma ≥ 10mm:** ***2D*** 81% (25/31) ***3D*** 94% (45/48) **≥ 6 mm:** ***2D*** 49% (51/105) ***3D*** 89%(149/168) **Polyps ≥ 10mm:** ***2D*** 63%(26/41) ***3D*** 86% (62/72) **≥ 6 mm:** ***2D*** 43% (64/149) ***3D*** 84% (214/255)	**By-patient** **Polyps ≥ 10mm:** ***2D*** 98% (676/689) ***3D*** 97% (1131/1161) **≥ 6 mm:** ***2D*** 95% (553/581) ***3D*** 85% (826/978)			

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Setting	Reference Standard Operator Characteristics CT test characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics
Macari 2004[149] Fair-to-Poor	Veterans Affairs Hospital in New York. Recruited from gastro clinic	OC with no unblinding during procedure to verify finding on CT that were not seen during CTC Same day CTC and OC. Performed by a gastroenterologist with 5 yrs experience or fellow under supervision of the gastroenterologist. 2D with 3D confirmation of any abnormality; 4x1 mm collimation; 1 mm reconstruction interval; Multidetector; No contrast; Vitrea 2	**Inclusion**: Those attending a gastroenterology clinic and scheduled to undergo a screening colonoscopy; > 50 yrs; no colorectal symptoms; had negative FOBT; no family history of CRC in first-degree relative. **Exclusion**: NR	**N**: 68 **Mean age**: 55 yrs **Female**: 0% **Race/Ethnicity**: NR **SES**: NR **Average risk:** 100%
Macari 2000[148] Fair	New York City Patient recruitment: NR	OC with no unblinding during procedure to verify findings on CT that were not seen during colonoscopy Same day CT colonography and optical colonoscopy. **Method 1:** 2D with 3D on abnormal areas. **Method 2:** 2D then 3D Two radiologists with training in CTC examined each data set with different methods. 2D and 3D; 5 mm collimation; 2.5 mm reconstruction interval; Single detector; No contrast; Advantage/Navigator	**Inclusion**: Patients scheduled for colonoscopy screening. **Exclusion**: < 18yrs; pregnancy; patients with IBD, CRC, polyps, or polyposis.	**N**: 42 **Mean age**: 56 yrs **Female**: 45% **Race/Ethnicity**: NR **SES**: NR Asymptomatic: 100% Family history: 29%

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Prevalence and Yield of Polyps	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Applicability	Comments
Macari 2004[149] Fair-to-Poor	**Prevalence** Any polyp: 57% (39/68 patients) Largest polyp 1-5 mm: 23 patients 6-9 mm: 13 ≥ 10 mm: 3 **Yield** 1-5 mm: 78 6-9 mm: 17 ≥ 10 mm: 3	**Per polyp** Any size: 21.4 (14.2, 31.1) 1-5 mm: 11.5 (5.4, 23.3) 6-9 mm: 52.9 (29.1, 75.5) ≥ 10 mm: 100 (36.8, 100)	**Per patient** Any size: 89.7 (72.7, 97.8) ≥ 10: 98.5 (91.7, 99.9)	NR	100% male population seen in a VA medical center. Small sample size. All had negative FOBT results and no prior history.	False positives of CT were not verified during colonoscopy, rather assumed to be residual fecal material. No per patient sensitivity, only per polyp.
Macari 2000[148] Fair	**Prevalence** Any polyp: 31% (13/42) **Yield** 1-5 mm: 10 6-9 mm: 5 >10 mm: 1	**Method 1-per polyp** 38% **Method 2-per polyp** 38% **For polyps ≥ 6 mm** 67% **For polyps ≥ 7 mm** 100%	**Method 1-per polyp** 100% **Method 2-per polyp** 96%	**Method 1-per polyp** 100% **Method 2-per polyp** 86% **NPV** **Method 1-per polyp** 73% **Method 2-per polyp** 72%	Patient recruitment to University medical center unknown. Population included 45% women, but the ethnic distribution is unknown. Small sample size.	2 false positives in one patient were attributed to residual stool.

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Setting	CT test characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics
Rex 1999[150] Fair/Poor	Veterans Affairs Hospital in Indianapolis	OC with no unblinding during procedure. Findings indicated on CTC, but not found during optical colonoscopy were reviewed on the colonoscopy video. Same day CTC and OC 2D and 3D; 5 mm collimation; 2 mm reconstruction interval; Single detector; No contrast; Bowman Gray Virtual Endoscopy (Free Flight)	**Inclusion**: Without symptoms; no history of colon polyps or CRC. Intentionally selected older and male patients to increase polyp prevalence. **Exclusion**: NR	**N**: 46 **Mean age**: 67.7 yrs **Female**: 2% **Race/Ethnicity**: NR **SES**: NR Never undergone colon exam: 63% Polyps detected on screening flex sig: 37%
Johnson 2007[138] Fair	Mayo Clinic, MN. Comparison of primary 2D and 3D interpretation and slice thickness of 1.25 vs. 2.5mm. 3D software allows for 360 degree panoramic display with virtual unfolding and dissecting of the colon along the longitudinal axis.	OC Same day CTC and OC Three radiologists who all had > 1000 colonoscopy-verified CT colonography examinations. 6 weeks between the two readings of an exam by the same reader. Performed by staff gastroenterologists or supervised by staff gastroenterologists and colorectal surgeons 1.25 and 2.5 mm collimation; 1.25 mm reconstruction interval; Multi detector; No contrast; Voxtool 5.4.46, GE Healthcare	**Inclusion**: NR **Exclusion**: melena; hematochezia; IBD; familial polpyposis; symptomatic.	**N**: 452 **Mean age**: 65 yrs (41-82) **Female**: 44% **Race/Ethnicity**: White 85% Asian 12% Hispanic 3% African American 1% Native American 0.2% **SES**: NR Asymptomatic: 100%

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Prevalence and Yield of Polyps	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Applicability	Comments
Rex 1999[150] Fair/Poor	**Prevalence of adenoma** 72% (33/46), which included 14/17 patients with polyps detected on FS. **Yield** All adenomas: 91 ≤ 5 mm: 63 6-9 mm: 14 10-19 mm: 10 ≥ 20 mm: 4	**Per patient** ***2D*** ≤ 5 mm: 19% 6-9 mm: 14% 10-19 mm: 67% ≥ 20 mm: 75% ***3D*** ≤ 5 mm: 25% 6-9 mm: 43% 10-19 mm: 83% ≥ 20 mm: 75% **By polyp** ***2D*** ≤ 5 mm: 8% 6-9 mm: 7% 10-19 mm: 30% ≥ 20 mm: 25% ***3D*** ≤ 5 mm: 11% 6-9 mm: 43% 10-19 mm: 60% ≥ 20 mm: 25%	**Per patient in adenomas ≥ 10 mm** 89%	NR	Poor. 98% male (67.7 yrs) population at a VA medical center who were intentionally selected to oversample older males to yield a high prevalence of polyps.	Flat adenomas were hard to identify. 3/4 >2.0 mm were flat adenomas and missed by CT. Included a FS + sample to increase polyp yield. Population was also intentionally selected to be male and > 60 yrs to increase polyp prevalence. Missed polyps on CT were due to: residual stool and water; collapsed segments; missed by reader. None of the positives found by CT, but not colonoscopy were found on visual inspection of the videos and were classified as false positives.
Johnson 2007[138] Fair	**Prevalence at least 1 adenomatous lesion** ≥ 10 mm: 5.8% (26/452) 6-9 mm: 6.6% (30/452) **Yield** Adenoma ≥ 10 mm: 26 Adenoma 6-9 mm: 38	**Per-Patient 1.25 mm; ≥ 10mm** 2D 3D 1 83%(5/6) 50%(4/8) 2 70%(7/10) 83%(5/6) 3 78%(7/9) 83%(10/12) 2D & 3D Review: 95%(18/19) **Per-Patient 1.25 mm; 6-9mm** 2D 3D 1 40%(4/10) 33%(4/12) 2 25%(2/8) 60%(6/10) 3 83%(10/12) 100%(8/8) 2D & 3D Review: 71%(10/14) ***Per lesion sensitivity of colonoscopy for lesions ≥ 10mm:*** 77%	**Per-Patient 1.25 mm; ≥ 10mm** 2D 3D 1 99%(134/135) 97%(134/138) 2 98%(137/140) 99%(142/144) 3 97%(143/147) 97%(137/141) 2D & 3D Review: 98%(205/210) **Per-Patient 1.25 mm; 6-9mm** 2D 3D 1 92%(120/131) 93%(125/134) 2 99%(140/142) 96%(134/140) 3 95%(137/144) 94%(136/145) 2D & 3D Review: 91%(196/215)		Asymptomatic population but did include persons with previous colonic resection	Study initiated prior to standard tagging procedures and mechanical insufflation that are commonly used in clinical practice today. Limited power due to multiple analyses and not primarily addressing overall accuracy.

Appendix D Table 1. Evidence table of CT colonography studies.

tudy	Setting	CT test characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics
Kim 2007[137] Fair	Korea Retrospective analysis to compare 2D and 3D interpretation 3D software allows for 380 degree panoramic display with virtual unfolding and dissecting of the colon along the longitudinal axis.	OC with segmental unblinding Same day CTC and OC 2 radiologists with 300 and 500 previous CTC examinations who did not participate in the original analysis of this data. Two months separated the 2D and 3D viewings. Colonoscopy was performed by 1/5 experienced gastroenterologists 2D and 3D; 2 mm collimation; 1 mm reconstruction interval; Multi detector; IV contrast; 2D software: Rapidia; 3D software: Perspective Filet View	**Inclusion**: NR **Exclusion**: Prior colorectal surgery; IBD; iron deficient anemia; +FOBT within 6 mo; < 40 yrs; history of familial adenomatous polyposis; polypectomy within 1 yr.	**N**: 96 **Mean age**: 54.8 yrs **Female**: 42% **Race/Ethnicity**: Asian 100% (assumed) **SES**: NR

Appendix D Table 1. Evidence table of CT colonography studies.

Study	Prevalence and Yield of Polyps	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Applicability	Comments
Kim 2007[137] Fair	**Yield** Polyp ≥ 10 mm: 12 Polyp 6-9 mm: 23 Polyp < 5 mm: 99 Advanced neoplasia: 9	**Per patient** Reader 1 2 ***≥ 6 mm*** 2D 64%(14/22) 59%(13/22) 3D 77%(17/22) 73%(16/22) ***≥ 8 mm*** 2D 92%(12/13) 92%(12/13) 3D 85%(11/13) 92%(12/13) ***≥ 10 mm*** 2D 100%(9/9) 100%(9/9) 3D 100%(9/9) 100%(9/9)	**Per patient** Reader 1 2 **≥ 6 mm** 2D 91%(67/74) 89%(66/74) 3D 99%(73/74) 89%(66/74) **≥ 8 mm** 2D 98%(81/83) 99%(82/83) 3D 99%(82/83) 98%(81/83) **≥ 10 mm** 2D 99%(86/87) 100%(87/87) 3D 100%(87/87) 99%(86/87)		Unknown. Full patient descriptions not available- although some high risk populations were clearly excluded. Generalizability to the US population is also unknown.	Reasons for false-negatives: flat lesions; poor bowel distention; close attachment to a fold; misinterpreted as feces.

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Primary Screening Test Evaluated	Setting	Reference/Gold Standard	Methods of FOBT collection	Inclusion/ Exclusion Criteria	Patient Characteristics:
Nakama 1999[169] Fair	Monohaem	Japan Asymptomatic adults participating in colorectal cancer check-up.	Colonoscopy 100%	3 consecutive days of collection without dietary or medicinal restrictions prior to colonoscopy.	**Inclusion**: Attending colonoscopy medical check-up; over 40 yrs. **Exclusion**: NR	**N**: 4611 **Age**: NR **Female**: NR **Ethnicity**: NR **SES**: NR
Morikawa 2005[163] 2007[340] Fair	Magstream	Japan Retrospective analysis of consecutive asymptomatic adults participating in comprehensive health examination program 1983-2002.	Colonoscopy 100%	1-time collection	**Inclusion**: Asymptomatic and voluntarily participated. **Exclusion**: Patients with reported symptoms of disease of lower gastrointestinal tract	**N**: 21,805 **Age**: 48.2 ± 9.3 yrs Range (21-90 yrs) <40 yrs (18.8%) **Female**: 28% **Ethnicity**: NR **SES**: NR
Allison 2007[159] Good	Flex-Sure OBT; Hemoccult Sensa	US Prospective analysis of asymptomatic, average-risk patients within a large HMO. April 1997-October1999.	Colonoscopy to those with +FOBT; Flexible sigmoidoscopy to -FOBT. 2 year follow-up in medical databases.	3-sample collection with vitamin C restriction for 3 days before and during collection.	**Inclusion:** HMO members; ≥ 50 yrs. **Exclusion:** IBD; active rectal bleeding; +FOBT within 12 months; history of colon cancer or polyps; colonoscopy or FS within 5 yrs; family history of colon cancer with either a single affected first-degree relative ≥ 55 yrs or ≥ 2 of any age; any barrier to understanding the consent form.	**N:** 5841 had at least one valid FOBT **Age:** 50-59 58.7% 60-69 30.4% ≥ 70 10.9% **Female:** 52.5% **Ethnicity:** White 74.1% Black 5.0% Asian 11.8% Hispanic 5.2% Other 3.9% **SES:** NR

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Study	Prevalence and Yield of Polyps	Test completion rate Test positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Applicability	Comments
Nakama 1999{Nakama, 1999 3718 /id} Fair	Colorectal cancer: 18 patients (0.4%) Adenomatous polyp or other colorectal diseases: 73 patients (1.6%)	***Test completion rate*** NR ***Test positivity rate*** NR	***1-day collection*** Cancer: 55.6%* Adenoma: 30.1%* ***2-day collection*** Cancer: 83.3% Adenoma: 50.7% ***3-day collection*** Cancer: 88.9% Adenoma: 54.8% *p<0.01 difference from 2- and 3-day	***1-day collection*** 97.1% ***2-day collection*** 96.0% ***3-day collection*** 93.9%** **p<0.05 difference from 1- and 2-day	***1-day collection*** Cancer: 6.1% CRC or adenoma: 19.6% ***2-day collection*** Cancer: 6.5% CRC or adenoma: 22.4% ***3-day collection*** Cancer: 4.8% CRC or adenoma: 16.9%	NR	Japanese population with unknown population characteristics-not clearly average risk. Its applicability to the US population is unknown.	
Morikawa 2005{Morikawa, 2005 561 /id} 2007{Morikawa, 2007 7705 /id} Fair	***Prevalence*** Invasive cancer: 79 pts (0.4%) High-grade dysplasia: 119 pts (0.5%) Adenoma ≥ 10 mm: 529 (2.4%) Adenoma ≤ 9 mm: 3615 (16.6%)	***Test completion rate*** NR ***Test positivity rate*** 5.6% (1231/21,805)	***Advanced neoplasia:*** 27.1% (23.9-30.3) Invasive cancer: 65.8% (55.4-76.3) High-grade dysplasia: 32.7% (24.3-41.2) Adenoma ≥ 10 mm: 20.0% (16.6-23.4) ***Neoplasia:*** 10.4 (9.5-11.3) ***Adenoma ≤ 9 mm***: 7.0%	***Advanced neoplasia:*** 95.1% (94.8-95.4) Invasive cancer: 94.6% (94.3-94.9) ***Neoplasia:*** 95.5% (95.2-95.8) ***Adenoma ≤ 9 mm***: 95.5%	***Advanced neoplasia:*** 16.0% ***Invasive cancer:*** 4.2% ***Neoplasia:*** 36.5% (calc)	***Neoplasia***: 81.2% (calc)	Japanese population that appears to be primary care and community-based setting. Unknown applicability to US population.	Retrospective analysis beginning in 1982.
Allison 2007[159] Good	***Prevalence of left-sided neoplasms in those attending FS or colonoscopy*** Cancer: 14 (0.3%) Adenoma ≥ 10 mm: 128 (2.7%)	***Test completion rate*** FlexSure: 97.7% HOSensa: 97.8% ***Test positivity rate*** FlexSure: 3.2% HOSensa: 10.1% Combination: 2.1%	***Distal cancer*** FlexSure: 81.8 (47.8 - 96.8) HOSensa: 64.3 (35.6 - 86.0) Combination: 64.3 (35.6 - 86.0) ***Distal adenoma ≥ 10 mm*** FlexSure: 29.5 (21.4 - 38.9) HOSensa: 41.3 (32.7 - 50.4) Combination: 22.8 (16.1 - 31.3)	***Distal cancer*** FlexSure: 96.9 (96.4 - 97.4) HOSensa: 90.1 (89.3 - 90.8) Combination: 98.1 (97.7 - 98.4) ***Distal adenoma ≥ 10 mm*** FlexSure: 97.3 (96.8 - 97.7) HOSensa: 90.6 (89.8 - 91.4) Combination: 98.4 (98.0 - 98.7)	***Distal cancer*** FlexSure: 5.2 (2.6 - 10.0) HOSensa: 1.5 (0.8 - 3.0) Combination: 7.4 (3.7 - 14.0) ***Distal adenoma ≥ 10 mm*** FlexSure: 19.1 (13.7 - 25.9) HOSensa: 8.9 (6.8 - 11.6) Combination: 24.0 (16.9 - 32.7)	NR	High applicability as drawn from an average-risk US population. 74% were Caucasian. Only considered left-sided lesions.	

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Primary Screening Test Evaluated	Setting	Reference/Gold Standard	Methods of FOBT collection	Inclusion/ Exclusion Criteria	Patient Characteristics:
Cheng 2002[161] Fair	OC-Hemodia	Taiwan Participants in a health screening program from January 1997-December 2000.	Colonoscopy 98.9%	3-day dietary restriction	**Inclusion**: Asymptomatic participants in health screening program and voluntarily participated. Those with history of polyps or family history were included. **Exclusion**: Incomplete colon examination; presence of related symptoms; history of CRC, colitis, of IBD; previous +FOBT; location or size of lesion not defined or not pathologic examination.	**N**:7411 **Age**: 46.8 ± 9.9 yrs >50 yrs 31.25% 41-50 41.51% **Female**: 44.8% (calc) **Ethnicity**: NR **SES**: NR
Levi 2007[162] Fair	OC-Micro (OC-Hemodia)	Israel	Colonoscopy 100%	3-day collection No dietary restrictions; stopping aspirin and anticoagulants prior to endoscopy	**Inclusion:** Referred for colonoscopy. **Exclusion:** Concurrent hospitalization; visible rectal bleeding; IBD; hematuria; menstruation at time of stool specimen; inability to prepare FIT	**N**: 1000 Analyzing subset with family history (N=80) **Age**: NR for subgroup **Female**: NR for subgroup **Ethnicity**: NR **SES**: NR
Launoy 2005[166] Fair	Magstream	France Patients aged 50-74 yrs attending a regular consultation with their physician were invited to participate. January 2001-December 2002.	366 of 434 screen+ pts attended colonoscopy Screen negative patients were followed through cancer registry January 2001-December 2003.	2 samples on different days with no dietary restrictions.	**Inclusion**: 50-74 yrs attending primary care physician. **Exclusion**: NR	**N**: 7421 **Age**: 50-54 20.9% 55-59 20.3% 60-64 19.8% 65-69 22.1% 70-74 16.8% **Female**: 57% **Ethnicity**: NR **SES**: NR

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Study	Prevalence and Yield of Polyps	Test completion rate Test positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Applicability	Comments
Cheng 2002{Cheng, 2002 4391 /id} Fair	***Prevalence*** Polyps: 719 (9.7%) Advanced neoplasm: 93 (1.3%) Cancer: 16 (0.2%)	***Test completion rate*** NR ***Test positivity rate*** Overall: 9.2%	***All polyps*** 16.8% (calc) ***Advanced neoplasm*** 48.4% (calc) ***Cancer*** 87.5% (calc)	***All polyps*** 91.6% (calc) ***Advanced neoplasm*** 91.3% (calc) ***Cancer*** 91.0% (calc)	***All polyps*** 17.7% (calc) ***Advanced neoplasm*** 6.6% (calc) ***Cancer*** 2.0% (calc)	***All polyps*** 91.1% (calc)	Applicability of Taiwanese population to US is unknown. This is also a fairly young population as 41% are <50 and 28% <40 yrs. Population appears to be fairly representative of an asymptomatic, primary care population.	***Prevalence*** Polyps: 719 (9.7%) Advanced neoplasm: 93 (1.3%) Cancer: 16 (0.2%)
Levi 2007[162] Fair	***Prevalence*** Colorectal cancer: 3 (3.8%) Advanced polyps (≥ 10 mm; ≥ 20% villous histologic characteristics; high-grade dysplasia)	***Test completion rate*** NR ***Test positivity rate*** Overall: 18.8% in subset (calc)	***FAMILY HISTORY ONLY*** ***Advanced neoplasm*** 55.6 (32.6 - 78.5)% ***Cancer*** 66.7 (13.3 - 120)%	***FAMILY HISTORY ONLY*** ***Advanced neoplasm*** 91.9 (85.2 - 98.7)% ***Cancer*** 83.1 (74.7 - 91.5)%			Small numbers in this subgroup.	
Launoy 2005{Launoy, 2005 586 /id} Fair	***Prevalence in those attending colonoscopy (iFOBT+) (n=366)*** CRC: 22 (6%) Adenoma ≥ 1 cm: 102 (27.9%) Adenoma ≤ 1 cm: 79 (21.6%) ***Prevalence in those not attending colonoscopy(n=68)*** CRC: 2 within 2 years of + screen ***Prevalence detected through cancer registry in those screening negative (n=6987)*** CRC: 4 (0.06%)	***Test completion rate*** NR ***Test positivity rate*** > 20 ng/ml: 5.8% > 50 ng/ml: 3.1% > 75 ng/ml: 2.0%	***At 2 years follow-up*** > 20 ng/ml: 0.85 (0.72-0.98) > 50 ng/ml: 0.68 > 75 ng/ml: 0.61	***At 2 years follow-up*** > 20 ng/ml: 0.94 (0.94-0.95) > 50 ng/ml: 0.97 > 75 ng/ml: 0.98	***For CRC*** > 20 ng/ml: 0.06 > 50 ng/ml: 0.09 > 75 ng/ml: 0.13 ***For Adenoma ≥ 1 cm*** > 20 ng/ml: 0.28 > 50 ng/ml: 0.40 > 75 ng/ml: 0.41	NR	French primary care population of unknown racial breakdown. The false negatives are likely to be underestimated by the cancer registry follow-up, falsely elevating the sensitivity.	

