Screening for Colorectal Cancer

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McMaster Evidence Review and Synthesis Centre Team:

Donna Fitzpatrick-Lewis, Ali Usman, Rachel Warren,

Meghan Kenny, Maureen Rice, Andy Bayer, Donna Ciliska, Diana Sherifali, Parminder Raina

McMaster University, Hamilton Ontario Canada

Evidence Review Clinical Expert:

Dr. J. Marshall

CTFPHC Working Group:

Maria Bacchus (Chair)

CTFPHC Working Group Members: Rick Birtwhistle, Jim Dickinson, Gabriela Lewin, Harminder Singh (non-voting member), Marcello Tonelli

PHAC Scientific Research Manager:

Lesley Dunfield

PHAC Scientific Officer

Amanda Shane

Abstract

Background: This report was produced for the Canadian Task Force on Preventive Health Care (CTFPHC) to provide guidelines on the screening of adults for colorectal cancer (CRC). The last CTFPHC guideline on this topic was published in 2001.

Purpose: To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.

Data Sources: The key question search was conducted in Medline, Embase and the Cochrane Library from January 2000 to November 2013.

Study Selection: The titles and abstracts of papers considered for the key question and sub-questions were reviewed in duplicate; any article marked for inclusion by either team member went on to full text screening. Full text review was done independently by two people with consensus required for inclusion or exclusion. All studies reporting adverse effects of screening or follow-up tests as a result of screening were included, regardless of design.

Data Abstraction: Review team members extracted data about the population, study design, intervention, analysis and results for outcomes of interest. One team member completed full abstraction, followed by a second team member who verified all extracted data and ratings. We assessed study quality using Cochrane's Risk of Bias tool and the GRADE framework. For the contextual questions, inclusion screening and abstraction were done by one person.

Analysis: Relative risks (RRs), and 95% confidence intervals (CIs) were calculated using random-effects models. Test properties were reported using mean or median and ranges.

Results: Meta-analysis of results of four moderate quality RCTs of screening with Guaiac Fecal Occult Blood Test (gFOBT) on CRC-specific mortality found a RR 0.82 (95%CI, 0.73, 0.92, $I^{2=}$67%), with an Absolute Risk Reduction (ARR) 2,654/million (1,128-4,010 fewer). Screening with gFOBT did not reduce all-cause mortality RR 1.00 (95% CI, 1.00-1.00, $I^{2=}$0%). For late stage CRC, screening with gFOBT reduced late stage CRC by 8% RR 0.92 (95%CI, 0.85-0.99, I^2 =0%).

One moderate quality RCT found that screening with Immunochemical Fecal Occult Blood Test (iFOBT) had a non-significant impact on CRC mortality RR 0.88 (95%CI, 0.72, 1.07). This was a one-time screen conducted in China. There were no data for iFOBT on all-cause mortality or incidence of late stage cancer.

The meta-analysis of primary screening with flexible sigmoidoscopy showed a relative reduction of 28% in CRC specific mortality with a pooled RR of 0.72 (95% CI; 0.65, 0.81, I^2=0%) and an ARR of 1,176 per million (95% CI; 830 to 1,486 fewer) in CRC specific mortality; RR 0.99 (0.97, 1.01, I^2=35%) for all-cause mortality and RR 0.75 (95%CI, 0.66- 0.86, I^2=23%); ARR 1,733/million (1,011, 2,368 fewer) for incidence of late stage cancer. Adverse events associated with FS are minor and major bleeding, infection and in rare cases death.

The overall median sensitivity (55% were for a single screen) for iFOBT was of 81.5% (range 53.3-100%) and a median specificity of 95.0% (range 87.2%-96.9%) with a median PPV 7.35% (range 4.0%-10.8%), a mean NPV 100% (range 99.7%-100%) and NNS 209 (range 41-430). The overall median sensitivity of gFOBT was 47.1% (range 12.9%-75.0%) and a median specificity

of 96.1% (90.1%-98.1%) with a PPV of 7.5 (1.5%-15%), a mean NPV of 99.55% (range 99.5%-99.6%) and the mean NNS 597 (range 239-936).

Limitations: There are no studies of effectiveness of colonoscopy, CT colonography or DNA tests on mortality or incidence of late stage CRC. The single iFOBT trial had only 8 year follow-up. The evidence used in this review could not answer several questions of interest including the optimal ages to begin and end screening, the optimal screening intervals, or if clinical benefits of screening differ for the various screening tests, or by subgroups.

Conclusion Screening for CRC with fecal occult blood testing or flexible sigmoidoscopy are effective screening tools for colorectal cancer. However no conclusions can be drawn regarding the relative effectiveness of colonoscopy as a screening tool, or new tools such as CT colonography or DNA screening on overall mortality or incidence of late stage CRC. Although there is a lack of data on the impact of iFOBT on mortality the test properties indicate that it is both sensitive and specific. It has been suggested that screening could be increased through better education about home-based fecal tests.