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Primary Screening Test Evaluated	Setting	Reference/Gold Standard	Methods of FOBT collection	Inclusion/ Exclusion Criteria	Patient Characteristics:
Itoh 1996[165] Fair	OC-Hemodia	Japan Patients 40 or older who worked for corporations participating in colorectal screening program were invited during 1991-1992.	Colonoscopies were offered to those who screened positive: 1207/1490 (81% compliance). Those screening negative were followed through a cancer registry and re-screened at 2 yrs.	1 time sample	**Inclusion**: Aged 40 and above; employee of corporations that take part in program **Exclusion**: NR	**N**: 27,860 **Age**: NR **Female**: 14% (calc) **Ethnicity**: NR **SES**: NR
Nakama 1996[167] Fair	Monohaem	Japan-rural Mainly asymptomatic patients > 40 yrs.	Colonoscopies were offered to those who screened positive-100% compliance with 2% receiving barium enema) All screened were followed through a cancer registry for up to 3 yrs.	1 time sample without dietary restrictions	**Inclusion**: NR **Exclusion**: those who had already been screened.	**N**: 3365 **Age**: 40-49 21% 50-59 24% 60-69 31% 70-79 23% 80+ 0.4% **Female**: 51% (calc) **Ethnicity**: NR **SES**: NR

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Prevalence and Yield of Polyps	Test completion rate Test positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Applicability	Comments
Itoh 1996[165] Fair	***Prevalence in those attending for colonoscopy*** CRC: 77/1207 (6.4%) ***Prevalence detected through cancer registry in those screening negative*** CRC: 12/26370 (0.05%)	***Test completion rate*** 84.3% ***Test positivity rate*** Overall: 5.3% Those with CRC: 86.5%	***For CRC:*** 86.5%	***For CRC:*** 94.9%	***For CRC:*** 5.2%	NR	Applicability of Japanese population to US is unknown. The population is asymptomatic, but age is not reported. Women are underrepresented. The false negatives are likely to be underestimated by the shorter term cancer registry follow-up, falsely elevating the sensitivity.	
Nakama 1996[167] Fair	***Prevalence in those attending for colonoscopy*** (n=157) CRC: 10 (6.4%) Polyps: 43 (27.4%) ***Prevalence detected through cancer registry in those screening negative (n=3,208)*** CRC: 4 (0.12%)	***Test completion rate*** 84.5% ***Test positivity rate*** Overall: 4.7%	***For CRC:*** ***First yr*** 90.9% ***Second yr*** 83.3% ***Third yr*** 71.4%	***For CRC*** 95.6%	6.4%	NR	Applicability of a rural Japanese population is unknown. The population is asymptomatic and of varied ages. The false negatives are likely to be underestimated by the shorter term cancer registry follow-up, falsely elevating the sensitivity.	

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Primary Screening Test Evaluated	Setting	Reference/Gold Standard	Methods of FOBT collection	Inclusion/ Exclusion Criteria	Patient Characteristics:
Allison 1996[160]	Hemoccult Sensa; HemeSelect; Nonrehydrated Hemmoccult II	Oakland, CA Patients > 50 yrs attending health appraisal at Kaiser Permanente (October 1990-October 1991).	Colonoscopy or FS FS was suggested for those with only + Hemoccult Sensa due to high FP rate during initial part of study. Those with neoplasm on FS or with Hemocult Sensa positive on repeating testing at 6 and 12 months or if preferred colonoscopy over FS were referred for colonoscopy. Follow-up information obtained from participants' medical records, cancer registry, and pathology files.	3 consecutive stool samples for each FOBT Advised to restrict vitamin C, aspirin or NSAIDs, and follow dietary restrictions.	**Inclusion**: > 50 yrs attending health appraisal. **Exclusion**: NR	**Total Study Population** **N**: 8,104 **Age**: 50-59 30.2% 60-69 39.0% ≥ 70 30.8% **Female**: 59.3% **Ethnicity**: Non-white 46.5% **SES**: NR 1312 FOBT+

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Prevalence and Yield of Polyps	Test completion rate Test positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Applicability	Comments
Allison 1996[160]	***Prevalence*** CRC: 35 Benign polyps: 107	***Test completion*** Hemocult Sensa: 91.4% HemeSelect: 62.2% Hemoccult Sensa and HemeSelect: ≤ 62.2% Hemoccult II: 93.5% ***Test positivity rates-Criteria ≥ 1 window positive*** Hemocult Sensa: 13.6% HemeSelect: 5.9% Hemoccult Sensa and HemeSelect: 3.0% Hemoccult II: 2.5%	***CRC*** Hemocult Sensa: 79.4%(64.3-94.5) HemeSelect: 68.8%(51.1-86.4) Hemoccult Sensa and HemeSelect: 65.6%(47.6-83.6) Hemoccult II: 37.1%(19.7-54.6)	***CRC*** Hemocult Sensa: 86.7%(85.9-87.4) HemeSelect: 94.4%(93.8-94.9) Hemoccult Sensa and HemeSelect: 97.3%(96.9-97.6) Hemoccult II: 97.7%(97.3-98.0)	***Carcinoma*** Hemoccult II Sensa: 2.5%(1.7-3.7) HemeSelect: 5.0%(3.2-7.6) Hemocult Sensa and HemeSelect: 9.0%(5.8-13.6) Hemoccult II: 6.6%(3.7-11.2) ***Polyp ≥ 10 mm*** Hemoccult II Sensa: 6.7%(5.3-8.4) HemeSelect: 15.5%(12.3-19.3) Hemocult Sensa and HemeSelect: 21.9%(16.9-27.9) Hemoccult II: 16.7%(11.9-22.8) ***Carcinoma or polyp*** Hemoccult II Sensa: 9.2%(7.6-11.2) HemeSelect: 20.5%(16.8-24.6) Hemocult Sensa and HemeSelect: 30.9%(25.1-37.3) Hemoccult II: 23.2%(17.7-29.9)	NA	Good. Sample is U.S. primary care population with minority representation. Colonoscopies or FS with follow-up Hemoccult II as an alternative "gold standard" were given only to those screening positive with medical record follow-up of the screen negative patients to address FN.	Used 2 yr medical record follow-up to determine TN and FN, which is inadequate for determination of polyps. Used only for CRC and is generally an overestimate of sensitivity compared to 100% colonoscopy. Test performance doesn't consider smaller lesion (< 10 mm).

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Primary Screening Test Evaluated	Setting	Reference/Gold Standard	Methods of FOBT collection	Inclusion/ Exclusion Criteria	Patient Characteristics:
Imperiale 2004[158]	Fecal DNA panel (*K-ras*; *p53*; *APC*; BAT-26; Long DNA) Hemoccult-non-rehydrated	US 81 sites including private practice and university based settings. Asymptomatic adults ≥ 50 yrs of average risk. August 2001-March 2003.	Colonoscopy	Fecal DNA panel-1 sample Hemoccult II-3 samples No dietary or medication modifications.	**Inclusion**: At least 50 yrs **Exclusion**: Gastrointestinal bleeding within preceding month; a change in bowel habits or recent onset of abdominal pain; previous colorectal cancer or polyps; prior resection of any part of the colon; iron-deficiency anemia; other visceral cancer; undergone colonoscopy, FS, or BE within preceding 10 yrs; +FOBT test within preceding 6 months; IBD, familial adenomatous polyposis or hereditary nonpoluposis colon cancer; ≥ 1 first degree relative with CRC or any first degree relative with CRC before 50 yrs.	**N**: 2507 for sens/spec calculations: 33-carcinoma 403-advanced adenomas 648-minor polyps (random subsample) 1423-no polyps (random subsample) **Age**: 69.5 yrs **Female**: 55.5% **Ethnicity**: Non-white 13% **SES**: NR
Haug 2007{Haug, 2007 5368 /id}	Fecal DNA (*K-ras*)	Germany Patients were recruited by their primary care physician as part of a general health examination.	Colonoscopy	1 sample (for group "A")	**Inclusion**: Participating in the ESTHER trial. **Exclusion**: NR	**N**: 441 **Age**: NR, but similar to total study population listed below 50-54 16% 55-59 17% 60-64 29% 65-69 24% 70-75 14% **Female**: 53% **Ethnicity**: NR **SES**: NR

Appendix D Table 2. Evidence table of trials testing high sensitivity guaiac tests, fecal immunochemical tests, fecal DNA.

Author, Year	Prevalence and Yield of Polyps	Test completion rate Test positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value	Applicability	Comments
Imperiale 2004[158]	***Prevalence*** Carcinoma: 33/4404 (0.75%) Advanced adenomas: 426/4404 (9.7%) Minor polyps: 1627/4404 (37%) No polyps: 2318/4404 (52.6%)	***Test completion rate*** NR ***Test positivity rate*** Fecal DNA:205/2505 (8.2%-calc) Hemoccult II: 146/2505 (5.8%-calc)	***CRC*** Fecal DNA: 51.6% Hemoccult II: 12.9% ***Advanced adenoma*** Fecal DNA: 15.1% Hemoccult II: 10.7%	***CRC (calculated)*** Fecal DNA: 92.4% Hemoccult II: 94.3% ***CRC+ Advanced dysplasia (calculated)*** Fecal DNA: 92.8% Hemoccult II: 94.4% ***Advanced adenoma (calculated)*** Fecal DNA: 93.2% Hemoccult II: 95.1% ***No polyp*** Fecal DNA: 94.4% Hemoccult II: 95.2%				
Haug 2007{Haug, 2007 5368 /id}	***Prevalence*** Advanced neoplasia: 7.0% (31/441) Invasive CRC: 1.6% (7/441) K-ras in patients with negative colonoscopy: 7.5% (22/293)	***Test completion rate*** NR ***Test positivity rate*** 26/434 (6.0%-calc)	**Advanced colorectal neoplasia** 0% (calc) 0/31	**Advanced neoplasia**: 95.1% (94.8-95.4) **Invasive cancer**: 94.6% (94.3-94.9) **Neoplasia**: 95.5% (95.2-95.8)			Self-selecting patient population with delayed time to colonoscopy perhaps affecting results.	

Appendix D Table 3. Key question 2B excluded studies

Reference	Reason for exclusion
Abdul Fattah A, Nakama H, Kamijo N. Clinico-pathological features of colorectal adenomatous polyps with negative results on immunochemical fecal occult blood test. *Eur J Med Res.* 1997;2:361-364.	Excluded for population
Abdul Fattah A, Nakama H, Zhang B, Uehara Y, Kamijo N, Fujimori K. Diagnostic value of immunochemical fecal occult blood test for small colorectal neoplasms. *European Journal of Medical Research* 1997;2(5):227 -30.	Excluded for study design
Abe N, Watanabe T, Nakashima M et al. Quantitative analysis of telomerase activity: a potential diagnostic tool for colorectal carcinoma. *Hepatogastroenterology.* 2001;48:692-695.	Did not include one of the specific screening tests
Ahlquist D, Skoletsky J, Boynton K et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology.* 2000;119:1219-1227.	Excluded for population
Ahlquist DA and Shuber AP. Stool screening for colorectal cancer: evolution from occult blood to molecular markers. Clinica Chimica Acta 2002;315:157-168.	Not an original study
Arnesen RB, Adamsen S, Svendsen LB, Raaschou HO, von BE, Hansen OH. Missed lesions and false-positive findings on computed-tomographic colonography: a controlled prospective analysis. *Endoscopy.* 2005;37:937-944.	Excluded for population
Arnesen RB, von BE, Adamsen S, Svendsen LB, Raaschou HO, Hansen OH. Diagnostic performance of computed tomography colonography and colonoscopy: a prospective and validated analysis of 231 paired examinations. *Acta Radiologica.* 2007;48:831-837.	Excluded for population
Banerjee S, Van Dam J. CT colonography for colon cancer screening. *Gastrointest Endosc.* 2006;63:121-133.	Excluded for study design
Barancin C, Roeder B, Cornett D et al. A retrospective analysis of abnormal findings on virtual colonoscopy compared with optical colonoscopy. *Gastroenterology.* 2006;130:A643.	Excluded for study design
Belo-Oliveira P, Curvo-Semedo L, Rodrigues H, Belo-Soares P, Caseiro-Alves F. Sigmoid colon perforation at CT colonography secondary to a possible obstructive mechanism: report of a case. *Diseases of the Colon & Rectum.* 2007;50:1478-1480.	Excluded for population
Berger BM, Schroy PC, III, Rosenberg JL et al. Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests. *Clinical Colorectal Cancer* 2006;5(5):338-43.	Excluded for quality
Bisseling TM, Dekker HM, Cools B, Nagengast FM. CT colonography to visualise the whole colon can be complementary to incomplete colonoscopy. *Netherlands Journal of Medicine* 2006;64 (10):389 -90.	Excluded for study design
Blue Cross Blue Shield Association. Fecal DNA Analysis for Colorectal Cancer Screening. 2006.	Source document
Blue Cross Blue Shield Association. Immunochemical versus guaiac fecal occult blood tests. 2004. Chicago IL: Blue Cross Blue Shield Association (BCBS).	Source document

Reference	Reason for exclusion
Blue Cross Blue Shield Association. Special report: fecal DNA analysis for colon cancer screening. *Technology Evaluation Center Assessment Program Executive Summary* 2006;21(6):1-2.	Excluded for study design
Blue Cross Blue Shield Association. CT colonography ('virtual colonoscopy') for colon cancer screening. 2004. Chicago IL: Blue Cross Blue Shield Association (BCBS).	Source document
Bond JH. Progress in refining virtual colonoscopy for colorectal cancer screening. *Gastroenterology* 2005;129(6):2103 -6.	Excluded for study design: Review
Booth RA. Minimally invasive biomarkers for detection and staging of colorectal cancer. *Cancer Lett.* 2007;249(1):87-96.	Excluded for study design
Brand RE, et al. Reproducibility of a Multitarget Stool-Based DNA Assay for Colorectal Cancer Detection. American Journal of Gastroenterology 2004; 99:1338-1341.	Excluded for population with cancer
Bruzzi JF, Moss AC, Brennan DD, MacMathuna P, Fenlon HM. Colonic surveillance by CT colonography using axial images only. *Eur Radiol.* 2004;14:763-767.	Excluded for population
Burch JA, Soares-Weiser K, St John DJ et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. *J Med Screen.* 2007;14:132-137	Excluded for study design
Burling D, Halligan S, Taylor S et al. Polyp measurement using CT colonography: agreement with colonoscopy and effect of viewing conditions on interobserver and intraobserver agreement. *AJR American Journal of Roentgenology* 2006;186(6):1597 -604 .	Did not report necessary outcomes
Burling D, Halligan S, Taylor SA, Honeyfield L, Roddie ME. CT colonography: automatic measurement of polyp diameter compared with manual assessment - an in-vivo study. *Clinical Radiology* 2007;62(2):145 -51.	Did not report necessary outcomes
Calistri D, et al. Fecal Multiple Molecular Test to Detect Colorectal Cancer Screening in Stool. Clinical Gastroenterology and Hepatology 2003; 1:377-383.	Excluded for population with cancer
Cash BD, Kim C, Cullen P et al. Accuracy of computed tomographic colonography for colorectal cancer (CRC) screening in asymptomatic individuals. *Gastroenterology.* 2006;130:A46.	Excluded for study design
Cash BD, Schoenfeld P, Rex D. An evidence-based medicine approach to studies of diagnostic tests: assessing the validity of virtual colonoscopy. *Clin Gastroenterol Hepatol.* 2003;1:136-144.	Inadequate application of reference standard
Castiglione G, Grazzini G, Miccinesi G et al. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. *J Med Screen.* 2002;9:99-103.	Did not report necessary outcomes
Castiglione G, Sala P, Ciatto S et al. Comparative analysis of results of guaiac and immunochemical tests for faecal occult blood in colorectal cancer screening in two oncological institutions. *European Journal of Cancer Prevention* 1994;3(5):399 -405.	Excluded for population
Castiglione G, Visioli CB, Ciatto S, Grazzini G, Bonanomi AG, Rubeca T, Mantellini P, Zappa M. Sensitivity of latex agglutination faecal occult blood test in the Florence District population-based colorectal cancer screening programme. *British Journal of Cancer.96.(11):1750.-4,* 2007.	Excluded for study design

Reference	Reason for exclusion
Castiglione G, Zappa M, Grazzini G et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. *British Journal of Cancer* 1996;74 (1):141 -4.	Inadequate application of reference standard
Castiglione G, Zappa M, Grazzini G et al. Screening for colorectal cancer by faecal occult blood test: comparison of immunochemical tests. *Journal of Medical Screening* 2000;7(1):35-7.	Excluded for quality Validation on subset 2x2
Chen HS, Sheen-Chen SM. Influence of age and gender on surveillance for colorectal tumors in low-risk asymptomatic population. *Anticancer Res.* 2002;22:399-403.	Did not report necessary outcomes
Chen JC, Dachman AH. Cecal mobility: a potential pitfall of CT colonography. *Am J Roentgenol.* 2006;186:1086-1089.	Did not report necessary outcomes
Chen, K, Jiao, DA, Zheng, S, Zhou, S, and Yu, H. Diagnostic value of fecal occult blood testing for screening colorectal cancer. *China National Journal New Gastroenterology* 1997;3[3], 166-168.	Excluded for population: Outcomes
Ciatto S, Martinelli F, Castiglione G et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. *Br J Cancer.* 2007;96:218-221.	Inadequate application of reference standard
Cohnen M, Vogt C, Aurich V, Beck A, Haussinger D, Modder U. Multi-slice CT-colonography in low-dose technique--Preliminary results. *Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin.* 2002;174:835-838.	Excluded for population
Cohnen M, Vogt C, Beck A et al. Feasibility of MDCT Colonography in ultra-low-dose technique in the detection of colorectal lesions: comparison with high-resolution video colonoscopy. *AJR.* 2004;American:1355-1359.	Excluded for population
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;291:1713-1719.	Excluded for population
Crawford NP, Colliver DW, Galandiuk S. Tumor markers and colorectal cancer: utility in management. *J Surg Oncol.* 2003;84:239-248.	Excluded for study design
Cruz-Correa M, Schultz K, Jagannath S et al. Performance characteristics and comparison of two fecal occult blood tests in patients undergoing colonoscopy. *Dig Dis Sci.* 2007;52:1009-1013.	Did not include one of the specific screening tests
Dachman AH, Lefere P, Gryspeerdt S, Morin M. CT colonography: visualization methods, interpretation, and pitfalls. *Radiologic Clinics of North America 45(2):347 -59.* 2007.	Excluded for study design
Deenadayalu DP, Rex DK. Fecal-based DNA assays: A new, noninvasive approach to colorectal cancer screening. Cleveland Clinic Journal of Medicine 2004; 71:497-503.	Excluded for population with cancer
Dehmeshki J, Halligan S, Taylor SA et al. Computer assisted detection software for CT colonography: effect of sphericity filter on performance characteristics for patients with and without fecal tagging. *European Radiology* 2007; 17(3):662 -8.	Did not answer primary question
Dong SM, et al. Detecting Colorectal Cancer in Stool With the Use of Multiple Genetic Targets. Journal of the National Cancer Institute 2001; 93(11):858-865.	Excluded for population with cancer

Reference	Reason for exclusion
Duff SE, Murray D, Rate AJ, Richards DM, Kumar NA. Computed tomographic colonography (CTC) performance: one-year clinical follow-up. *Clinical Radiology* 2006; 61(11):932 -6.	Excluded for population
ECRI. Fecal DNA testing for colorectal cancer (CRC). 2006. ECRI.	Source document
Edwards JT, Mendelson RM, Fritschi L et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. *Radiology* 2004;230(2):459-64.	Inadequate application of reference standard
Eguchi S, et al. Mutations fo the p53 Gene in the Stool of Patient with Resectable colorectal Cancer. Cancer 1996; 77(Suppl.):1707-1710.	Excluded for population with cancer
Erturk SM, Mortele KJ, Oliva MR, Barish MA. State-of-the-art computed tomographic and magnetic resonance imaging of the gastrointestinal system. *Gastrointestinal Endoscopy Clinics of North America* 2005;15(3):581-614.	Excluded for study design
Fattah AS, Nakama H, Kamijo N, Fujimori K, Zhang B. Colorectal adenomatous polyps detected by immunochemical occult blood screening. *Hepato-Gastroenterology* 1998;45(21):712 -6.	Excluded for study design
Ferrucci JT. Colon cancer screening with virtual colonoscopy: promise, polyps, politics. *AJR.* 2001;177:975-988.	Excluded for study design
Fletcher JG, Booya F, Melton Z et al. Automated polyp measurement with CT colonography: preliminary observations in a phantom colon model. *Am J Roentgenol.* 2007;188:945-952.	Did not answer primary question
Florie J, van Gelder RE, Stoker J. Colonography by computed tomography. *European Journal of Gastroenterology & Hepatology.* 2005;17:809-813.	Excluded for study design
Fraser CG, Matthew CM, Mowat NA, Wilson JA, Carey FA, Steele RJ. Immunochemical testing of individuals positive for guaiac faecal occult blood test in a screening programme for colorectal cancer: an observational study. *Lancet Oncology* 2006;7(2):127-31.	Excluded for population
Fraser CG, Matthew CM, Mowat NA, Wilson JA, Carey FA, Steele RJ. Evaluation of a card collection based faecal immunochemical test in screening for colorectal cancer using a two-tier reflex approach. *Gut.* 2007;56(10)1415-8.	Excluded for population
Ganeshan A, Upponi S, Uberoi R, D'Costa H, Picking C, Bungay H. Minimal-preparation CT colon in detection of colonic cancer, the Oxford experience. *Age & Ageing* 2007;36(1):48 -52.	Excluded for study design
Gluecker T, Dorta G, Keller W, Jornod P, Meuli R, Schnyder P. Performance of multidetector computed tomography colonography compared with conventional colonoscopy. *Gut.* 2002;51:207-211.	Excluded for population
Gluecker T, Meuwly JY, Pescatore P et al. Effect of investigator experience in CT colonography. *Eur Radiol.* 2002;12:1405-1409.	Excluded for population
Gopalswamy N, Stelling HP, Markert RJ, Maimon HN, Wahlen SD, Haddy RI. A comparative study of eight fecal occult blood tests and HemoQuant in patients in whom colonoscopy is indicated. *Arch Fam Med.* 1994;3:1043-1048.	Excluded for population

Reference	Reason for exclusion
Grazzini G, Castiglione G, Isu A et al. Colorectal cancer screening by fecal occult blood testing: results of a population-based experience. *Tumori* 2000;86(5):384-8.	Inadequate application of reference standard
Greenberg PD, Bertario L, Gnauck R et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol.* 2000;95:1331-1338.	Excluded for population-high proportion screen positive or symptomatic.
Guittet L, Bouvier V, Mariotte N et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* 2007;56 (2):210 -4.	Inadequate application of reference standard
Halligan	Duplicative review content. Does not provide additional primary articles
Halligan S, Altman DG, Mallett S et al. Computed tomographic colonography: assessment of radiologist performance with and without computer-aided detection. *Gastroenterology* 2006;131 (6):1690 -9.	Excluded for population
Halligan S, Altman DG, Taylor SA et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. *Radiology.* 2005;237:893-904.	Excluded for study design
Halligan S, Park SH, Ha HK. Causes of false-negative findings at CT colonography. *Radiology.* 2006;238:1075-1076.	Excluded for study design
Halligan S, Taylor SA, Dehmeshki J et al. Computer-assisted detection for CT colonography: external validation. *Clinical Radiology* 2006;61(9):758 -63 ; discussion 764 -5.	Did not answer primary question
Halligan S, Taylor SA. CT colonography: Results and limitations. *European Journal of Radiology* 2007;61(3):400 -8.	Excluded for study design
Hara AK, Johnson CD, Reed JE et al. Detection of colorectal polyps with CT colography: initial assessment of sensitivity and specificity. *Radiology.* 1997;205:59-65.	Excluded for population
Harewood GC. What is the most sensitive screening method for the detection of colon cancer? *Nature Clinical Practice Gastroenterology & Hepatology* 2005;134-5.	Excluded for study design
Hasegawa Y, et al. Detection of K-*ras* mutation in DNAs isolated from feces of patients with colorectal tumors by mutant-allele-specific amplicication (MASA). Oncogene 1995; 10:1441-1445.	Excluded for population with cancer
Haug U, Brenner H. New stool tests for colorectal cancer screening: a systematic review focusing on performance characteristics and practicalness. *Int J Cancer.* 2005;117:169-176.	Source document
Haug U, Wente MN, Seiler CM, Rothenbacher D, Buchler MW, Brenner H. Tumor M2 pyruvate kinase as a stool marker for colorectal cancer: stability at room temperature and implications for application in the screening setting. *Clinical Chemistry* 2006;52 (4):782 -4.	Excluded for study relevance
HAYES and Inc. Computed Tomography Colonography (Virtual Colonoscopy). 2006. Lansdale, PA: HAYES, Inc.	Source document
HAYES and Inc. Fecal DNA testing for colorectal cancer screening and monitoring. 2002. Lansdale, PA: HAYES, Inc.	Source document

Reference	Reason for exclusion
Haykir R, Karakose S, Karabacakoglu A, Sahin M, Kayacetin E. Three-dimensional MR and axial CT colonography versus conventional colonoscopy for detection of colon pathologies. *World Journal of Gastroenterology.* 2006;12:2345-2350.	Excluded for population
Hoepffner N, Shastri YM, Hanisch E et al. Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study. *Alimentary Pharmacology & Therapeutics* 2006;23(1):145-54.	Excluded for population
Hoff G, Grotmol T, Thiis-Evensen E, Bretthauer M, Gondal G, Vatn MH. Testing for faecal calprotectin (PhiCal) in the Norwegian Colorectal Cancer Prevention trial on flexible sigmoidoscopy screening: comparison with an immunochemical test for occult blood (FlexSure OBT). *Gut.* 2004;53:1329-1333.	Excluded for study relevance
Hope RL, Chu G, Hope AH, Newcombe RG, Gillespie PE, Williams SJ. Comparison of three faecal occult blood tests in the detection of colorectal neoplasia. *Gut* 1996;39(5):722 -5.	Excluded for population
Hoppe H, Quattropani C, Spreng A, Mattich J, Netzer P, Dinkel HP. Virtual colon dissection with CT colonography compared with axial interpretation and conventional colonoscopy: preliminary results. *AJR.* 2004;American:1151-1158.	Excluded for population
Hughes K, Leggett B, Del Mar C et al. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. *Australian & New Zealand Journal of Public Health* 2005;29(4):358-64.	Did not report necessary outcomes
Hwang I, Wong RK. Limitations of virtual colonoscopy. *Ann.Intern.Med.* 142 (2):154-155, 2005.	Excluded for study design
Iannaccone R, Catalano C, Mangiapane F et al. Colorectal polyps: detection with low-dose multi-detector row helical CT colonography versus two sequential colonoscopies. *Radiology.* 2005;237:927-937.	Excluded for population
Iannaccone R, Laghi A, Catalano C et al. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. *Gastroenterology.* 2004;127:1300-1311.	Excluded for population
Iannaccone R, Laghi A, Catalano C et al. Detection of colorectal lesions: lower-dose multi-detector row helical CT colonography compared with conventional colonoscopy. *Radiology.* 2003;229:775-781.	Excluded for population
Itzkowitz SH, Jandorf L, Brand R et al. Improved fecal DNA test for colorectal cancer screening. *Clinical Gastroenterology & Hepatology* 2007;5(1):111 -7.	Excluded due to study design
Jeanson A, Jamart J, Maisin JM et al. Assessment of the new immunological test Hemoblot for detecting occult blood in faeces. *Eur J Cancer Prev.* 1994;3:407-412.	Excluded for population
Jensch S, van Gelder RE, Florie J et al. Performance of radiographers in the evaluation of CT colonographic images. *AJR American Journal of Roentgenology* 2007;188 (3):W249 -55.	Excluded for population
Johnson CD, MacCarty RL, Welch TJ et al. Comparison of the relative sensitivity of CT colonography and double-contrast barium enema for screen detection of colorectal polyps. *Clinical Gastroenterology & Hepatology* 2004;2(4):314-21.	Inadequate application of reference standard
Johnson CD, Toledano AY, Herman BA et al. The clinical role of extracellular bioimpedance tomography (Gastro-Mida(x)) in the diagnosis of colorectal diseases. *Gastroenterology* 2003;125(3):688 -95.	Excluded for population

Reference	Reason for exclusion
Juchems MS, Fleiter TR, Pauls S, Schmidt SA, Brambs HJ, Aschoff AJ. CT colonography: comparison of a colon dissection display versus 3D endoluminal view for the detection of polyps. *European Radiology* 2006;16(1):68 -72.	Excluded for population
Kalra N, Suri S, Bhasin DK et al. Comparison of multidetector computed tomographic colonography and conventional colonoscopy for detection of colorectal polyps and cancer. *Indian Journal of Gastroenterology* 2006;25(5):229 -32.	Excluded for population
Kay CL, Kulling D, Hawes RH, Young JW, Cotton PB. Virtual endoscopy--comparison with colonoscopy in the detection of space-occupying lesions of the colon. *Endoscopy* 2000;32(3):226-32.	Excluded for population
Lefkovitz Z, Shapiro R, Koch S, Cappell MS. The emerging role of virtual colonoscopy. *Med Clin North Am.* 2005;89:111-38, viii.	Excluded for study design
Lenhard K, Bommer GT, Asutay S et al. Analysis of promoter methylation in stool: a novel method for the detection of colorectal cancer. *Clinical Gastroenterology & Hepatology.* 2005;3:142-149.	Excluded for population
Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. *Alimentary Pharmacology & Therapeutics.* 2006;23:1359-1364.	Excluded for population
Levi Z, Rozen P, Hazazi R et al. Can quantification of faecal occult blood predetermine the need for colonoscopy in patients at risk for non-syndromic familial colorectal cancer? *Alimentary Pharmacology & Therapeutics.* 2006;24:1475-1481.	Excluded for population-proportion of symptomatic patients >10%
Levin B, Hess K, Johnson C. Screening for colorectal cancer. A comparison of 3 fecal occult blood tests. *Archives of Internal Medicine* 1997;157 (9):970 -6.	Excluded for quality: low followup rates
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. *International Journal of Cancer* 2006;118(12):3078 -83.	Excluded for population
Lida Y, Munemoto Y, Miura S et al. Clinicopathologic studies of immunologic fecal occult blood test for colorectal cancer. *J Gastroenterol.* 1995;30:192-200.	Excluded for population
Lin OS, Kozarek RA, Schembre DB et al. Risk stratification for colon neoplasia: screening strategies using colonoscopy and computerized tomographic colonography. *Gastroenterology.* 2006;131:1011-1019.	Excluded for study design
Liu HH, Huang TW, Chen HL, Wang TH, Lin JT. Clinicopathologic significance of immunohistochemical fecal occult blood test in subjects receiving bidirectional endoscopy. *Hepatogastroenterology.* 2003;50:1390-1392.	Did not report correct outcomes
Macari M, Bini EJ, Xue X et al. Colorectal neoplasms: prospective comparison of thin-section low-dose multi-detector row CT colonography and conventional colonoscopy for detection. *Radiology.* 2002;224:383-392.	Excluded for population
Macari M, Bini EJ. CT colonography: where have we been and where are we going? *Radiology* 2005;237(3):819-33.	Excluded for study design
MacCarty RL, Johnson CD, Fletcher JG, Wilson LA. Occult colorectal polyps on CT colonography: implications for surveillance. *AJR American Journal of Roentgenology* 2006;186(5):1380-3.	Excluded for population

Reference	Reason for exclusion
Mak T, Lalloo F, Evans DG, Hill J. Molecular stool screening for colorectal cancer. *Br J Surg.* 2004;91:790-800.	Excluded for study design
McFarland EG, Pilgram TK, Brink JA et al. CT colonography: multiobserver diagnostic performance. *Radiology.* 2002;225:380-390.	Excluded for population
Medical Services Advisory Committee. Faecal occult blood testing for population health screening. 2004. Canberra: Medical Services Advisory Committee (MSAC).	Duplicative review content. Does not provide additional primary articles
Menardo G. Sensitivity of diagnostic examinations for colorectal polyps. *Techniques in Coloproctology 8 Suppl* 2004;2:s273 -5.	Excluded for study design
Miyoshi H, Oka M, Sugi K, Saitoh O, Katsu K, Uchida K. Accuracy of detection of colorectal neoplasia using an immunochemical occult blood test in symptomatic referred patients: comparison of retrospective and prospective studies. *Intern Med.* 2000;39:701-706.	Excluded for population
Munikrishnan V, Gillams AR, Lees WR, Vaizey CJ, Boulos PB. Prospective study comparing multislice CT colonography with colonoscopy in the detection of colorectal cancer and polyps. *Diseases of the Colon & Rectum.* 2003;46:1384-1390.	Excluded for population
Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *British Journal of Cancer* 2003;89 (1):23-8.	Excluded for study design
Nakama H, bdul Fattah AS, Zhang B, Kamijo N, Fujimori K, Miyata K. Detection rate of immunochemical fecal occult blood test for colorectal adenomatous polyps with severe dysplasia. *Journal of Gastroenterology* 1997;32(4):492 -5.	Excluded for study design
Nakama H, Fattah A, Zhang B, Uehara Y, Wang C. A comparative study of immunochemical fecal tests for detection of colorectal adenomatous polyps. *Hepatogastroenterology.* 2000;47:386-389.	Excluded for study design
Nakama H, Kamijo N, Fattah AS, Zhang B. Immunologic detection of fecal occult blood from upper digestive tract diseases. *Hepato-Gastroenterology* 1998;45(21):752 -4.	Excluded for population
Nakama H, Kamijo N, Fujimori K, Fattah AS, Zhang B. Relationship between fecal sampling times and sensitivity and specificity of immunochemical fecal occult blood tests for colorectal cancer: a comparative study. *Diseases of the Colon & Rectum* 1997;40(7):781 -4.	Excluded for study design
Nakama H, Kamijo N, Fujimori K, Horiuchi A, Fattah AS, Zhang B. Characteristics of colorectal cancer with false negative result on immunochemical faecal occult blood test. *J Med Screen.* 1996;3:115-118.	Excluded for study design
Nakama H, Kamijo N, Miyata K, bdul Fattah AS, Zhang B, Uehara Y. Sensitivity and specificity of several immunochemical tests for colorectal cancer. *Hepato-Gastroenterology* 1998;45(23):1579 -82 .	Excluded for study design
Nakama H, Kamijo N. Accuracy of immunological fecal occult blood testing for colorectal cancer screening. *Prev Med.* 1994;23:309-313.	Excluded for study design
Nakama H, Kayano T, Katsuura T et al. Comparison of predictive value for colorectal cancer in subjects with and without rectal bleeding. *Hepato-Gastroenterology* 1999;46 (27):1730 -2.	Excluded for study design

Reference	Reason for exclusion
Nakama H, Zhang B, bdul Fattah AS, Kamijo N, Fukazawa K. Relationships between a sign of rectal bleeding and the results of an immunochemical occult blood test, and colorectal cancer. *European Journal of Cancer Prevention* 2000;9(5):325 -8.	Did not report necessary outcomes
Nakama H, Zhang B, Fattah AA, Kamijo N, Zhang X. Characteristics of colorectal cancer that produce positive immunochemical occult blood test results on stool obtained by digital rectal examination. *Can J Gastroenterol.* 2001;15:227-230.	Excluded for quality
Nakama H, Zhang B, Fattah AS, Zhang X. Colorectal cancer in iron deficiency anemia with a positive result on immunochemical fecal occult blood. *Int J Colorectal Dis.* 2000;15:271-274.	Did not report necessary outcomes
Nakama H, Zhang B, Kamijo N. Sensitivity of immunochemical fecal occult blood test for colorectal flat adenomas. *Hepato-Gastroenterology* 2004;51(59):1333 -6.	Excluded for study design
Ness R, Et al. The Cost-Effectiveness of Fecal DNA Testing for Colorectal Cancer. Gastroenterology 2003: 124(4) Suppl A458.	Abstract only
Nio CY, de Vries AH, Stoker J. Perceptive errors in CT colonography. *Abdom Imaging.* 2006. (Epub ahead of print)	Excluded for study design
Nollau P, et al. Detection of K-*ras* Mutations in Stools of Patients with Colorectal Cancer by Mutant-Enriched PCR. International Journal of Cancer 1996;66:332-336.	Excluded for population with cancer
Novis B. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *Gastrointest Endosc.* 2000;52:700-701.	Excluded for study design
O'Connor SD, Summers RM, Yao J, Pickhardt PJ, Choi JR. CT colonography with computer-aided polyp detection: volume and attenuation thresholds to reduce false-positive findings owing to the ileocecal valve. *Radiology* 2006;241(2):426 -32.	Did not report necessary outcomes
O'Hare A, Fenlon H. Virtual colonoscopy in the detection of colonic polyps and neoplasms. *Best Practice & Research in Clinical Gastroenterology.* 2006;79-92.	Excluded for study design
Ontario Ministry of Health and Long-Term Care. Computed tomographic colonography (virtual colonoscopy). 2003. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS).	Excluded for study design
Park SH, Ha HK, Kim MJ et al. False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. *Radiology.* 2005;235:495-502.	Excluded for population
Pescatore P, Glucker T, Delarive J et al. Diagnostic accuracy and interobserver agreement of CT colonography (virtual colonoscopy). *Gut* 2000;47(1):126-30.	Excluded for population
Petrelli N, Michalek AM, Freedman A, Baroni M, Mink I, Rodriguez-Bigas M. Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. *Surgical Oncology 3(1):27-36.* 1994.	Excluded for quality: low followup
Pickhardt PJ, Lehman VT, Winter TC, Taylor AJ. Polyp volume versus linear size measurements at CT colonography: implications for noninvasive surveillance of unresected colorectal lesions. *AJR American Journal of Roentgenology 186 (6):1605 -10.* 2006.	Did not report correct outcomes

Reference	Reason for exclusion
Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Annals of Internal Medicine* 2004;141(5):352-9.	Did not report necessary outcomes
Pineau BC, Paskett ED, Chen GJ et al. Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology* 2003;125(2):304-10.	Excluded for population
Pineau BC, Paskett ED, Chen GJ, Durkalski VL, Espeland MA, Vining DJ. Validation of virtual colonoscopy in the detection of colorectal polyps and masses: rationale for proper study design. *International Journal of Gastrointestinal Cancer* 2001;30(3):133-40.	Did not report necessary outcomes
Rennert G, Rennert HS, Miron E, Peterburg Y. Population colorectal cancer screening with fecal occult blood test. *Cancer Epidemiology, Biomarkers & Prevention.* 2001;10:1165-1168.	Excluded for study design
Rennert G. Fecal occult blood screening--trial evidence, practice and beyond. *Recent Results Cancer Res.* 2003;163:248-253.	Inadequate application of reference standard
Reuterskiold MH, Lasson A, Svensson E, Kilander A, Stotzer PO, Hellstrom M. Diagnostic performance of computed tomography colonography in symptomatic patients and in patients with increased risk for colorectal disease. *Acta Radiologica* 2006;47(9):888 -98.	Excluded for population
Robinson MH, Marks CG, Farrands PA, Thomas WM, Hardcastle JD. Population screening for colorectal cancer: comparison between guaiac and immunological faecal occult blood tests. *British Journal of Surgery 81 (3):448 - 51.* 1994.	Inadequate application of reference standard
Robinson MH, Marks CG, Farrands PA, Whynes DK, Bostock K, Hardcastle JD. Is an immunological faecal occult blood test better than Haemoccult? A cost-benefit study. *European Journal of Surgical Oncology 21(3):261 -4.* 1995.	Inadequate application of reference standard
Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med.* 2007;120:203-210.	Excluded for population
Rozen P, Knaani J, Papo N. Evaluation and comparison of an immunochemical and a guaiac faecal occult blood screening test for colorectal neoplasia. *European Journal of Cancer Prevention* 1995;4(6):475 -81.	Excluded for population: high proportion of surveillance and sypmtomatic
Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. *Cancer* 2000;89(1):46-52.	Inadequate application of reference standard
Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. *Digestive Diseases & Sciences* 1997;42(10):2064 -71 .	Inadequate application of reference standard
Saar B, Meining A, Beer A et al. Prospective study on bright lumen magnetic resonance colonography in comparison with conventional colonoscopy. *British Journal of Radiology* 2007;80 (952):235 -41.	Excluded for population
Saito H, Soma Y, Nakajima M et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep.* 2000;7:815-819.	Excluded for study design
Saito H. Screening for colorectal cancer: current status in Japan. *Diseases of the Colon & Rectum.* 2000;43:Suppl-84.	Excluded for study design

Reference	Reason for exclusion
Saitoh O, Kojima K, Kayazawa M et al. Comparison of tests for fecal lactoferrin and fecal occult blood for colorectal diseases: a prospective pilot study. *Intern Med.* 2000;39:778-782.	Excluded for population-high proportion screen positive or symptomatic.
Scholefield JH. Immunochemical testing for colorectal cancer. *Lancet Oncology* 2006;7(2):101-3.	Excluded for study design
Scott RG, Edwards JT, Fritschi L, Foster NM, Mendelson RM, Forbes GM. Community-based screening by colonoscopy or computed tomographic colonography in asymptomatic average-risk subjects. *The American journal of gastroenterology.* 2004;99:1145-1151.	Inadequate application of reference standard
Selcuk D, Demirel K, Ozer H et al. Comparison of virtual colonoscopy with conventional colonoscopy in detection of colorectal polyps. *Turkish Journal of Gastroenterology* 2006;17(4):288 -93.	Excluded for population
Shastri YM, Naumann M, Oremek GM et al. Prospective multicenter evaluation of fecal tumor pyruvate kinase type M2 (M2-PK) as a screening biomarker for colorectal neoplasia. *International Journal of Cancer* 2006;119 (11):2651 -6.	Did not include one of the specific screening tests
Shi R, Schraedley-Desmond P, Napel S et al. CT colonography: influence of 3D viewing and polyp candidate features on interpretation with computer-aided detection. *Radiology* 2006;239 (3):768 -76.	Excluded for population
Shuber AP, et al. A Discriminant DNA Marker Panel for Detection of Colorectal Adenomas. American Journal of Gastroenterology 2005;100(9):393.	Abstract only
Sidransky D, et al. Identification of *ras* Oncogene Mutations in the stool of patients with Curable Colorectal Tumors. Science 1992; 256:102-105.	Excluded for population with cancer
Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. *Cancer.* 2006;107:2152-2159.	Excluded for population-high proportion of screen positive
Smith-Ravin J, et al. Detection of c-Ki-*ras* mutations in faecal samples from sporadic colorectal cancer patients. Gut 1995; 36:81-86.	Excluded for population with cancer
Sosna J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. *AJR Am J Roentgenol.* 2003;181:1593-1598.	Used as source document
Spinzi G, Belloni G, Martegani A, Sangiovanni A, Del FC, Minoli G. Computed tomographic colonography and conventional colonoscopy for colon diseases: a prospective, blinded study. *Am J Gastroenterol.* 2001;96:394-400.	Excluded for population
St John DJ, Young GP, McHutchison JG, Deacon MC, Alexeyeff MA. Comparison of the specificity and sensitivity of Hemoccult and HemoQuant in screening for colorectal neoplasia. *Annals of Internal Medicine* 1992;117 (5):376 -82 .	Excluded for population
Stelling HP, Maimon HN, Smith RA, Haddy RI, Markert RJ. A comparative study of fecal occult blood tests for early detection of gastrointestinal pathology. *Arch Intern Med.* 1990;150:1001-1005.	Excluded for population
Summers RM, Yao J, Pickhardt PJ et al. Computed tomographic virtual colonoscopy computer-aided polyp detection in a screening population. *Gastroenterology* 2005;129(6):1832 -44.	Did not answer primary question

Reference	Reason for exclusion
Syngal S, Stoffel E, Chung D et al. Detection of stool DNA mutations before and after treatment of colorectal neoplasia. *Cancer* 2006;106 (2):277 -83.	Excluded for population
Tagore KS, Lawson MJ, Yucaitis JA et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. *Clinical Colorectal Cancer* 2003;3(1):47-53.	Excluded for population
Tagore KS, Levin TR, Lawson MJ. The evolution to stool DNA testing for colorectal cancer. *Alimentary Pharmacology & Therapeutics.* 2004;1225-1233.	Excluded for study design
Thomeer M, Carbone I, Bosmans H et al. Stool tagging applied in thin-slice multidetector computed tomography colonography. *J Comput Assist Tomogr.* 2003;27:132-139.	Excluded for population
Tonus C, Neupert G, Sellinger M. Colorectal cancer screening by non-invasive metabolic biomarker fecal tumor M2-PK. *World Journal of Gastroenterology* 2006;12(43):7007 -11.	Did not include one of the specific screening tests
Traverso G, et al. Detection of APC Mutation in Fecal DNA from Patients with Colorectal Tumors. The New England Journal of Medicine 2002;346:311-320	Excluded for population with cancer
Traverso G, Shuber A, Olsson L et al. Detection of proximal colorectal cancers through analysis of faecal DNA. *Lancet.* 2002;359:403-404.	Excluded for population
Uchida K, Matsuse R, Miyachi N et al. Immunochemical detection of human blood in feces. *Clinica Chimica Acta* 1990;189 (3):267 -74 .	Excluded for study design
van Gelder RE, Florie J, Stoker J. Colorectal cancer screening and surveillance with CT colonography: current controversies and obstacles. *Abdominal Imaging* 2005;30(1):5-12.	Excluded for study design
Vilkin A, Rozen P, Levi Z et al. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *American Journal of Gastroenterology* 2005;100(11):2519 -25.	Excluded for population
Villa E, et al. Identification of Subjects at Risk for Colorectal Carcinoma Through a Test Based on K-*ras* Determiniation in the stool. Gastroenterology 1996; 110:1346-1353.	Excluded for population with cancer
Vironen J, Kellokumpu S, Andersson LC, Kellokumpu I. Comparison of a peanut agglutinin test and an immunochemical faecal occult blood test in detecting colorectal neoplasia in symptomatic patients. *Scandinavian Journal of Clinical & Laboratory Investigation* 2004;64 (2):140 -5.	Excluded for population
Wessling J, Domagk D, Lugering N et al. Virtual colonography: identification and differentiation of colorectal lesions using multi-detector computed tomography. *Scandinavian Journal of Gastroenterology 40(4):468 -76.* 2005.	Excluded to to study quality
Whitney D, Skoletsky J, Moore K et al. Enhanced retrieval of DNA from human fecal samples results in improved performance of colorectal cancer screening test. *Journal of Molecular Diagnostics* 2004;6(4):386-95.	Excluded for population
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. *Alimentary Pharmacology & Therapeutics.* 2003;18:941-946.	Excluded for population

Reference	Reason for exclusion
Wong WM, Lam SK, Cheung KL et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer* 2003;97(10):2420 -4.	Excluded for population
Woo HY, Mok RS, Park YN et al. A prospective study of a new immunochemical fecal occult blood test in Korean patients referred for colonoscopy. *Clin Biochem.* 2005;38:395-399.	Excluded for population
Xing PX, Young GP, Ho D, Sinatra MA, Hoj PB, McKenzie IF. A new approach to fecal occult blood testing based on the detection of haptoglobin. *Cancer.* 1996;78:48-56.	Excluded for population
Xynopoulos D, Stasinopoulou M, Dimitroulopoulos D et al. Colorectal polyp detection with virtual colonoscopy (computed tomographic colonography); the reliability of the method. *Hepato-Gastroenterology* 2002;49 (43):124 -7.	Excluded for population
Yamamoto M, Nakama H. Cost-effectiveness analysis of immunochemical occult blood screening for colorectal cancer among three fecal sampling methods. *Hepato-Gastroenterology 47(32):396 -9.* 2000;-Apr.	Inadequate application of reference standard
Yasumoto T, Murakami T, Yamamoto H et al. Assessment of two 3D MDCT colonography protocols for observation of colorectal polyps. *Am J Roentgenol.* 2006;186:85-89.	Excluded for population
Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology* 2001;219(3):685-92.	Excluded for population
Yee J, Kumar NN, Hung RK, Akerkar GA, Kumar PR, Wall SD. Comparison of supine and prone scanning separately and in combination at CT colonography. *Radiology.* 2003;226:653-661.	Excluded for population
Yeshwant SC, Summers RM, Yao J, Brickman DS, Choi JR, Pickhardt PJ. Polyps: linear and volumetric measurement at CT colonography. *Radiology* 2006;241(3):802 -11.	Did not report necessary outcomes
Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K. Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *American Journal of Gastroenterology* 1995;90(7):1076 -9.	Excluded for population
Young GP, St John DJ, Cole SR et al. Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. *Journal of Medical Screening* 2003;10(3):123 -8.	Excluded for population
Young GP, St John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. *Am J Gastroenterol.* 2002;97:2499-2507.	Excluded for study design
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;92:151-154.	Inadequate application of reference standard
Zhu WX, Lin JJ. Reverse passive hemagglutination for detection of fecal occult blood. A comparison with Japanese Immudia-Hem SP Kit. *Chin Med J (Engl).* 1988;101:519-522.	Excluded for population

Appendix D Table 4. Characteristics of studies using high sensitivity guaiac fecal occult blood tests or fecal immunochemical tests.

Study ID	FIT/High sensitivity	Test Name	Currently available for use in the US?	FDA approved?	Is population a screening or primary care comparable?	Use colonoscopy gold standard?	Did all participants receive gold standard?	Provide Sens/Spec? Reported	Provide Sens/Spec? Calculate	Other Outcomes
Screening populations-all patients receiving colonoscopy										
Liu 2003	FIT (latex agglut)	OC-Hemodia	N	N	Y (perhaps)	Y	Y	Y		PPV, NPV
Rozen 1997	FIT; High sensitivity	FlexSure OBT, HemeSelect; HOSensa	N (FlexSure, HemeSelect) Y (HOSensa)	Y	Y (close, only 22% avg risk, but rest were surveillance or FHx)	Y	Y	Y		PPV, NPV
Nakama 2001	FIT	Immudia-HemSp	N (same as HemeSelect)	N	Y (likely)	Y	Y	Y		PPV, NPV
Fattah 1998	FIT (comb monoclonal ab)	Monohaem	Unknown	Y	Y	Y	Y	Y		
Nakama 2004	FIT (latex agglutination)	OC-Hemodia	N	N	Y	Y	Y	Y		
Nakama 1999	FIT (comb monoclonal ab)	Monohaem	Unknown	Y	Y	Y	Y	Y		
Nakama 2000	FIT	Monohaem	Unknown	Y	Y-likely	Y	Y	N	N	PPV
Nakama 2000	FIT	Monohaem	Unknown	Y	Y	Y	Y		Y	
Morikawa 2005	FIT	Magstream	N, but same as HemeSelect which was discontinued	N	Y	Y	Y	Y		
Screening populations-only selected patients receive colonoscopy										
Castiglione 1994	FIT; High sensitivity	HemeSelect; HOSensa	N (HemeSelect) Y (HOSensa)	Y	12.5% sympt	Y	N:+ and high risk	Y- est FN		PPV
Nakama 1996	FIT	Monohaem	Unknown	Y	Y	Y	N: +	Y-from F/U		PPV

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Study ID	FIT/High sensitivity	Test Name	Currently available for use in the US?	FDA approved?	Is population a screening or primary care comparable?	Use colonoscopy gold standard?	Did all participants receive gold standard?	Provide Sens/Spec?		Other Outcomes
								Reported	Calculate	
Robinson 1994	FIT	HemeSelect	N	Y	Y	Y or FS, or BE	N: +	Y		PPV
Zappa 2001	FOBT, FIT (RPHA)	Hemeselect/Immudia	N (Hemeselect, Immudia)	Y N	Y	Y (or DCBE)	N: +	Y-est		
Yamamoto 2000	FIT (latex agglut inhib)	Iatro-Hemcheck	N	N	Y	Y	N: +	Y		
Allison 1996	High sens, FIT	HOSensa, HemeSelect	Y (HOSensa); N (HemeSelect)	Y	Y	Y (HOS to FS)	N: + HS; +HOS to FS, then colo	Y		
Launoy 2005	FIT	Magstream	N	N	Y	Y	N: +	Y-est		PPV-estimated
Rennert 2001	High sensitivity	HOSensa	Y	Y	Y	Y	N: + suggested	Y-est from registry f/u		PPV
Petrelli 1994	FIT; High sensitivity	HemeSelect; HOSensa	N (HemeSelect) Y (HOSensa)	Y	Y (very symptomatic-self-selection?)	Y	N			PPV
Castiglione 2000	FIT	Immudia-HemSp, OC-Hemodia	N (ImmSP-same as HemeSelect)	N	Y	Y	N			PPV
Levin 1997	High sensitivity	HOSensa	Y	Y	Y	Y, or FS/BE	N			PPV
Hughes 2005	FIT	Inform (known as InSure)	Y	Y	Y	Y	N			PPV

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Grazzini 2000	FIT	Not Reported (OC-Sensor-reported elsewhere)	Y	Y	Y	Y or FS/BE	N			PPV
Ciatto 2006	FIT	OCHemodia	N	N	Y	Y	N			PPV
Smith 2006	FIT; High sensitivity	Insure; HOSensa	Y	Y	Y	Y	N			PPV
Robinson 1995	FIT	HemeSelect	N	Y	Y	Y (or FS/sig/BE)	N			PPV
Castiglione 1996	FIT	HemeSelect	N	Y	Y	Y	N			PPV
Guittet 2007	FIT	Magstream	N	N	Y	Y	N			PPV
Chen 1997	FIT	RPHA	N	N	Y	Y	N			PPV
Not screening population- all receive colonoscopy										
Rozen 2000	FIT; High sensitivity	FlexSure OBT; HOSensa	N (FlexSure) Y (HOSensa	Y	N-21% avg; 47% fam hx; 26% surv	Y or FS	N-52% colo; 48% FS w/in 4 yrs	Y		PPV
Rozen 1995	FIT; High sensitivity	BM-Test Colon Albumin; HOSensa	N (BMTCA) Y (HOS)	N (BMTCA) Y (HOS)	N (Avg-25; FHx-40; Surv-27)	59% (FS-41%)	Y	Y		
Stelling 1990	FIT	Monohaem	Unknown	Y (MH)	N	Y	Y	Y		PPV, NPV
Vironen 2004	FIT, peanut agglut	Hemolex, PNA	Unknown	Unknown	N	Y	Y	Y		
Young 2003	FIT	Insure; FlexSure OBT	Y (Insure) N (FlexSure OBT)	Y	N	Y	Y	Y		

Appendix D Table 4. Characteristics of studies using high sensitivity guaiac fecal occult blood tests or fecal immunochemical tests.

Study ID	FIT/High sensitivity	Test Name	Currently available for use in the US?	FDA approved?	Is population a screening or primary care comparable?	Use colonoscopy gold standard?	Did all participants receive gold standard?	Provide Sens/Spec?		Other Outcomes
								Reported	Calculate	
Greenberg 2000	FIT; High sensitivity	FlexSure OBT, HemeSelect; HOSensa	N (FlexSure, HemeSelect) Y (HOSensa)	Y	N	Y	Y	Y		
Li 2006	FIT	Hemosure	Y	Y	N	Y	Y	Y		
Nakama 1998	FIT	Hemcheck	Unknown	N	N	Y	Y	Y		
Hope 1996	FIT	Monohaem, BM-Test Colon Albumin	Unknown (MH) N (BMTCA)	Y(MH) N	N	Y	Y	Y		
Yoshinaga 1995	FIT	OC-Hemodia	N	N	N	Y	Y	Y		
Iida 1995	FIT	OC-Hemodia	N	N	N	Y or BE	Y	Y		
Gopalswamy 1994	FIT; High sensitivity	HemeSelect, Monohaem, FECA-EIA; Coloscreen, HOSensa	Y (HOS) N (HS, FECA) Unknown (MH)	Y (HS, MH, HOS)	N	Y (BE 7%)	Y	Y		PPV, NPV
Woo 2005	3 x FIT (anti-globin x 2, latex agglut)	Occultech, Instant-view, HM-Jack	Y (Occultech and Instant-view are now Quickvue); N (HM-Jack)	Y (Occu; InsView) N(HMJ)	N	Y	Y	Y		PPV
Levi 2006	FIT (latex agglut)	OC-Micro	Y	Y	N	Y	Y	Y		PPV, NPV
Nakama 2000	5 x FIT (RPHA, comb monoclonal Ab, latex agglut inhib, latex agglut)	Immudia-Hemsp, Monohaem, Iatro Hemcheck, LA Hemochaser, OC-Hemodia	Unknown (MH) N	Y (MH) N (others)	N	Y	Y	Y		

Appendix D Table 4. Characteristics of studies using high sensitivity guaiac fecal occult blood tests or fecal immunochemical tests.

Study ID	FIT/High sensitivity	Test Name	Currently available for use in the US?	FDA approved?	Is population a screening or primary care comparable?	Use colonoscopy gold standard?	Did all participants receive gold standard?	Provide Sens/Spec?		Other Outcomes
								Reported	Calculate	
Nakama 1998	5 x FIT (RPHA, comb monoclonal Ab, latex agglut inhib, latex agglut)	Immudia-Hemsp, Monohaem, Iatro Hemcheck, LA Hemochaser, OC-Hemodia	Unknown (MH) N	Y (MH) N (others)	N	Y	Y	Y		
Fattah 1997	FIT (comb monoclonal ab)	Monohaem	Unknown	Y	N	Y	Y		Y	
Nakama 1997	FIT (latex agglut)	OC-Hemodia	N	N	N	Y	Y		Y	
Fraser 2006	FIT (anti-human globin)	Instant-View	Y (Quickvue)	Y	N	Y	Y	Y		
Jeanson 1994	FIT	Hemoblot	N	N	N	Y	Y	Y		
Fraser 2007	FIT	Not Reported			N	Y	Y	Y		+/- LR
Levi 2007	FIT	OC-Micro	Y	Y	N	Y	Y	Y		PPV, LR
Wong 2003	FIT; High sensitivity	FlexSure OBT; HOSensa	N (FlexSure) Y (HOSensa)	Y	N	Y	Y	Y		PPV
Saitoh 2000	FIT	LA hemochaser	Unknown	N	N	Y	Y	Y		
Miyoshi 2000	FIT	Immudia-HemSp, OC-hemodia, Immunohemostick	N	N	N	Y	Y	Y		
Vilkin 2005	FIT	OC-Sensor	Unknown	N	N	Y	Y	Y		
Hoepffner 2006	FIT; High sensitivity	Prevent ID CC	Unknown	N	N	Y	Y	Y		

Appendix D Table 4. Characteristics of studies using high sensitivity guaiac fecal occult blood tests or fecal immunochemical tests.

Study ID	FIT/High sensitivity	Test Name	Currently available for use in the US?	FDA approved?	Is population a screening or primary care comparable?	Use colonoscopy gold standard?	Did all participants receive gold standard?	Provide Sens/Spec?		Other Outcomes
								Reported	Calculate	
Not screening population-not all receiving colonoscopy										
Fattah 1997	FIT	Monohaem	Unknown	Y	N	Y	N	Y		
Levi 2006	FIT; High sensitivity	OC-Micro; HOSensa	Y	Y	N	Y	N	Y		PPV
Nakama 1999	FIT (comb monoclonal ab)	Monohaem	Unknown	Y	N	Y (4% DCBE instead)	N	N		PPV
James 1992	FIT	HemoQuant	N	N	N	Y	N	Y		

Appendix D Table 5. List of Fecal Immunochemical Tests

Test	Marketed in US	FDA approved
Monohaem	unknown	yes
Insure and Inform same test	yes	yes
HemeSelect	no	yes
Magstream-currently used in Australia	no	no
Immundia-HemSP-Japan	no	no
OC-Sensor	no	no
OC-Micro-same as OC Sensor	unknown	yes
OC-Hemodia-test for OC-Sensor	no	no
FlexSure OBT-now Hemoccult-ICT	yes	yes
BM-Test Colon Albumin	no	no
Prevent ID CC	unknown	unknown
Diagnostik	unknown	unknown
Occultech and Instant-view are now Quickvue	yes	yes
HM-Jack	no	no
LA Hemochaser	unknown	no
Hemosure	yes	yes
Feca EIA	no	no

Appendix E. Study Details. KQ3a Harms of colonoscopy and flexible sigmoidoscopy

Colonoscopy. We found 16 fair-to-good quality studies that evaluated clinically significant adverse events from colonoscopy conducted in predominantly asymptomatic persons (see Appendix E Table 1). Study details for the four trials that included colonoscopy as followup procedures for flexible sigmoidoscopy are discussed in the following section.[6,82,173,175]

Kim and colleagues conducted a fair-quality prospective cohort study (n=3163) examining colonoscopies performed in a predominantly average-risk, asymptomatic population through a university medical center in the US.[182] The population mean age was 57 years old, and approximately 56 percent women. All procedures were conducted by one of ten experienced gastroenterologists. The authors reviewed all significant adverse events, defined as those requiring hospital admission and/or medical or surgical treatment. In the published manuscript, they reported only complications of perforations. The authors reported seven (0.2 percent) perforations, four of which required surgical repair.

Ko and colleagues reported their findings in a recent abstract from a fair-quality prospective cohort study (n=18,271) in the US evaluating the incidence of serious complications from screening and surveillance colonoscopy in persons enrolled through the Clinical Outcomes Research Initiative (CORI).[177] Additional information was obtained through personal communication with the study investigators.[183] This study was given a fair-quality rating, instead of good quality rating, because full details in manuscript form are not yet available, and the investigators are currently determining if any of those persons lost to follow-up died. Approximately 90 percent of the population was age 50 to 79 years, and 45 percent were women. All procedures were conducted by 89 gastroenterologists at 19 separate practice sites; trainees participated in approximately 10 percent of the procedures. They reported all serious adverse events for persons with followup at 30 days. Their cohort included an additional 3,104 persons at the 7-day followup, who were lost to followup at 30 days. In total, they found 45 (0.25 percent) serious complications, including 4 (0.02 percent) perforations, 25 (0.14 percent) episodes of bleeding requiring hospitalization, five (0.03 percent) cases of diverticulitis requiring hospitalization, and two (0.02 percent) post-polypectomy syndrome. The authors found no deaths in the persons with 30-day followup and are currently determining if any of those persons lost to followup died.

Rathgaber and colleagues conducted a fair-quality retrospective cohort study (n procedures =12,407) looking at all colonoscopies performed between 2002 and 2004 through a large multi-specialty community group practice in the US.[172] The population's mean age was approximately 60 years and 52

percent women. Eight gastroenterologists conducted all procedures. Their main outcome measures were any perforation or bleeding complications within 30 days of colonoscopy. In total, they found 14 (0.11 percent) serious complications, including two (0.02 percent) perforations, 11 (0.09 percent) episodes of bleeding requiring hospitalization, and one (0.008 percent) cerebral vascular accident (CVA).

Levin and colleagues conducted a fair-quality retrospective cohort study (n procedures =16,318) looking at all colonoscopies performed in an asymptomatic population between 1994 and 2002 in a large HMO in the US.[185] The indications for colonoscopy were positive screening test, surveillance, or primary screening. There were a total of 11,083 polypectomies. The population's mean age was approximately 62 years and 40 percent were women. Nearly all procedures were conducted by physician endoscopists. Ninety six percent of these physician endoscopists were gastroenterologists. The study's main outcome measures were serious complications requiring hospitalization and deaths within 30 days of colonoscopy. In total, they found 44 (0.27 percent) serious complications requiring hospitalization, including 15 (0.09 percent) perforations, 15 (0.09 percent) episodes of bleeding, six (0.04 percent) cases of diverticulitis, six (0.04 percent) post-polypectomy syndrome, and two (0.01 percent) other serious complications. They also found a total of 10 deaths. Only one (0.006 percent) death, however, appeared to be directly related to colonoscopy with polypectomy.

Ko and colleagues conducted a fair-quality prospective cohort study (n=502) evaluating colonoscopies performed in an asymptomatic population at a university medical center in the US.[176] The population was age 40 years and older, approximately 58 percent were aged 50 to 59 years and 51 percent were women. Eight gastroenterologists conducted all procedures. The study's outcome measures included both major and minor complications, as well as patient perceptions after colonoscopy. In total, they found eight (1.6 percent) serious complications that they defined as requiring unexpected medical attention, including hospitalization or an emergency department or clinic visit.

Lee and colleagues conducted a fair-quality prospective cohort study (n=1000) looking at colonoscopies performed in an asymptomatic population at a university hospital in Taiwan.[178] The population was age 19 years and older with a mean age of 51 years, and 43 percent women. All procedures were conducted by seven gastroenterologists. The study's main outcome measure was assessment of post procedural abdominal pain. While the authors found three (0.3 percent) persons with severe abdominal pain, it is unclear if these cases required additional medical attention. The authors state that no

complications were noted during their study followup, therefore these three cases are not included in the meta-analysis for total serious complications from colonoscopy.

Cotterill and colleagues conducted a fair-quality prospective cohort study (n=324) looking at colonoscopies performed in an asymptomatic population through a rural practice in Canada.[174] The population was age 22 to 80 years and 44 percent were women. Two family practice physicians conducted all procedures. The study's outcome measures included perforation, bleeding requiring hospitalization, and problems related to sedation requiring hospitalization. The study found no serious complications.

Pickhardt and colleagues reported a fair-quality prospective study that was designed to evaluate CT colonography for colorectal cancer screening in an average-risk population in three US medical centers.[136] Colonoscopies (n= 1239) were performed as a reference standard. The population was age 40 to 79 years, with an average age of 58 years old, and 41 percent were women. All colonoscopies were conducted by physician endoscopists, 14 were gastroenterologists and three were colorectal surgeons. While the duration of followup for adverse events is unclear, they found one (0.08 percent) episode of delayed bleeding requiring hospitalization after polypectomy. The authors did not report any other significant adverse events from colonoscopy.

Korman and colleagues conducted a fair quality large retrospective cohort study (n procedures =116,000) looking at all colonoscopies performed in 1999 through 45 endoscopic ambulatory surgery centers in the US.[170] General population characteristics and indications for colonoscopy are not described. All procedures were conducted by 264 gastroenterologists. The study's outcome measure was perforation. The population with complications had a mean age of 70 years and was 73 percent women. In total, they found 37 (0.03 percent) perforations. They did not consider other types of adverse events.

Nelson and colleagues conducted a good quality prospective cohort study (n=3196) evaluating colonoscopies in asymptomatic screening population between 1994 and 1997 at 13 Veteran Administration (VA) medical centers in the US.[179] The population was age 50 to 75 years, with a mean age of 63 years, and only three percent were women. Gastroenterologists conducted all procedures. They reported all major adverse events (i.e. requiring transfusion, hospitalization, surgery, or resulting in death) within 30 days of the colonoscopy. In total, they found 18 (0.56 percent) serious complications, including seven (0.22 percent) episodes of major bleeding, one (0.03 percent) new arrhythmia, four (0.12 percent) myocardial infarction or cerebral vascular accident, four (0.12 percent) other major complication, and one (0.03 percent) death.

Robinson and colleagues reported a fair-quality study that was part of a large randomized controlled trial designed to evaluate FOBT screening on colorectal cancer mortality in an average-risk population in the UK.[181] Persons who were FOBT positive received subsequent colonoscopy or double-contrast barium enema. At recruitment the study population was age 50 to 74 years. Details about endoscopists are not reported. The authors reported the adverse events for colonoscopy (n procedures = 1474) including death within 30 days of the procedure. In total, they found seven (0.47 percent) major complications, including one (0.3 percent) perforation, one (0.07 percent) major bleeding, and one (0.07 percent) snare entrapment. They found no deaths.

Newcomer and colleagues conducted a fair-quality prospective cohort study (n=250) among consecutive employed persons undergoing elective outpatient colonoscopies through a multi-specialty clinic in the US.[180] The population was age 18 to 70 years, with a mean age of 52 years, and 43 percent were women. Details about endoscopists are not reported. The study's main outcome measure was unplanned work absence within 7 days of colonoscopy. While they found 10 (4 percent) persons with unplanned work absence, it is unclear if these cases required additional medical attention. The authors state that no complications were noted during the study's followup period. Therefore these cases are not included in the meta-analysis for total serious complications from colonoscopy.

Flexible sigmoidoscopy. We found eight fair-to-good quality studies that evaluated clinically significant adverse events from flexible sigmoidoscopy for colorectal cancer screening in a general-risk population (see Appendix E Table 1).

Levin and colleagues conducted a fair-quality retrospective cohort study (n procedures =109,534) looking at all flexible sigmoidoscopies performed in an average-risk screening population for colorectal cancer between 1994 and 1996 in a large HMO in the US.[185] The population was age 50 to 79 years, mean age 61 years, and 48 percent were women. All procedures were conducted by gastroenterologists, other physicians, nurses or physician assistants. The study's main outcome measures were complications requiring hospitalization within 4 weeks of the procedure. In total, they found five cardiovascular deaths that may have been attributed to the procedure (0.004 percent) and 24 total complications (0.02 percent). There were only seven were 'serious' adverse events (0.006 percent), which included two perforations, two lower GI bleeds requiring transfusion, two diverticulitis, and one unexplained colitis.

Segnan and colleagues reported a fair-quality study that used the baseline results from a large ongoing multi-center randomized controlled trial in Italy to evaluate once-only flexible sigmoidoscopy screening in an average-risk screening population for colorectal cancer.[82] The population was age 55 to 64 years, and 50 percent were women. Gastroenterologists in hospital endoscopy units conducted all procedures. The authors reported the adverse events for the flexible sigmoidoscopies (n procedures = 9911) and followup colonoscopies (n procedures = 775). In total, they found one (0.01 percent) perforation and one (0.01 percent) severe abdominal pain from flexible sigmoidoscopy, and one (0.1 percent) perforation and one (0.1 percent) significant bleed from colonoscopy. They also found 60 (0.6 percent) minor self-limited complications from flexible sigmoidoscopy and 30 (four percent) minor self-limited complications from colonoscopy. These complications included chemical colitis, allergic reaction, mild vagal symptoms, abdominal pain, self-limited bleeding, and two seizures in persons receiving anti-epileptic treatment.

Jain and colleagues conducted a fair-quality retrospective cohort study (n procedures =5017) evaluating all flexible sigmoidoscopies performed in an average-risk screening population for colorectal cancer between 1995 and 2001 at a large HMO in the US.[184] The population was age 50 to 75 years, or greater than 75 years without major medical conditions. Registered gastroenterology nurses conducted all procedures. The authors reported that they found no deaths or complications from perforation, bleeding, or infection. It is unclear if they looked for all serious adverse events, therefore this study is not included in the meta-analysis for total serious complications from flexible sigmoidoscopy.

Wallace and colleagues conducted a fair-quality prospective cohort study (n procedures =3701) looking at flexible sigmoidoscopies performed in an average risk screening population for colorectal cancer between 1995 and 1997 in a large HMO in the US.[186] The population included individuals age 50 years and older, mean age 59 years, and 50 percent were women. Most procedures were conducted by gastroenterologists, and some by trained nonphysician staff (e.g., nurse practitioner and physician assistants). The study's outcome measures included both major and minor complications. They found no major complications, including death, perforation, or bleeding requiring transfusions.

Thiis-Evensen and colleagues reported a fair-quality study that was part of a larger population-based randomized controlled trial in Norway evaluating colorectal cancer screening in an average-risk population.[6] At recruitment, the population was age 50 to 59 years, average age at followup was 67 years, and the population included 50 percent women at baseline and 48 percent were women at followup. The

authors reported the adverse events for the baseline and follow-up flexible sigmoidoscopies, n procedures = 446, and follow-up colonoscopies, n procedures = 521. They found no major complications, including perforation or bleeding, except for one person who was briefly hospitalized for "water intoxication," after bowel preparation.

Kewenter and colleagues reported a fair-quality study that is part of a larger population based randomized controlled trial in Sweden to evaluate colorectal cancer screening in an average-risk population.[175] Persons who were FOBT positive received subsequent endoscopy (either flexible sigmoidoscopy or colonoscopy) or double-contrast barium enema. The population was age 60 to 64 years at recruitment. Details about endoscopists were not reported. The authors reported the adverse events for the flexible sigmoidoscopies (n procedures = 2108) and colonoscopies (n procedures = 190). In 113 cases, colonoscopies were performed for possible adenomas above the sigmoid colon seen on barium enema. They found three (0.14 percent) perforations from flexible sigmoidoscopy, two (1.05 percent) perforations from colonoscopy, and one (0.5 percent) major bleeding from colonoscopy. All perforations and major bleeding episodes were from polypectomies.

Atkin and colleagues reported a fair-quality study that represents the pilot results from a large ongoing multi-center randomized controlled trial in the UK to evaluate once-only flexible sigmoidoscopy screening in an average-risk screening population for colorectal cancer.[173] The population included individuals age 55 to 64 years. Details about endoscopists were not reported. The authors reported the adverse events for flexible sigmoidoscopies (n procedures = 1285) and follow-up colonoscopies (n procedures = 76). While they found a total of 40 bleeding episodes, it is unclear the significance of these episodes (i.e. major versus minor), and if they were from flexible sigmoidoscopy or colonoscopy. They also found three (0.2 percent) other complications from flexible sigmoidoscopy, including myocardial infarction, syncope, and severe diarrhea.

Viiala and colleagues reported a fair-quality study that represents the initial cohort of persons in a prospective cohort study of a community based flexible sigmoidoscopy CRC screening program in Western Australia.[187] The population included individuals age 55 to 64 years. Endoscopists were gastroenterologist, surgeons, or supervised registrars and general practitioners. The authors reported the adverse events for flexible sigmoidoscopies (n procedures = 3402). They found no perforation or significant bleeding during the screening period. It is unclear if they looked for all serious adverse events, therefore this study is not included in the meta-analysis for total serious complications from flexible sigmoidoscopy.

Appendix E Table 1. Evidence table for KQ3A.

Study Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics	Procedure Information
Colonoscopy					
Kim 2007[182]	Prospective Cohort Single institution, US Recruitment through referrals for screening colonoscopy	**Operator:** 5 gastroenterologists	**Inclusion:** Referral from PCP for CRC screening **Exclusions:** Polyp surveillance, history of bowel disorder (e.g., inflammatory bowel disease, the polyposis syndrome, HNPCC)	**Age:** 57.0 (mean) **% female:** 56. **% ethnic origin:** NR **SES:** NR **% symptomatic:** 2	**Colonoscopies:** 3163 **Completion Rate:** Unknown
Ko 2007[177] Fair	Multicenter, enrolled in Clinical Outcomes Research Initiative (CORI), US Prospective Cohort	**Operator:** 89 gastroenterologists at 19 different practice sites **Experience:** Trainees participated in 10% of procedures **# procedures performed:** NR	**Inclusion:** Age 40+, undergoing colonoscopy at a participating CORI site, average risk screening, surveillance, or evaluation of another abnormal screening test **Exclusion:** Recent visible gastrointestinal bleeding, personal history of inflammatory bowel disease, incomplete colonoscopy due to poor bowel preparation	**Age:** 40-49 years: 5.7% 50-59 years: 37.5% 60-69 years: 31.2% 70-79 years: 20.2% >=80 years: 5.4% **% female:** 45 **% ethnic origin:** White: 90.3 AA: 7.6 Asian/PI: 1.4 Hispanic: 1.3 Native American: 0.5 Unknown: 0.3 **% symptomatic:** 0%	**Colonoscopies:** 18271 **Completion Rate:** 100%
Levin 2006[171] Fair	Kaiser Permanente, Northern California Region (KPNC), US Retrospective Cohort	**Operator:** Gastroenterologists***:*** 96% Internists: 2% Not identified: 2% **Experience:** NR **# procedures performed:** 80% <150 procedures	**Inclusion:** 1994 to 2002, age 40+, f/u for positive screening test, surveillance for previous polyp or CRC, primary screening **Exclusion:** Symptomatic	**Mean Age:** 62 **% female:** 40.3 **% ethnic origin:**NR **% symptomatic:** 0	**Colonoscopies:** 16318 **Completion Rate:** 464/16318 (2.8%) 25% missing data on depth of completion
Cotterill 2005[174] Fair	Rural Ontario, Canada Prospective Cohort	**Operator:** 2 FP **Experience:** NR **# procedures performed:** NR	**Inclusion:** Age 50-75 average risk, or with a family history of CRC if younger than 50 **Exclusion:** Life expectancy <10 years, clinical indication for colonoscopy, previous colonoscopy in last 10 years, contraindications to colonoscopy	**Age (range):** 22-80 **% female:** 44.1 **% ethnic origin:** NR **% symptomatic:** NR	**Colonoscopies:** 324 (152 screening) **Completion Rate:** 94%

Reference Quality	FollowUp	Mortality	Perforation or bleeding	Other major adverse effects	Applicability
Colonoscopy					
Kim 2007[182]	NR	**NR**	**Perforation** ***Total:*** 7/3163 (0.2%) ***Polypectomy:*** NR 4 of the 7 required surgical intervention **Bleeding** ***Total:*** NR ***Polypectomy:*** NR	No other adverse effects reported	Good
Ko 2007[177] Fair	30 days	**Total:** NR **Polypectomy:** NR	**Perforation** ***Total:*** 4/18271 (0.02%) ***Polypectomy:*** NR **Bleeding** ***Total:*** 25/18271 (0.14%) bleeding requiring hospitalization ***Polypectomy:*** NR	**Total:** All serious: 45/18271 (0.25%) Diverticulitis requiring hospitalization: 5/18271 (0.03%) Post-polypectomy syndrome: 2/18271 (0.02%)	Good
Levin 2006[171] Fair	30 days	**Total:** 10/16,318 (0.06%) **Polypectomy**: 1/16,318 (0.006%)	**Perforation** ***Total:*** 15/16318 (0.09%) ***Polypectomy:***12/11083 (0.11%) **Bleeding** ***Total:*** Any bleeding: 53/16318 (0.32%) Serious bleeding: 15/16318 (0.09%) ***Polypectomy:*** Any bleeding: 53/11083 (0.48%) Serious bleeding: 15/11083 (0.13%)	**Total:** All serious: 44/16,318 (0.2%) Postpolypectomy syndrome: 6/16318 (0.04%) Diverticulitis: 6/16,318 (0.04%) Other serious illness: 2/16,318 (0.01%) ***Polypectomy:*** All serious: 78/11083 (0.70%) Postpolypectomy syndrome: 6/11,083 (0.06%) Diverticulitis: 5/11083 (0.05%) Other serious illness: 2/11,083 (0.02%)	Good
Cotterill 2005[174] Fair	NR	**Total:** NR **Polypectomy:** NR	**Perforation** ***Total:*** 0/152 (0%) **Bleeding** ***Total:*** 0/152 (0%)	No other adverse effects reported	Good

Reference Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics	Procedure Information
Colonoscopy					
Rathgaber 2006[172] Fair	Western Wisconsin; Multi-specialty community group practice Retrospective Cohort	**Operator:** 8 Gastroenterologists **Experience:** NR **# procedures performed:** NR	**Inclusion:** Included all colonoscopies done from 2002-2004 **Exclusion:** NR	**Age:** 59.7 **% female:** 52.2 **% ethnic origin:** NR **% symptomatic:** NR	**Colonoscopies:** 12407 **Completion Rate:** 98.4%
Newcomer 1999[180] Fair	Minneapolis, MN; Large multispecialty clinic Prospective Cohort	**Operator:** NR **Experience:** NR **# procedures performend:** NR	**Inclusion:** Age 18-70 years, full-time or part-time employed, scheduled to work the following day **Exclusion:** Not specified	**Age:** 52.0 **% female:** 42.6% **% ethnic origin:** NR **% symptomatic:** NR	**Colonoscopies:** 270 (results for 250 reported) **Completion Rate:** 98%
Korman 2003[170] Fair	Multiple endoscopic ambulatory surgery centers in US Retrospective Cohort	**Operator:** 264 Gastroenterologists **Experience:** NR **# procedures performed:** NR	**Inclusion:** All patients with perforation in 1999 **Exclusion:** Not specified	*Only given those with perforation:* **Age:** 69.4 **% female:** 73 **% ethnic origin:** NR **% symptomatic:** NR	**Colonoscopies:** 116000 **Completion Rate:** NR

Reference Quality	Followup	Mortality	Perforation or bleeding	Other adverse effects	Applicability
Colonoscopy					
Rathgaber 2006[172] Fair	30 days	**Total:** NR **Polypectomy:** NR	**Perforation** ***Total:*** 2/12407 (0.016%) (perforations in diagnostic colonoscopies) ***Polypectomy:*** 0/5074 (0%) **Bleeding *Total***: Any bleeding: 25/12407 (0.20%) Requiring transfusions: 11/12,407 (0.09%) ***Polypectomy:*** 23/5074 (0.46%)	**Total:** 28/12,407 (0.22%) Posterior circulation cerebral vascular event:1/12,407 (0.008%) ***Polypectomy:*** Posterior circulation cerebral vascular event:1/5074 (0.02%)	Fair
Newcomer 1999[180] Fair	7 days	**Total:** 0 **Polypectomy:** 0	**Perforation** ***Total:*** 0 **Bleeding** ***Total:*** 0	***Total:*** Unplanned work absence: 10/250 (4%)	Fair
Korman 2003[170] Fair	NR	**Total:** NR **Polypectomy:** NR	**Perforation** ***Total:*** 37/116000 (0.03%) ***Polypectomy:*** 0 **Bleeding** ***Total:*** NR ***Polypectomy:*** NR	No other adverse effect reported	Fair

Reference Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics	Procedure Information
Colonoscopy					
Nelson 2002[179] Good	13 VA Medical Centers, US Prospective Cohort	**Operator:** Gastro **Experience (range):** 1-23 **# procedures performed:** Avg p/y 100-750	**Inclusion:** Age 50-75, from 1994-1997, asymptomatic screening **Exclusion:** Symptoms of lower GI disease, rectal bleeding past 6 mo, significant change in bowel habits, abdominal pain, prior colonic disease (including polyps), prior exam w/I 10 yrs, significant medical problems, limited life expectancy, need for special precaution, women of childbearing potential	**Mean age:** 63.0 **% female:**3.2 **% ethnic origin:** NR **% symptomatic:** 0	**Colonoscopies:** 3196 **Completion Rate:** 3107/3196 (97.2%)
Ko 2006[176] Fair	Academic medical center, Seattle, WA, US Prospective Cohort	**Operator:** 8 endoscopists **Experience:** NR **# procedures performed:** 200-500 endoscopies in same year as study; trainee participated in 36% of procedures	**Inclusion:** Age 40+, undergoing colonoscopy for screening, surveillance of polyps, family history of CRC or polyps, evaluation of another abnormal screening test **Exclusion:** Recent history of GI bleeding, anemic, IBD	**Age:** 57.8% aged 50-59 **% female:** 50.8 **% ethnic origin:** white :92.0% Afr-Amer: 2.6% Asian/Pac Isl: 3.0% Oth/mix: 2.4% Hispanic: 2.2% % **symptomatic:** 0	**Colonoscopies:** 502 470 with followup at both 7 and 30 days; 9 persons with no followup and excluded from analyses **Completion Rate:**99%
Robinson 1999[181] Fair	UK Participants identified through Family Health Service Authority lists and general practice registries, screen positive persons with endoscopic followup RCT of FOBT	**Operator:** NR **Experience:** NR **# procedures performed:** NR	**Inclusion:** Age 50 to 75; FOBT screen positive **Exclusion:** Identified by their doctor as having a serious illness, including CRC, within previous 5 years	**Age (range)**: 50-75 **% female:** 51.9 invited to complete FOBT **Ethnic origin:** NR **% symptomatic:** NR	**Colonoscopies:** 1474 **Completion Rate:** NR

Reference Quality	Followup	Mortality	Perforation or bleeding	Other adverse effects	Applicability
Colonoscopy					
Nelson 2002[179] Good	30 days	**Total:** 1/3196 (.03%) **Polypectomy:** NR	**Perforation** ***Total:*** 0 **Bleeding** ***Total:*** Major bleeding requiring hosp, transfusion or surgery: 7/3196 (0.22%) Minor bleeding: 6/3196 (0.22%) ***Polypectomy:*** 7/1672 (0.42%)	**Total:** All serious: 18/3196 (0.56%) New arrythmia: 1/3196 (0.03%) MI/CVA: 4/3196 (0.12%) Other major: 4/3196 (0.12%) Vasovagal: 188/3196 (5.4%) Oxygen desat: 141/3196 (4.4%) Abdominal pain last >2 hr: 24/3196 (0.8%) Abdominal pain resulting in colo termination: 29/3196 (3.9%)	Good/fair
Ko 2006[176] Fair	7 and 30 days	**Total:** NR	**Perforation** ***Total:*** 0 **Bleeding** ***Total:*** GI Bleed requiring medical attention: *0-6 days:*2/479 (0.4%) *7-30 days:*2/493 (0.4%) Requiring blood transfusion: *0-6 days:*1/479 (0.2%) *7-30 days:*1/493 (0.2%)	**Total:** ***Hospitalization:*** 0-6 days: 2/479 (0.4%) 7-30 days: 3/493 (0.6%) ***ED:*** 0-6 days: 2/479 (0.4%) 7-30 days: 1/493 (0.2%)	Good/fair
Robinson 1999[181] Fair	30 days	**Total:** 0	**Perforation** ***Total:*** 5/1474 (0.3%) ***Polypectomy:*** NR **Bleeding** ***Total:*** Major GI bleeding: 1/1474 (0.07%) **Polypectomy:** NR	Snare Entrapment: 1/1474 (0.07%)	Good

Reference Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics	Procedure Information
Colonoscopy					
Lee 2006[178] Fair	Taiwan, university hospital Prospective Cohort	**Operator:** 7 endoscopists **Experience:** NR **# procedures performed:** >500	**Inclusion:** Age 19 to 84, consecutive persons, "asymptomatic but susceptible" **Exclusion:** advanced CRC, diverticulosis, non-IBS related abdominal pain	**Age:** 51 **% female:** 43.1 **% ethnic origin:** Chinese: 100% **% symptomatic:** NR	**Colonoscopies:**1000 **Completion Rate:** 97.6%
Pickhardt 2003[136] Fair	Multicenter (3), US Prospective cohort (comparing CTC)	**Operator:** ***Gastro*:** 14 ***Colo Surgeon:*** 3 **Experience:** NR **# procedures performed:** NR	**Inclusion:** Age 50 to 79 with average risk of CRC, or 40+ with a family history of CRC, 2002-2003 **Exclusion:** FOBT positive; iron deficiency anemia; rectal bleeding; unintentional weight loss; previous CT colonography or barium enema; personal history of adenomatous polyps, CRC, IBD; history of FAP or HNPC; rejection for CT colonography; medical condition precluding NaP prep; pregnancy	**Age:** 57.8 **% female:** 41.0 **% ethnic origin:** NR **% symptomatic:** 0	**Colonoscopies:** 1239 **Completion Rate:** 99.4%
Flexible Sigmoidoscopy					
Levin 2002[185] Fair	Kaiser Permanente, Northern CA, US Retrospective Cohort	**Operator:** Gastroenterologist, non-Gastroenterologist MD or nurse; gastroenterologists supervise flex sig facilities **Experience:** NR **# procedures performed:** NR	**Inclusion:** age 50-79, 'average' risk for CRC, with screening flex sig at KP facility in Northern CA between 1994-1996 **Exclusion:** h/o colorectal polyps, h/o CRC, serious family history, pts with colonoscopy same day as flex sig	**Age:** 61.0 **% female:** 48.6 **% ethnic origin:** NR **% symptomatic:** 0	**Flex Sig:** 109534 **Completion Rate:** NR

Reference Quality	Followup	Mortality	Perforation or bleeding	Other adverse effects	Applicability
Colonoscopy					
Lee 2006[178] Fair	24 hours	**Total:** NR	**Perforation** ***Total:*** NR **Bleeding** ***Total:*** NR	Severe abdominal pain: 3/1000 (0.3%)	Fair
Pickhardt 2003[136] Fair	NR	**Total:** NR	**Perforation** ***Total:*** NR **Bleeding** ***Total:*** 1/1239 (0.08%) ***Polypectomy:*** 1 with unknown denominator	No other adverse effect reported	Good
Flexible Sigmoidoscopy					
Levin 2002[185] Fair	NR	**Total:** 10/109,534 (0.009%) Cardiovascular deaths 5/109,534 (0.004%) (remaining 5 appear unrelated to flex sig) **Polypectomy:** NR	**Perforation** ***Total:*** 2/109534 (0.002%) requiring surgery ***Polypectomy:*** NR **Bleeding** ***Total:*** Any bleeding:11/109534 (0.01%) Serious bleeding: 2/109534 (0.002%) ***Polypectomy:*** NR	***Total:*** All complications 24/109,534 (0.02%) All 'serious' complications 7/109,534 (0.06%) Fever 4/109,534 (0.003%) Abdominal pain 4/109,534 (0.003%) GI bleed, no transfusion 9/109,534 (0.008%)	Good

Reference Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics:	Procedure Information
Flexible Sigmoidoscopy					
Atkin 1998[173] Fair	22 general practices in UK in two areas (Welwyn Garden City and Leicester) RCT	**Operator:** NR **Experience:** NR **# procedures performed:** NR	**Inclusion:** Age 55-64 years, asymptomatic screening population **Exclusion:** CRC, IBD, colorectal endoscopy within past 2 years, or severe illness	**Age(Range):** 55-64 **% female:** NR **% ethnic origin:** NR **% symptomatic:** NR	**Flex Sig:** 1285 **Followup colonoscopies:** 76 **Completion Rates:** NR
Segnan 2002[82] Fair	General practices, Italy RCT	**Operator:** Specialist gastroenterologists in hospital endoscopy units **Experience:** NR **# procedures performed**:	**Inclusion:** Age 55 to 64 years **Exclusion:** history of CRC, history of colorectal polyps, IBD, colorectal endoscopy within 2 years, family history of CRC, or medical condition that would preclude benefit from screening	**Age(Range):** 55-64 **% female:** 50.0 **% ethnic origin:** NR **% symptomatic:** NR	**Flex Sig:** 9911 **Followup colonoscopies:** 775 **Completion Rate:** ***Flex sig:*** 119 incomplete ***Colonoscopy:*** 188 incomplete
Thiis-Evensen 1999[6] Hoff 2001[188] Fair	Population based, Norway RCT	**Operator:** NR **Experience:** NR **# procedures performed:** NR	**Inclusion**: age 50 to 59, representing an average risk population, screening **Exclusion:** NR	**Age:** ***i:*** 50-59 (range) ***fu:***67 (avg) **% female:** ***i:*** 50.0 ***fu:*** 47.9 **% ethnic origin:** NR **SES:** NR **% symptomatic:** ***i:*** NR ***fu:***17.6% IBD or abdominal complaints	**Flex Sig:** 446 **Followup colonoscopies:** 521 **Completion Rate:** NR

Reference Quality	Followup	Mortality	Perforation or bleeding	Other adverse effects	Applicability
Flexible Sigmoidoscopy					
Atkin 1998[173] Fair	1 day	**Total:** 0	**Perforation** ***Total:*** NR **Bleeding** ***Total:*** 40/1285 (3.1%) ***Polypectomy:*** 14/288 (4.9%)	***Total:*** MI: 1/1,285 (0.08%) Vasovagal syncope: 1/1,285 (0.08%) Diarrhea: 1/1,285 (0.08%)	Fair
Segnan 2002[82] Fair	NR	**Total:** NR **Polypectomy:** NR	**Perforation** ***Total:*** Flexible Sig: 1/9911(0.01%) Colonoscopy: 1/775 (0.13%) ***Polypectomy:*** NR **Bleeding** ***Total:*** Flexible Sig: 0/9911(0%) Colonoscopy: 1/775 (0.13%) ***Polypectomy:*** Colonoscopy: 1, denominator not reported	***Flex sig:*** Severe abdominal pain: 1/9911 (0.01%) Minor self-limited complications: 60/9911 (0.6%) ***Colonoscopy:*** Minor self-limited complications: 30/775 (4%)	Good/fair
Thiis-Evensen 1999[6] Hoff 2001[188] Fair	14 days	**Total:** 0 **Polypectomy:** 0	**Perforation** ***Total:*** 0 **Bleeding** ***Total:*** 0	1/415 (0.24%) water intoxication due to "over-anxious bowel cleansing" resulting in 24 hour hospital stay.	Good/fair

Reference Quality	Setting/Study Design	Screening test operator characteristics	Inclusion/ Exclusion Criteria	Patient Characteristics	Procedure Information
Flexible Sigmoidoscopy					
Wallace 1999[186] Fair	HMO, US Prospective Cohort	**Operator:** ***NP:*** 1 ***PA:*** 2 ***Gastro:*** 15 * all trained **Experience:** NR **# procedures performed:** NR	**Inclusion:** Age 50 or older, no new lower GI symptoms, no acute cardiopulmonary disease, negative FOBT, no first-degree relative with CRC at 55 or younger, 1995-1997 **Exclusion:** NR	**Age:** 59 **% female:** 50.5 **% ethnic origin:** NR **% symptomatic:** 0	**Flex Sig:** 3701 **Completion Rate:** NR
Kewenter 1996[175] Fair	Population based, Sweden RCT for FOBT	**Operator:** NR **Experience:** NR **# of procedures performed:** NR	**Inclusion:** Age 60-64 at the time of recruitment (recruitment was based on year of birth), FOBT positive on initial screen or positive on both initial and re-test FOBT **Exclusion:** NR	**Age (range):** 60-64 **% female:** NR **% ethnic origin:** NR **% symptomatic:** NR	**Flex Sig:** 2108 **Followup colonoscopies:** 190 113 colonoscopies done for proximal lesions seen on DCBE **Completion Rate:** NR
Jain 2002[184] Fair	Kaiser Permanente, Hawaii, US Retrospective Cohort	**Operator:** Registered GI nurses **Experience:** NR **# procedures performed**: >50	**Inclusion:** Age 50 to 75 (or above 75 if no major medical conditions), free of GI symptoms, no first degree relatives with CRC below age 60, not at high risk for CRC, negative FOBT, referral to colorectal screening clinic **Exclusion:** NR	**Age**: >50 **% female:** NR **% ethnic origin:** NR **% symptomatic:** 0%	**Flex Sig:** 5017 **Completion Rate:** NR
Viiala 2007[187] Fair	Hospital conducting community based screening program, Australia Prospective Cohort	**Operator:** Gastroenterologists, surgeons, or supervised registrars and general practitioners **Experience:** NR **# of procedures performed:** NR	**Inclusion:** Age 55 to 64, asymptomatic and average-risk for CRC **Exclusion:** NR	**Age:** 60 **% female:** 41 **% ethnic origin:** NR **% symptomatic:** 0%	**Flex Sig:** 3402 **Completion Rate:** NR

Reference Quality	Followup	Mortality	Perforation or bleeding	Other adverse effects	Applicability
Flexible Sigmoidoscopy					
Wallace 1999[186] Fair	NR	**Total:** 0	**Perforation** ***Total:*** 0 **Bleeding** ***Total:*** 0	No other adverse effect reported	Good
Kewenter 1996[175] Fair	1, 3, and 12 days	**Total:** NR	**Perforation** ***Total:*** Flexible Sig: 3/2108 (0.14%) Colonoscopy: 2/190 (1.05%) ***Polypectomy:*** Flexible Sig: 3/413 (0.7%) Colonoscopy: 2/113 (1.8%) **Bleeding** ***Total:*** Flexible Sig: 0/2108 (0%) Colonoscopy: 1/190 (0.5%) ***Polypectomy:*** Flexible Sig: 0/413 (0%) Colonoscopy: 1/113 (0.9%)	No other adverse effect reported	Fair
Jain 2002[184] Fair	NR	**Total:** 0	**Perforation** ***Total:*** 0/5017 (0%) **Bleeding** ***Total:*** 0/5017 (0%)	Reported no infections, no other adverse effects reported	Good
Viiala 2007[187] Fair	NR	**Total:** NR	**Perforation** ***Total:*** Flexible Sig: 0/3402 (0%) **Bleeding** ***Total:*** Flexible Sig: 0/3402 (0%)	No other adverse effect reported	Fair

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Abaskharoun R, Depew W, Vanner S. Changes in renal function following administration of oral sodium phosphate or polyethylene glycol for colon cleansing before colonoscopy. *Can J Gastroenterol.* 2007;21:227-231.	Excluded for study relevance
Ainley E. Hyperphosphataemia after bowel preparation with oral sodium phosphate. *Endoscopy* 2006;38(7):759.	Excluded for study design
Anderson JC, Pollack BJ, Shaw RD. Virtual colonoscopy. *N Engl J Med.* 2000;342:738-739.	Excluded for study design
Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons from a 10-year study. *American Journal of Gastroenterology* 2000;95 (12):3418 -22.	Excluded for setting
Araghizadeh FY, Timmcke AE, Opelka FG, Hicks TC, Beck DE. Colonoscopic perforations. *Diseases of the Colon & Rectum.* 2001;44:713-716.	Excluded for setting
Arora A, Singh P. Colonoscopy in patients 80 years of age and older is safe, with high success rate and diagnostic yield. *Gastrointestinal Endoscopy* 2004;60(3):408-13.	Excluded for population
Aydogan T, Kanbay M, Uz B et al. Fatal hyperphosphatemia secondary to a phosphosoda bowel preparation in a geriatric patient with normal renal function. *Journal of Clinical Gastroenterology* 2006;40(2):177.	Excluded for study design
Aziz F, Milman P, McNelis J. Abdominal pain after colonoscopy: can it be acute cholecystitis? *Digestive Diseases & Sciences.* 2007;52:2660-2661.	Excluded for population
Baillie J. Postpolypectomy bleeding. *American Journal of Gastroenterology 102 (6):1151 -3.* 2007.	Excluded for study design
Barkun A, Chiba N, Enns R et al. Commonly used preparations for colonoscopy: efficacy, tolerability, and safety--a Canadian Association of Gastroenterology position paper. *Canadian Journal of Gastroenterology.* 2006;699-710.	Excluded for study design
Basson MD, Etter L, Panzini LA. Rates of colonoscopic perforation in current practice. *Gastroenterology.* 1998;114:1115.	Excluded for study design
Belsey J, Epstein O, Heresbach D. Systematic review: oral bowel preparation for colonoscopy. *Alimentary Pharmacology & Therapeutics 25(4):373 -84 .* 2007.	Excluded for study relevance
Beyea A, Block C, Schned A. Acute phosphate nephropathy following oral sodium phosphate solution to cleanse the bowel for colonoscopy. *American Journal of Kidney Diseases 50(1):151 -4.* 2007.	Excluded for study design
Blondon H, Compan F. Feasibility of colonoscopy without sedation. A retrospective study of 502 procedures. *Gastroenterologie Clinique et Biologique* 2006;30(2):328 -9.	Did not report necessary outcomes
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;391:157-160.	Excluded for study design
Bowles CJ, Leicester R, Romaya C, Swarbrick E, Williams CB, Epstein O. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? *Gut.* 2004;53:277-283.	Excluded for population
Bretthauer M, Thiis-Evensen E, Huppertz-Hauss G et al. NORCCAP (Norwegian colorectal cancer prevention): a randomised trial to assess the safety and efficacy of carbon dioxide versus air insufflation in colonoscopy. *Gut* 2002;50(5):604 -7.	Excluded for setting
Brooker JC, Saunders BP, Shah SG, Williams CB. Endoscopic resection of large sessile colonic polyps by specialist and non-specialist endoscopists. *Br J Surg.* 2002;89:1020-1024.	Excluded for setting
Brynitz S, Kjaergard H, Struckmann J. Perforations from colonoscopy during diagnosis and treatment of polyps. *Ann Chir Gynaecol.* 1986;75:142-145.	Excluded for setting

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Cammarota G, Cesaro P, Cazzato A et al. Hydrogen peroxide-related colitis (previously known as "pseudolipomatosis"): a series of cases occurring in an epidemic pattern. *Endoscopy.* 2007;39:916-919.	Excluded for study relevance
Carl DE, Sica DA. Acute phosphate nephropathy following colonoscopy preparation. *Am J Med Sci.* 2007;334:151-154.	Excluded study design
Church J, Delaney C. Randomized, controlled trial of carbon dioxide insufflation during colonoscopy. *Diseases of the Colon & Rectum* 2003;46 (3):322 -6.	Excluded for setting
Clarke GA, Jacobson BC, Hammett RJ, Carr-Locke DL. The indications, utilization and safety of gastrointestinal endoscopy in an extremely elderly patient cohort. *Endoscopy.* 2001;33:580-584.	Excluded for population
Cobb WS, Heniford BT, Sigmon LB et al. Colonoscopic perforations: incidence, management, and outcomes. *Am Surg.* 2004;70:750-757.	Excluded for setting
Colonoscopes may spread HCV and HPV. *AIDS Patient Care & Stds.* 2003;17:257-258.	Excluded for study design
Conigliaro R, Rossi A. Implementation of sedation guidelines in clinical practice in Italy: results of a prospective longitudinal multicenter study. *Endoscopy.* 2006;38:1137-1143.	Excluded for setting
Dafnis G, Ekbom A, Pahlman L, Blomqvist P. Complications of diagnostic and therapeutic colonoscopy within a defined population in Sweden. *Gastrointestinal Endoscopy* 2001;54 (3):302 -9.	Excluded for population
de GP, Slagt C, de Graaf JL, Loffeld RJ. Fatal aspiration of polyethylene glycol solution. *Netherlands Journal of Medicine* 2006;64 (6):196 -8.	Excluded for setting
de Zwart IM, Griffioen G, Shaw MP, Lamers CB, de Roos A. Barium enema and endoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. *Clin Radiol.* 2001;56:401-409.	Excluded for study quality
Di LF, Vigano P, Pilati S, Mantovani N, Togliani T, Pulica C. Splenic rupture after colonoscopy. A case report and review of the literature. *Chir Ital.* 2007;59:755-757.	Excluded for study design
DiPrima RE, Barkin JS, Blinder M, Goldberg RI, Phillips RS. Age as a risk factor in colonoscopy: fact versus fiction. *Am J Gastroenterol.* 1988;83:123-125.	Excluded for setting
Dobrowolski S, Dobosz M, Babicki A, Glowacki J, Nalecz A. Blood supply of colorectal polyps correlates with risk of bleeding after colonoscopic polypectomy. *Gastrointest Endosc.* 2006;63:1004-1009.	Excluded for setting
Dominitz JA, Eisen GM, Baron TH et al. Complications of colonoscopy. *Gastrointest Endosc.* 2003;57:441-445.	Excluded for study design
Doniec JM, Lohnert MS, Schniewind B, Bokelmann F, Kremer B, Grimm H. Endoscopic removal of large colorectal polyps: prevention of unnecessary surgery? *Diseases of the Colon & Rectum* 2003;46(3):340 -8.	Excluded for setting
Eckardt VF, Kanzler G, Schmitt T, Eckardt AJ, Bernhard G. Complications and adverse effects of colonoscopy with selective sedation. *Gastrointest Endosc.* 1999;49:560-565.	Excluded for population
Edwards JK, Norris TE. Colonoscopy in rural communities: can family physicians perform the procedure with safe and efficacious results? *Journal of the American Board of Family Practice* 2004;17(5):353-8.	Excluded for population
Farley DR, Bannon MP, Zietlow SP, Pemberton JH, Ilstrup DM, Larson DR. Management of colonoscopic perforations. *Mayo Clin Proc.* 1997;72:729-733.	Excluded for setting

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. *Journal of the National Cancer Institute* 2003;95(3):230-6.	Excluded for population
Gedebou TM, Wong RA, Rappaport WD, Jaffe P, Kahsai D, Hunter GC. Clinical presentation and management of iatrogenic colon perforations. *Am J Surg.* 1996;172:454-457.	Excluded for population
Gibbs DH, Opelka FG, Beck DE, Hicks TC, Timmcke AE, Gathright JB, Jr. Postpolypectomy colonic hemorrhage. *Dis Colon Rectum.* 1996;39:806-810.	Excluded for setting
Gidwani AL, Makar R, Garrett D, Gilliland R. A prospective randomized single-blind comparison of three methods of bowel preparation for outpatient flexible sigmoidoscopy. *Surgical Endoscopy 21(6):945 -9.* 2007.	Excluded for study relevence
Giusti de MM, Sgreccia A, Carmenini E, Morelli S. Infective endocarditis from Enterococcus faecalis complicating colonoscopy in Heyde's syndrome. *Postgraduate Medical Journal* 2004;80 (948):619 -20.	Excluded for population
Gladman MA, Shami SK. Medical mystery: an unusual complication of colonoscopy--the answer.[comment]. *N Engl J Med.* 2007;357:2309-2310.	Excluded for study design
Gonlusen G, Akgun H, Ertan A, Olivero J, Truong LD. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing: clinical patterns and renal biopsy findings. *Archives of Pathology & Laboratory Medicine* 2006;130 (1):101-6.	Excluded for study design
Gupta A. Splenic rupture following colonoscopy: rare in the U.K.? *Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland* 2006;4(6):389.	Excluded for study relevance
Hanson JM, Plusa SM, Bennett MK, Browell DA, Cunliffe WJ. Glutaraldehyde as a possible cause of diarrhoea after sigmoidoscopy. *British Journal of Surgery* 1998;85(10):1385 -7.	Excluded for study relevance
Harnik IG. Pyogenic liver abscess presenting after malignant polypectomy. *Digestive Diseases & Sciences.* 2007;52:3524-3525.	Excluded for study design
Heldwein W, Dollhopf M, Rosch T et al. The Munich Polypectomy Study (MUPS): Prospective Analysis of Complications and Risk Factors in 4000 Colonic Snare Polypectomies. *Endoscopy.* 2005;37:1116-1122.	Excluded for setting
Ho, C., Jacobs, P., Sandha, G., Noorani, H. Z., and Skidmore, B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectiveness. 2006. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA).	Excluded for study relevance
Hookey LC, Depew WT, Vanner S. The safety profile of oral sodium phosphate for colonic cleansing before colonoscopy in adults. *Gastrointest Endosc.* 2002;56:895-902.	Did not report necessary outcomes
Hookey LC, Depew WT, Vanner SJ. Combined low volume polyethylene glycol solution plus stimulant laxatives versus standard volume polyethylene glycol solution: a prospective, randomized study of colon cleansing before colonoscopy. *Canadian Journal of Gastroenterology.* 2006;101-5, 2006.	Excluded for setting
Hookey LC, Vanner S. A review of current issues underlying colon cleansing before colonoscopy. *Canadian Journal of Gastroenterology 21(2):105 -11.* 2007.	Excluded for study relevence
Iqbal CW, Chun YS, Farley DR. Colonoscopic perforations: a retrospective review. *J Gastrointest Surg.* 2005;9:1229-1235.	Excluded for population
Johanson JF, Popp JW, Jr., Cohen LB et al. A randomized, multicenter study comparing the safety and efficacy of sodium phosphate tablets with 2L polyethylene glycol solution plus bisacodyl tablets for colon cleansing. *Am J Gastroenterol.* 2007;102:2238-2246.	Excluded for study design
Johnson C, Mader M, Edwards DM, Vesy T. Splenic rupture following colonoscopy: two cases with CT findings. *Emergency Radiology 13(1):47-9.* 2006.	Excluded for study design

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Josemanders DF, Spillenaar Bilgen EJ, van Sorge AA, Wahab PJ, de Vries RA. Colonic explosion during endoscopic polypectomy: avoidable complication or bad luck? *Endoscopy.* 2006;38:943-944.	Excluded for setting
Karajeh MA, Sanders DS, Hurlstone DP. Colonoscopy in elderly people is a safe procedure with a high diagnostic yield: a prospective comparative study of 2000 patients. *Endoscopy* 2006;38(3):226 -30.	Excluded for setting
Kastenberg D, Barish C, Burack H et al. Tolerability and patient acceptance of sodium phosphate tablets compared with 4-L PEG solution in colon cleansing: combined results of 2 identically designed, randomized, controlled, parallel group, multicenter phase 3 trials. *Journal of Clinical Gastroenterology 41(1):54 -61.* 2007.	Excluded for study relevance
Katsinelos P, Kountouras J, Paroutoglou G et al. Endoloop-assisted polypectomy for large pedunculated colorectal polyps. *Surgical Endoscopy.* 2006;1257-61, 2006.	Excluded for setting
Kavic SM, Basson MD. Complications of endoscopy. *Am J Surg.* 2001;181:319-332.	Excluded for study quality
Ker TS, Wasserberg N, Beart RW, Jr. Colonoscopic perforation and bleeding of the colon can be treated safely without surgery. *Am Surg.* 2004;70:922-924.	Excluded for setting
Kim HS, Kim TI, Kim WH et al. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. *American Journal of Gastroenterology* 2006;101(6):1333 -41.	Excluded for setting
Kirby E. Colonoscopy procedures at a small rural hospital. *Canadian Journal of Rural Medicine* 2004;9(2):89 -93.	Excluded for population
Ko CW, Sonnenberg A. Comparing risks and benefits of colorectal cancer screening in elderly patients. *Gastroenterology.* 2005;129:1163-1170.	Excluded for study design
Ladas SD, Karamanolis G, Ben-Soussan E. Colonic gas explosion during therapeutic colonoscopy with electrocautery. *World Journal of Gastroenterology.* 2007;13:5295-5298.	Excluded for study design
Lagares-Garcia JA, Kurek S, Collier B et al. Colonoscopy in octogenarians and older patients. *Surgical Endoscopy* 2001;15(3):262 -5.	Excluded for population
Lambert A, Nguyen SQ, Byrn JC, Fishman EW, Shen HY. Small-bowel perforation after colonoscopy. *Gastrointestinal Endoscopy* 2007;65 (2):352 -3.	Excluded for study design
Larsen IK, Grotmol T, Almendingen K, Hoff G. Impact of colorectal cancer screening on future lifestyle choices: a three-year randomized controlled trial. *Clinical Gastroenterology & Hepatology* 2007;5(4):477 -83.	Did not report necessary outcomes
Lee JG, Vigil H, Leung JW. A randomized controlled trial of total colonic decompression after colonoscopy to improve patient comfort. *Am J Gastroenterol.* 2001;96:95-100.	Excluded for setting
Leslie K, Tay T, Neo E. Intravenous fluid to prevent hypotension in patients undergoing elective colonoscopy. *Anaesthesia & Intensive Care* 2006;34(3):316 -21.	Excluded for setting
Levin B, Smith RA, Feldman GE et al. Promoting early detection tests for colorectal carcinoma and adenomatous polyps: a framework for action: the strategic plan of the National Colorectal Cancer Roundtable. *Cancer.* 2002;95:1618-1628.	Excluded for study relevance
Lo AY, Beaton HL. Selective management of colonoscopic perforations. *J Am Coll Surg.* 1994;179:333-337.	Excluded for setting
Luchtefeld MA, Kim DG. Colonoscopy in the office setting is safe, and financially sound ... for now. *Diseases of the Colon & Rectum* 2006;49 (3):377 -81 ; discussion 381 -2.	Excluded for study quality
Luebke T, Baldus SE, Holscher AH, Monig SP. Splenic rupture: an unusual complication of colonoscopy: case report and review of the literature. *Surgical Laparoscopy , Endoscopy & Percutaneous Techniques* 2006;16(5):351 -4.	Excluded for study design

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Luning TH, Keemers-Gels ME, Barendregt WB, Tan AC, Rosman C. Colonoscopic perforations: a review of 30,366 patients. *Surg Endosc.* 2007;21(6):994-7.	Excluded for setting
Macrae FA, Tan KG, Williams CB. Towards safer colonoscopy: a report on the complications of 5000 diagnostic or therapeutic colonoscopies. *Gut.* 1983;24:376-383.	Excluded for setting
Marin Gabriel JC, Rodriguez MS, de la Cruz BJ et al. Electrolytic disturbances and colonoscopy: bowel lavage solutions, age and procedure. *Revista Espanola de Enfermedades Digestivas* 2003;95 (12):863 -75 .	Excluded for setting
Marriott D, Stark D, Harkness J. Veillonella parvula discitis and secondary bacteremia: a rare infection complicating endoscopy and colonoscopy?. [Review] [4 refs]. *Journal of Clinical Microbiology 45(2):672 -4.* 2007.	Excluded for study design
Marwan K, Farmer KC, Varley C, Chapple KS. Pneumothorax, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema following diagnostic colonoscopy. *Annals of the Royal College of Surgeons of England 89(5):W20 -1.* 2007.	Excluded for study design
Mathus-Vliegen EM, Kemble UM. A prospective randomized blinded comparison of sodium phosphate and polyethylene glycol-electrolyte solution for safe bowel cleansing. *Alimentary Pharmacology & Therapeutics.* 2006;23:543-552.	Excluded for population
Maule WF. Screening for colorectal cancer by nurse endoscopists. *N Engl J Med.* 1994;330:183-187.	Excluded for setting
McCallion K, Mitchell RM, Wilson RH et al. Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening. *Gut* 2001;48(4):522-5.	Excluded for study design
Miles A, Wardle J, Atkin W. Receiving a screen-detected diagnosis of cancer: the experience of participants in the UK flexible sigmoidoscopy trial. *Psychooncology.* 2003;12:784-802.	Excluded for study relevance
Miles A, Wardle J. Adverse psychological outcomes in colorectal cancer screening: does health anxiety play a role? *Behav Res Ther.* 2006;44:1117-1127.	Excluded for setting
Misra T, Lalor E, Fedorak RN. Endoscopic perforation rates at a Canadian university teaching hospital. *Canadian Journal of Gastroenterology* 2004;18(4):221 -6.	Excluded for setting
Mitchell RM, McCallion K, Gardiner K, Collins J, Watson P. Colonoscopy has a high diagnostic yield and low complication rate in older patients. *Age & Ageing* 2002;31(4):323 -5.	Excluded for population
Nagler J, Poppers D, Turetz M. Severe hyponatremia and seizure following a polyethylene glycol-based bowel preparation for colonoscopy. *Journal of Clinical Gastroenterology* 2006;40(6):558 -9.	Excluded for study design
Nelson D. Colonoscopy and polypectomy. *Hematology - Oncology Clinics of North America* 2002;16(4):867 -74 .	Excluded for study design
Nelson RL, Abcarian H, Prasad ML. Iatrogenic perforation of the colon and rectum. *Dis Colon Rectum.* 1982;25:305-308.	Excluded for setting
Nivatvongs S. Complications in colonoscopic polypectomy: lessons to learn from an experience with 1576 polyps. *Am Surg.* 1988;54:61-63.	Excluded for setting
Palitz AM, Selby JV, Grossman S et al. The Colon Cancer Prevention Program (CoCaP): rationale, implementation, and preliminary results. *HMO Pract.* 1997;11:5-12.	Did not report necessary outcomes
Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Noninvasive colorectal cancer screening. *Journal of Medical Screening* 2002;9(1):7-10.	Excluded for study relevance

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Parra-Blanco A, Kaminaga N, Kojima T, Endo Y, Tajiri A, Fujita R. Colonoscopic polypectomy with cutting current: is it safe? *Gastrointest Endosc.* 2000;51:676-681.	Excluded for setting
Pearl JP, McNally MP, Elster EA, DeNobile JW. Benign pneumoperitoneum after colonoscopy: a prospective pilot study. *Mil Med.* 2006;171:648-649.	Excluded for study relevance
Perez RF, Gonzalez CP, Legaz Huidobro ML et al. Endoscopic resection of large colorectal polyps. *Revista Espanola de Enfermedades Digestivas* 2004;96(1):36-47.	Excluded for setting
Pfefferkorn U, Hamel CT, Viehl CT, Marti WR, Oertli D. Haemorrhagic shock caused by splenic rupture following routine colonoscopy. *International Journal of Colorectal Disease 22(5):559 -60.* 2007.	Excluded for study design
Qadeer MA, Vargo JJ, Khandwala F, Lopez R, Zuccaro G. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. *Clin Gastroenterol Hepatol.* 2005;3:1049-1056.	Excluded for study relevance
Rainis T, Keren D, Goldstein O, Stermer E, Lavy A. Diagnostic yield and safety of colonoscopy in Israeli patients in an open access referral system. *Journal of Clinical Gastroenterology* 2007;41(4):394 -9.	Excluded for population
Rasmussen M, Kronborg O. Upper gastrointestinal cancer in a population based screening program with fecal occult blood test for colorectal cancer summary for patients in. *Scand J Gastroenterol.* 2002;37:25.	Did not report necessary outcomes
Regula J, Rupinski M, Kraszewska E et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *New England Journal of Medicine* 2006;355(18):1863 -72.	Excluded for study quality
Rerknimitr R. Sorbitol can be the cause of colonic explosion.[comment]. *Endoscopy 39(3):257 .* 2007.	Excluded for study design
Rex DK, Schwartz H, Goldstein M et al. Safety and colon-cleansing efficacy of a new residue-free formulation of sodium phosphate tablets. *American Journal of Gastroenterology* 2006;101(11):2594 -604.	Excluded for setting
Ristikankare M, Hartikainen J, Heikkinen M, Janatuinen E, Julkunen R. The effects of gender and age on the colonoscopic examination. *Journal of Clinical Gastroenterology* 2001;32(1):69 -75.	Excluded for population
Ristikankare M, Julkunen R, Mattila M et al. Conscious sedation and cardiorespiratory safety during colonoscopy. *Gastrointest Endosc.* 2000;52:48-54.	Excluded for setting
Rollino C, Tomasini C, Di PR et al. Cholesterol embolism after colonoscopy: a case report. *Gastrointest Endosc.* 2006;63:730-732.	Excluded for population
Rosen L, Bub DS, Reed JF, III, Nastasee SA. Hemorrhage following colonoscopic polypectomy. *Dis Colon Rectum.* 1993;36:1126-1131.	Excluded for setting
Sanaka MR, Super DM, Mullen KD, Ferguson DR, McCullough AJ. Use of tegaserod along with polyethylene glycol electrolyte solution for colonoscopy bowel preparation: a prospective, randomized, double-blind, placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2006;23(5):669 -74.	Excluded for setting
Schoenfeld PS, Cash B, Kita J, Piorkowski M, Cruess D, Ransohoff D. Effectiveness and patient satisfaction with screening flexible sigmoidoscopy performed by registered nurses. *Gastrointest Endosc.* 1999;49:158-162.	Excluded for setting
Shah P. Splenic rupture as complication of colonoscopy. *Indian J Gastroenterol.* 2007;26:150-Jun.	Excluded for study design
Shah PR, Raman S, Haray PN. Splenic rupture following colonoscopy: rare in the UK? *Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland* 2005;3(4):293 -5.	Excluded for study design

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Shah SG, Brooker JC, Thapar C, Williams CB, Saunders BP. Patient pain during colonoscopy: an analysis using real-time magnetic endoscope imaging. *Endoscopy* 2002;34(6):435 -40.	Excluded for setting
Shah SG, Brooker JC, Williams CB, Thapar C, Saunders BP. Effect of magnetic endoscope imaging on colonoscopy performance: a randomised controlled trial. *Lancet.* 2000;356:1718-1722.	Excluded for setting
Shah SG, Saunders BP, Brooker JC, Williams CB. Magnetic imaging of colonoscopy: an audit of looping, accuracy and ancillary maneuvers. *Gastrointest Endosc.* 2000;52:1-8.	Excluded for setting
Shapero TF, Alexander PE, Hoover J, Burgis E, Schabas R. Colorectal cancer screening: video-reviewed flexible sigmoidoscopy by nurse endoscopists--a Canadian community-based perspective. *Can J Gastroenterol.* 2001;15:441-445.	Excluded for setting
Sica DA, Carl D, Zfass AM. Acute phosphate nephropathy--an emerging issue. *Am J Gastroenterol.* 2007;102:1844-1847.	Excluded for study design
Smith RR, Ragput A. Mucosal tears on endoscopic insufflation resulting in perforation: an interesting presentation of collagenous colitis. *J Am Coll Surg.* 2007;205:725.	Excluded for population
Srivastava V, Pink J, Swarnkar K, Feroz A, Stephenson BM. Colonoscopically induced appendicitis. *Colorectal Dis.* 2004;6:124-125.	Excluded for study design
Sumanac K, Zealley I, Fox BM et al. Minimizing postcolonoscopy abdominal pain by using CO(2) insufflation: a prospective, randomized, double blind, controlled trial evaluating a new commercially available CO(2) delivery system.[see comment]. *Gastrointestinal Endoscopy* 2002;56 (2):190 -4.	Did not report necessary outcomes
Takahashi Y, Tanaka H, Kinjo M, Sakumoto K. Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. *Diseases of the Colon & Rectum 48* 2005;(6):1295 -300.	Excluded for setting
Tan JJ, Tjandra JJ. Which is the optimal bowel preparation for colonoscopy - a meta-analysis. *Colorectal Disease* 2006;8(4):247 -5*8.*	Excluded for study relevance
Taupin D, Chambers SL, Corbett M, Shadbolt B. Colonoscopic screening for colorectal cancer improves quality of life measures: a population-based screening study. *Health & Quality of Life Outcomes.* 2006;4:82.	Excluded for setting
Taylor SA, Halligan S, O'Donnell C et al. Cardiovascular effects at multi-detector row CT colonography compared with those at conventional endoscopy of the colon. *Radiology.* 2003;229:782-790.	Excluded for population
Thomas-Gibson S, Thapar C, Shah SG, Saunders BP. Colonoscopy at a combined district general hospital and specialist endoscopy unit: lessons from 505 consecutive examinations. *J R Soc Med.* 2002;95:194-197.	Excluded for population
Tiwari A, Melegros L. Colonoscopic perforation. *Br J Hosp Med.* 2007;68:429	Excluded for study design
Tormey WP. Hyponatraemia after colonoscopy. *Lancet.* 2001;357:1621-1622.	Excluded for study design
Tran DQ, Rosen L, Kim R, Riether RD, Stasik JJ, Khubchandani IT. Actual colonoscopy: what are the risks of perforation? *Am Surg.* 2001;67:845-847.	Excluded for setting
Tsoraides SS, Gupta SK, Estes NC. Splenic rupture after colonoscopy: case report and literature review. *J Trauma.* 2007;62:255-257.	Excluded for study design
Tulchinsky H, Madhala-Givon O, Wasserberg N, Lelcuk S, Niv Y. Incidence and management of colonoscopic perforations: 8 years' experience. *World Journal of Gastroenterology* 2006;12(26):4211 -3.	Excluded for setting

Appendix E Table 2. Key question 3A excluded studies.

Reference	Reason for exclusion
Viiala CH, Zimmerman M, Cullen DJ, Hoffman NE. Complication rates of colonoscopy in an Australian teaching hospital environment. *Internal Medicine Journal* 2003;33(8):355 -9.	Excluded for population
Vokurka J. Iatrogenic perforation during an endoscopic examination of the gastrointestinal tract. *Bratislavske Lekarske Listy* 2004;105(10-11):387 -9.	Did not report necessary outcomes
Walter LC, Lewis CL, Barton MB. Screening for colorectal, breast, and cervical cancer in the elderly: a review of the evidence. *American Journal of Medicine* 2005;118(10):1078 -86.	Excluded for study design
Wan J, Zhang ZQ, Zhu C et al. Colonoscopic screening and follow-up for colorectal cancer in the elderly. *World Journal of Gastroenterology.* 2002;8:267-269.	Excluded for study quality
Watanabe K, Oshitani N, Kamata N et al. Efficacy and endoscopic prediction of cytapheresis therapy in patients with refractory and steroid-dependent ulcerative colitis. *Aliment Pharmacol Ther.* 2006;24 Suppl 4:147-152.	Excluded for population
Waye JD, Lewis BS, Yessayan S. Colonoscopy: a prospective report of complications. *J Clin Gastroenterol.* 1992;15:347-351.	Excluded for setting
Webb WA, McDaniel L, Jones L. Experience with 1000 colonoscopic polypectomies. *Ann Surg.* 1985;201:626-632.	Excluded for population
Winkleman BJ, Matthews DE, Wiebke EA. Colorectal cancer screening at a Veterans Affairs hospital. *Am J Surg.* 2003;186:468-471.	Excluded for setting
Yano H, Okada K, Monden T. Adhesion ileus caused by tattoo	Excluded for study relevence
Yoong KK, Heymann T. Colonoscopy in the very old: why bother? *Postgraduate Medical Journal* 2005;81(953):196 -7.	Excluded for population
Zerey M, Paton BL, Khan PD et al. Colonoscopy in the very elderly: a review of 157 cases. *Surg Endosc.* 2007;21:1806	Excluded for study design
Zubarik R, Fleischer DE, Mastropietro C et al. Prospective analysis of complications 30 days after outpatient colonoscopy. *Gastrointest Endosc.* 1999;50:322-328.	Excluded for setting
Zubarik R, Ganguly E, Benway D, Ferrentino N, Moses P, Vecchio J. Procedure-related abdominal discomfort in patients undergoing colorectal cancer screening: a comparison of colonoscopy and flexible sigmoidoscopy. *American Journal of Gastroenterology* 2002;97(12):3056 -61.	Excluded for setting

Appendix F. Study Details KQ3b Harms of CT colonography

CT colonography. We found five fair quality cohort studies that addressed potential adverse effects of screening CT colonography. (see Appendix F Table 1)

Kim and colleagues reported their findings from a fair quality, prospective cohort of 3120 CT colonographies conducted in a predominantly average risk, asymptomatic population at a US university based medical center.[182] Their cohort was 56 percent women with a mean age of 57 years old. It is unclear the duration of follow-up for adverse events. They found no clinically significant adverse events from CT colonography.

Pickhardt and colleagues presented their findings from a fair quality study of 16 medical centers from five countries participating in the Working Group on Virtual Colonoscopy.[190,228] Their retrospective cohort included 21,923 studies, of which 11,707 were screening CT colonographies for average risk, asymptomatic persons. Each center conducted chart reviews to identify clinically significant adverse events requiring hospitalization, follow-up at each center was variable, generally up to 30 days. They found an overall perforation rate of 0.009 percent (2/21,923), symptomatic perforation rate of 0.0045 percent (1/21,923); however none of the perforations were in the screening subgroup. They also reported on other clinically significant adverse events, which included exacerbation of renal failure in 0.009 percent (2/21,923) persons, and chest pain (without myocardial infarction) in 0.0045 percent (1/21,923) persons.

Sosna and colleagues reported their findings from a fair quality retrospective chart review of all CT colonographies conducted over a 48 month period in 11 imaging centers in Israel.[191] Their cohort included 11,870 studies, for both screening and diagnostic purposes, breakdown by indication is not reported. Their cohort was 42 percent women, ages 38 to 90 years, with an average age of 60 years. They found an overall perforation rate of 0.06 percent (7/11,870), however only one of these perforations was in the screening subgroup. It is unclear how many of these cases were symptomatic, though four of the seven cases required surgical intervention. The perforation rate for those in the screening subgroup cannot be calculated because the breakdown of studies by indication is not reported. It is unclear if they collected additional information on other clinically significant adverse events.

Edwards and colleagues reported their findings from a small, fair quality, prospective cohort of 340 CT colongraphies conducted in an average risk, asymptomatic population in Australia.[189] Their cohort was 49 percent women, ages 50 to 54 and 65 to 69 years old. It is unclear the duration of follow-up for adverse events. They found no clinically significant adverse events from CT colonography. They reported 3

syncopal events associated with the magnesium citrate/sodium picosulphate (SPS) bowel preparation which was discontinued and replaced with a polyethylene glycol (PEG)/SPS bowel prep.

Pickhardt and colleagues reported their findings from a fair quality, prospective cohort of 1247 CT colonographies conducted in an average risk, asymptomatic population in three US medical centers.[136,189] Their cohort was 41 percent women, ages 40 to 79 years, with an average age of 58 years old. It is unclear the duration of follow-up for adverse events. They found no clinically significant adverse events from CT colonography.

Radiation exposure. Jensch and colleagues systematically searched PubMed from 1996 to 2004 for studies investigating CT Colonography.[192] They found 36 institutions published 74 studies, and contacted each research institution for their current scan protocol. Twenty-eight of the 36 institutions provided their current protocol, and estimates of effective radiation dose were then calculated with the IMPACT Patient Dosimetry Calculator. In 2004, they found a median dose of 10.2mSv, with a range of radiation doses of 2.4 to 23.4mSv per two positions, both supine and prone. From 1998 to 2004 the range of radiation doses was 1.2mSv to 23.4mSv. The range of radiation doses from 1998 to 2004 did not vary significantly even though use of multi-detector CT scanners (MDCT) increased over time from 17 percent in 1999 to 96 percent of institutions in 2004.

VanGelder and colleagues systematically searched Medline from 1997 to 2001 for English language articles that addressed diagnostic accuracy of CT colonography and supplied the required specifications to calculate effective radiation dose.[193] In addition, scan parameter information was updated by contacting authors and additional investigators who were known to perform research on the diagnostic accuracy of CT colonography who were present at the Second International Symposium on Virtual Colonoscopy in 2000. Effective radiation doses were calculated with the IMPACT patient Dosimetry Calculator. They included the scan protocols from 13 centers that performed research CT colonography in 2002. They found a median dose of 8.8mSv, with a range of radiation doses from approximately four to 18mSv for dual positioning, both supine and prone.

Appendix F Table 1. Evidence table key question 3B.

Reference	Setting/Study Design	Screening test operator characteristics	Patient Characteristics:	Inclusion/ Exclusion Criteria	Procedure
CT Colonography					
Kim 2007[182]	Prospective Cohort Single institution, US recruitment through referrals for screening colonoscopy	5 gastro-radiologists experienced in CTC	**Age, mean:** 57.0 yr **% female:** 56 **% ethnic origin:** NR **SES:** NR **% symptomatic:** 2	**Inclusion:** PCP referral for CRC screening **Exclusions:** polyp surveillance, history of bowel disorder (e.g., inflammatory bowel disease, the polyposis syndrome, HNPCC)	**Total CT Colonoscopies:** 3120
Pickhardt 2006[190] Fair	International (5 countries), 16 medical centers part of the Working Group on Virtual Colonoscopy All CTC conducted Retrospective Cohort	**Operator:** 'experienced' radiologists; direct physician monitoring of CTC in 45.8% of cases **Experience:** at 11/16 center more than 1000 CTC performed	**Age:** NR **% female:** NR **% ethnic origin:** NR **SES:** NR **% symptomatic:** 46.6	**Inclusion:** all patients undergoing CTC from 1997-2005 **Exclusion:** NR, implies no exclusions	**Total CT Colonoscopies:** 21923 Screening (asx): 11707 Diagnostic (sx):10216 **Total incomplete procedures:** NR
Edwards 2004[189] Fair	Australia General risk screening population, randomly selected from voting database Prospective Cohort	**Operator:** 2 MD **Experience:** >120 CTC exams each	**Age (range):** 50-54 and 65-69 **% female:** 49.2 **% ethnic origin:** NR **SES** % high SES: 32.5 % med SES: 33.7 % low SES: 33.7 **% symptomatic:** 0	**Inclusion:** age 50-54; 65-69 **Exclusion:** personal hx of polyps or CRC, first-degree relative with CRC, CRC screening past 5 years, hx of rectal bleeding, change in bowel habit, wt loss, or severe medical illness.	**Total CT Colonoscopies:** 340 **Total incomplete procedures**: NR
Sosna 2006[191] Fair	Israel, 11 outpatient imaging centers All CTC during 48 month period Retrospective Cohort	**Operator:** Staff radiologists, resident radiologists, 6 non-academic centers: non-radiologist physicians	**Age, mean:** 59.9 yr **% female:** 42.4 **% ethnic origin:** NR **SES:** NR **% symptomatic:** NR	**Inclusion:** all patients undergoing CTC from 2001 to 2004 **Exclusion:** NR, implies no exclusions	**Total CT Colonoscopies:** 11870 **Total incomplete procedures:** NR

Appendix F Table 1. Evidence table key question 3B.

Reference	Setting/Study Design	Screening test operator characteristics	Patient Characteristics:	Inclusion/ Exclusion Criteria	Procedure
Pickhardt 2003[136] Fair	Multicenter (3), US Avg. risk screening population, recruitment through referrals for screening colonoscopy Prospective Cohort	**Operator:** 6 Radiologist **Experience:** minimum of 25 CTC read	**Age, mean**: 57.8 yr **% female:** 41.0 **% ethnic origin:** NR **SES:** NR **% symptomatic:** 0	**Inclusion:** 50-79 yr, avgerage risk, or 40+ with a family history of CRC, 2002-2003 **Exclusions:** FOBT positive; iron deficiency anemia; rectal bleeding; unintentional weight loss; previous CTC or barium enema; personal history of adenomatous polyps, CRC, IBD; history of FAP or HNPC; rejection for CTC; medical condition precluding NaP prep; pregnancy	**Total CT Colonoscopies:** 1247 **Total incomplete procedures:** 6/1253 (99.5%)

Appendix F Table 1. Evidence table key question 3B.

Reference	Perforation	Radiation dose	Other adverse effects	Applicability
Kim 2007[182]	**Total Perforations:** 0/3120 (0%) No perforations from 246 (7.9%) followup therapeutic OC	NR	**Total Perforations:** 0/3120 (0%) No other adverse effects from 246 (7.9%) followup therapeutic OC	Fair
Pickhardt 2006[190]	**Total Perforations:** 2/21923 (0.009%) Screening: 0/11707 (0% Diagnostic: 2/10216 (0.02%)	NR	Exacerbated acute renal failure: 2/21,923 (0.009%) Chest pain (not MI): 1/21,923 (0.0045%)	Good
Edwards 2004[189] Fair	**Total Perforations:** NR	<5mSv	Syncope- 3 from mag citrate/SPS bowel prep (abandoned, so no denominator known) No adverse events from PEG/SPS bowel prep Minor events- mild nausea, abdominal pain, flushing/sweating	Good
Sosna 2006[191] Fair	**Total Perforations:** 7/11870 (0.06%) Screening: 1/11870 (0.008%) Diagnostic: 6/11870 (0.05%)	NR	NR	Fair
Pickhardt 2003[136] Fair	**Total Perforations:** NR	NR	Reported no adverse effects	Good

Appendix F Table 2. Key question 3B excluded studies

Reference	Reason for exclusion
Banerjee S, Van Dam J. CT colonography for colon cancer screening. *Gastrointest Endosc.* 2006;63:121-133.	Excluded for study design
Blue Cross Blue Shield Association. CT colonography ('virtual colonoscopy') for colon cancer screening. 2004. Chicago IL: Blue Cross Blue Shield Association (BCBS).	Excluded for study design
Brenner DJ, Georgsson MA. Mass screening with CT colonography: should the radiation exposure be of concern? *Gastroenterology* 2005;129(1):328 -37.	Excluded for study design
Brenner H, Arndt V, Stegmaier C, Ziegler H, Sturmer T. Reduction of clinically manifest colorectal cancer by endoscopic screening: empirical evaluation and comparison of screening at various ages. *European Journal of Cancer Prevention* 2005;14(3):231 -7.	Excluded for study design
Buls N, de MJ, Covens P, Stadnik T. Health screening with CT: prospective assessment of radiation dose and associated detriment. *Jbr-Btr: Organe de la Societe Royale Belge de Radiologie.* 2005;88:12-16.	Excluded for study design
Burling D, Halligan S, Slater A, Noakes MJ, Taylor SA. Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. *Radiology* 2006;239 (2):464 -71.	Excluded for study quality
Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen.* 2003;10:117-122.	Did not report necessary outcomes
Florie J, van Gelder RE, Stoker J. Colonography by computed tomography. *European Journal of Gastroenterology & Hepatology.* 2005;17:809-813.	Excluded for study design
Frush DP, Applegate K. Computed tomography and radiation: understanding the issues. *J Am Coll Radiol.* 2004;1:113-119.	Excluded for study design
Gluecker TM, Johnson CD, Harmsen WS et al. Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences. *Radiology* 2003;227(2):378 -84.	Did not report necessary outcomes
Hur C, Gazelle GS, Hsu EH, Halpern EF, Podolsky DK. The effect of prior colonic imaging on endoscopic productivity: potential impact of computed tomographic colonography. *Clinical Gastroenterology & Hepatology* 2005;3(11):1124 -7.	Excluded for study relevance
Khan KY, Xiong T, McCafferty I et al. Frequency and impact of extracolonic findings detected at computed tomographic colonography in a symptomatic population. *British Journal of Surgery* 2007;94(3):355 -61.	Excluded for study relevance
Limburg PJ, Fletcher JG. Making sense of CT colonography-related complication rates. *Gastroenterology.* 2006;131:2023-2024.	Excluded for study design
Macari M, Bini EJ. CT colonography: where have we been and where are we going? *Radiology* 2005;237(3):819-33.	Excluded for study design
Marin Gabriel JC, Rodriguez MS, de la Cruz BJ et al. Electrolytic disturbances and colonoscopy: bowel lavage solutions, age and procedure. *Revista Espanola de Enfermedades Digestivas* 2003;95(12):863 -75.	Did not include one of the specific screening tests

Appendix F Table 2. Key question 3B excluded studies

Reference	Reason for exclusion
Marshall KG. Population-based fecal occult blood screening for colon cancer: will the benefits outweigh the harm? *CMAJ Canadian Medical Association Journal.* 2000;163:545-546.	Excluded for study design
Nakama H, Kamijo N, Fujimori K, Horiuchi A, Fattah AS, Zhang B. Characteristics of colorectal cancer with false negative result on immunochemical faecal occult blood test. *J Med Screen.* 1996;3:115-118.	Did not report necessary outcomes
Neri E, Caramella D, Vannozzi F, Turini F, Cerri F, Bartolozzi C. Vasovagal reactions in CT colonography. *Abdom Imaging.* 2007;32:552-555.	Excluded population
O'Hare A, Fenlon H. Virtual colonoscopy in the detection of colonic polyps and neoplasms. *Best Practice & Research in Clinical Gastroenterology.* 2006;79-92.	Excluded for study design
Ontario Ministry of Health and Long-Term Care. Computed tomographic colonography (virtual colonoscopy). 2003. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS).	Excluded for study design
Prokop M. Cancer screening with CT: dose controversy. *Eur Radiol.* 2005;15:D55-D61.	Excluded for study design
Sallam BM, Pilch-Kowalczyk A, Gruszczyska K, Baron J, Pugliese F. Diagnostic performance of CT colonography in a population with high prevalence of large bowel disease. *Medical Science Monitor* 2007;13 Suppl 1:105 -10.	Excluded for population
Sosna J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. *AJR Am J Roentgenol.* 2003;181:1593-1598.	Excluded for study design
Sosna J, Sella T, Bar-Ziv J, Libson E. Perforation of the colon and rectum--a newly recognized complication of CT colonography. *Seminars in Ultrasound, CT & MR* 2006;27(2):161 -5.	Excluded for study design
Taylor SA, Halligan S, O'Donnell C et al. Cardiovascular effects at multi-detector row CT colonography compared with those at conventional endoscopy of the colon. *Radiology.* 2003;229:782-790.	Excluded for population
van Gelder RE, Florie J, Stoker J. Colorectal cancer screening and surveillance with CT colonography: current controversies and obstacles. *Abdominal Imaging* 2005;30(1):5-12.	Excluded for study design
Zhang B, Fattah A, Nakama H. Characteristics and survival rate of elderly patients with colorectal cancer detected by immunochemical occult blood screening. *Hepatogastroenterology.* 2000;47:414-418.	Excluded for study relevance

Appendix F Table 3. Selected studies addressing extra-colonic findings on CT colonography

Study, Year (Reference) Study Design	Population, *n* Follow-up	Description of Extracolonic Findings (as Reported in Study)	Work-up of Extracolonic Findings (with Final Disposition at End of Study)
"Average-risk" populations			
Pickhardt et al., 2008 [341] Prospective cohort study	2195 Asymptomatic Follow-up: chart review, up to 18 mo	9.3% (204 of 2195) at least "moderate" or "high" clinical significance	7.2% (157 of 2195) recommended to have additional diagnostic evaluation 6.1% (133 of 2195) had additional diagnostic evaluation 2.5% (55 of 2195) with confirmed diagnosis of an unsuspected condition of at least "moderate" importance 1.0% (22 of 2195) required surgical procedures as follow-up
Kim et al., 2007 [182] Prospective cohort study	3120 98% asymptomatic Follow-up: NR	2.2% (70 of 3120) persons with potentially important finding (C-RADS E4) 8.5% (265 of 3120) persons with probably unimportant finding (C-RADS E3) 47.8% (1490 of 3120) persons with clinically unimportant finding (C-RADS E2)	7.7% (241 of 3120) recommended to have additional diagnostic evaluation 0.3% (8 of 3120) persons with extracolonic malignancy (treatment NR)
Pickhardt et al., 2007 [342] Prospective cohort study	2014 Presumed asymptomatic Follow-up: chart review, unclear duration	Only evaluated extracolonic GI tumors 0.5% (10 of 2014) persons with focal extracolonic GI tumors	0.5% (10 of 2014) had further diagnostic evaluation 0.3% (7 of 2014) required surgical resection 0.05% (1 of 2014) required endoscopic resection All GI tumors found to be benign
Chin et al., 2005 [235] Prospective cohort study	432 Asymptomatic Follow-up: through general practitioner, 2 y	27.3% (118 of 432) persons with any extracolonic findings 7.4% (32 of 432) persons with clinically relevant extracolonic findings	7.4% (32 of 432) required further diagnostic evaluation: 1.8% (8 of 432) cancer or aneurysms 5.5% (24 of 432) benign lesions 1.4% (6 of 432) ongoing follow-up at 2 y, none required treatment at 2 y
Gluecker et al., 2003 [343] Prospective cohort study	681 Asymptomatic Follow-up: chart review, at least 12 mo	69% (469 of 681) persons with any extracolonic finding 10% (71 of 681) persons with findings of "high" clinical importance 27% (183 of 681) persons with findings of "moderate" clinical importance	Total 94 follow-up diagnostic procedures 15 follow-up diagnostic procedures in 183 persons with "moderate" findings 1% (9 of 681) needed treatment
Pickhardt et al., 2003 [136] Prospective cohort study	1245 Asymptomatic Follow-up: NR	4.5% (56 of 1245) persons with findings of "high" clinical importance >13% (169 of 1245) persons with findings of "moderate" clinical importance	0.4% (5 of 1245) extracolonic malignancy (treatment NR)
Asymptomatic surveillance populations			
Ginnerup Pederson et al., 2003 [344] Prospective cohort study	75 Asymptomatic, undergoing surveillance Follow-up: chart review, 6 mo	65% (49 of 75) persons with any extracolonic finding 12% (9 of 75) persons with extracolonic findings warranting additional workup	11% (8 of 75) had further diagnostic evaluation 3% (2 of 75) had surgery because of findings or complications of workup
Hara et al., 2000 [345] Prospective cohort study	264 Asymptomatic but 162 undergoing surveillance Follow-up: chart review, 7–22 mo	41% (109 of 264) with any extracolonic findings 11% (30 of 264) persons with extracolonic findings of "high" clinical importance 17% (46 of 264) persons with extracolonic findings of "moderate" clinical importance	6.8% (18 of 264) had further diagnostic evaluation 1.9% (5 of 264) had surgery because of malignant or nonmalignant findings 1.5% (4 of 264) required ongoing follow-up

*C-RADS = Colonography Reporting and Data System; GI = gastrointestinal; NR = not reported.

Appendix G. Colorectal cancer screening studies awaiting assessment

Study/Trial Name	Country	Main Study Question(s)	Study Design	Population Addressed	Status
Flexible Sigmoidoscopy					
SCORE- Italian Sig. Screening (parallel to UK Flex Sig study)	Italy	Estimate the impact of this strategy on CRC incidence and mortality and the duration of the protective effect.	Multicenter RCT	Ages 55-64 Random sample drawn from NHS registry, population based screening population	Baseline findings published. Final results not published as of 3/2008
PLCO Cancer Screening Trial	US	Determine if screening with flexible sigmoidoscopy q5 years can reduce mortality from CRC.	Multicenter RCT	Ages 55-74, screening population	Enrollment closed 2001, screening until 2006. Additional follow-up for 10 yrs. Final results not published as of 3/2008
UK/MRC/NHS R&D 'once only' flexible sigmoidoscopy UK Flexible Sigmoidoscopy Screening Trial (UKFSST)	UK	Determine if single flexible sigmoidoscopy screening offered at around age 60 can lower the incidence and mortality of CRC.	Multicenter RCT, with longterm registry followup	Ages 55-64, screening population	Flexible sigmoidoscopy completed in 1999 Final results not published as of 3/2008
Norwegian CRC Prevention Trial (NORCCAPS)	Norway	Determine if screening with flexible sigmoidoscopy or flexible sigmoidoscopy and FOBT can reduce mortality and morbidity of CRC.	RCT	Ages 50-64 Population based screen population	Completed (1999-2001 w/ 5 yr follow-up), results from the 5 year followup expected in 2007 Final results not published as of 3/2008
Colonoscopy studies					
Colonoscopy or FOBT in Screening Healthy Participants for Colorectal Cancer #NCT00102011	US	Determine how well colonoscopy works compared to FOBT in screening health participants for colorectal cancer.	Multicenter RCT	Ages 50-69, average risk	Currently recruiting patients No new publications as of 3/2008
National Polyp Study	US	Assess surveillance strategies in patients after removal of newly diagnosed adenomas.	Multicenter RCT	Persons with removal of one or more adenomas	Completed No new publications as of 3/2008
Japan Polyp Study	Japan	Evaluate the follow-up surveillance strategies in patients who have undergone colonoscopies for the control of colorectal cancer (removal of polyps by high resolution chromoendooscopy).	Multicenter RCT	Ages 40-69, previously average risk prior to initial colonoscopies	Began 2000, assumed to be ongoing No new publications as of 3/2008

Study/Trial Name	Country	Main Study Question(s)	Study Design	Population Addressed	Status
A Follow-up Colonoscopy Examination in Patients who had Previously Undergone Screening Colonoscopy	China	Determine the prevalence of colonic neoplasm in patients who had previously undergone screening colonoscopy; and to determine the optimal time interval for re-screening in average risk individuals.	Prospective cohort	Ages 50-70, previously asymptomatic prior to initial colonoscopy; participants from prior screening colonoscopy trials [Sung Gastroenterology 2003; Leung, JG 2004]	Ongoing No new publications as of 3/2008
Pooling project on followup colonoscopies Primary author: Elena Martinez	US (assumed)	Assess followup lesions in surveillance colonoscopies.	8 Pooled prospective (assumed) cohorts	Unknown	Manuscript is currently in submission
Complications of colonoscopy from CORI	US	Assess 30d complications of colonoscopy using CORI dataset	Prospective (assumed) cohort	Unknown	Manuscript is currently in submission
Adverse events following routine colonoscopy in the Medicare population	US	Determine rates of adverse events following routine colonoscopy in a population based cohort of Medicare beneficiaries	Case-control analyses	Random sample of Medicare beneficiaries at average risk for colorectal cancer	Abstract presented No new publications as of 3/2008
Fecal Tests					
Screening tests in Detecting Colorectal Cancer Study PI: David Ahlquist	US	Compare the performance characteristics (sensitivity, specificity, and predictive values) of fecal occult blood (FOB) testing and multitarget DNA-based assay panel (MTAP) testing applied to stools and plasma in identifying colorectal cancer. Compare the detection rates of colorectal neoplasia using MTAP alone, flexible sigmoidoscopy alone, and combination sigmoidoscopy and FOB testing.	RCT	Average risk for CRC	Ongoing No new publications as of 3/2008
CT Colonography					
National CT Colonography Trial (ACRIN) #NCT00084929	US	Compare the sensitivity of CTC vs colonoscopy for detecting lesions in asymptomatic participants. Also will address interobserver variation, effect of colonic preparations, patient acceptance, and cost.	Multicenter RCT	Age 50 years and older, asymptomatic persons	Ongoing Abstract of initial findings presented, manuscript in submission

Study/Trial Name	Country	Main Study Question(s)	Study Design	Population Addressed	Status
Munich Colorectal Cancer Prevention Trial	Germany	Compare colonoscopy, CTC, flexible sigmoidoscopy, and blood tests such as fecal occult blood test (FOBT) and imHb immunochemical fecal occult blood testing (FIT), and also combinations of blood testing (FOBT, FIT) and sigmoidoscopy, in their detection of neoplastic lesions 6 mm and 10 mm and larger.	Prospective cohort	Age 50 years and older, screening population	Abstract presented No new publications as of 3/2008
Virtual Colonoscopy for Primary Colorectal Screening	US	Determine if CTC screening and surveillance of sub-cm polyps is safe and effective	Prospective case-control	50 yrs and older, screening population	Article in press
Clinical and economic impact of unsuspected extracolonic findings at screening CTC	US	Evaluate frequency and estimated costs of additional diagnostic workup for extracolonic findings detected at CTC screening	Prospective cohort	Asymptomatic adults undergoing CTC screening	Manuscript in submission