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List of Acronyms

AE	Adverse events
ARR	Absolute risk reduction
BE	Barium enema
C	Control group
CRC	Colorectal cancer
CT	Computed tomography
CTFPHC	Canadian Task Force on Preventive Health Care
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
FAP	Familial Adenomatous Polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
FP	False positive
FN	False negative
FS	Flexible sigmoidoscopy
gFOBT	Guaiac fecal occult blood testing
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
I	Intervention group
IBD	Inflammatory Bowel Disorder
iFOBT	Immunochemical fecal occult blood testing
KQ	Key question
NNS	Number needed to screen
NNH	Number needed to harm
NPV	Negative predictive value
PHAC	Public Health Agency of Canada
PPV	Positive predictive value
RCT	Randomized controlled trial
ROB	Risk of bias
RR	Risk ratio
RSR	Relative survival ratios
SIGN	Scottish International Guidelines Network
USPSTF	United States Preventive Services Task Force

Chapter 1: Introduction

Purpose and Background

This report will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to provide guidelines on the screening of adults for colorectal cancer. The last CTFPHC guideline on this topic was published in 2001[1] and recommended screening for asymptomatic adults over 50 years of age with flexible sigmoidoscopy (FS) or fecal occult blood test (FOBT). This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.

Definition

Colorectal cancer (CRC) is a malignant tumor on the walls of the large intestine, including the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. Tumors in the tissues of the small intestine or anus are not considered to be CRC.[2]

Prevalence and Burden of Colorectal Cancer

In 2012, colorectal cancer was the third most common cancer worldwide[3], resulting in 694, 000 deaths.[4] In Canada, colorectal cancer is the third most common cancer in both men and women. In 2013, there was an estimated 23,800 new cases of colorectal cancer (13,200 men and 10, 600 women) and 9,200 deaths in Canada. For men in Canada, colorectal cancer is the second leading cause of death from cancer; for women it is third. Colorectal cancer represents 12% of all cancer deaths in Canada.[5]

Age standardized incidence of colorectal cancer for men in Canada is 60/100,000 and 40/100,000 for women; for mortality it is 23/100,000 for men and 14/100,000 for women. One in 13 Canadian males and one in 15 Canadian females are expected to develop colorectal cancer in their lifetime. One in 29 men and one in 31 women will die from colorectal cancer. Fifty-three percent of newly diagnosed colorectal cases are in adults ≥70 years of age. All provinces have implemented screening programs since 2010 (2007 in some provinces), but screening rates are of the order of 30%.[5]

Risk Factors

Characteristics that may increase risk include older age, family history of colorectal cancer, obesity (BMI ≥30kg/m2), high alcohol consumption (>2 drinks/day for men and >1/day for women),[6-8] Ashkenazi Jewish ethnicity,[6, 7, 9, 10] physical inactivity,[6, 8-10] smoking,[6, 7, 9-11] and low fibre diet.[6-8, 10]

Rationale for Screening and Screening Strategies

There is general acceptance of the importance of screening for colorectal cancer. Screening identifies pre-invasive polyps, neoplasia and adenoma which, if treated, may lead to lower incidence of metastatic disease and death. There are different types and sizes of polys, many of which will never develop into cancer and others which may take years to become cancerous;[12] the number, type, and size of polyps are all factors in progression to cancer.[13] Screening methods used vary from non-invasive fecal occult blood tests to invasive endoscopies. What is still in question is which test is best suited for screening people who are lacking clinical signs or symptoms of colorectal cancer; when should screening begin and end; how often should people be screened; and what are the difference in test properties between the various screening modalities.

Current Clinical Practice

For people who are at average risk of colorectal cancer The Canadian Cancer Society recommends that men and women age 50 and over have a stool test (guaiac-based fecal occult blood test [gFOBT] or fecal immunochemical test [iFOBT]) at least every 2 years.[14] Those who screen positive will have a follow-up procedure that may be a colonoscopy, barium enema or flexible sigmoidoscopy. Current compliance with these recommendations in Canada is quite low with only 32.2% of asymptomatic people aged 50 to 74 having been screened.[15]

Other Guidelines

The US Preventive Services Task Force (USPSTF) 2008 guidelines recommended screening for adults 50 to 70 years of age with FOBT, sigmoidoscopy, or colonoscopy.[16] The 2011 Scottish International Guidelines Network (SIGN) guidelines recommended population screening with gFOBT.[17] Canadian Provincial guidelines vary in the population eligible for screening, the screening test, the cutpoint for iFOBT and the screening interval, although the majority recommends screening using FOBT every 2 years for ages 50 to 74 years.

Chapter 2: Methods

Review Approach

The protocol for this systematic review has been published with PROSPERO 2014: CRD42014009777.
(http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009777#.U_d6IPldVBk)

Analytic Framework and Key Questions

The analytic framework for this prevention focused review is presented in Figure 1.

KEY QUESTIONS

1. What is the effectiveness of each colorectal cancer screening test[i] to reduce colorectal cancer-specific mortality, all-cause mortality, or incidence of late stage colorectal cancer in asymptomatic adults who are not at high risk for colorectal cancer?[ii]
    a. What is the optimal age to start and stop screening and the optimal screening interval of asymptomatic adults not at high risk for colorectal cancer?
    b. What is the evidence that the clinical benefits of screening differ for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancer?[iii]
2. What are the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the colorectal cancer screening tests to detect colorectal cancer?
3. What is the incidence of harms[iv] of screening for colorectal cancer in adults not at high risk for colorectal cancer? What is the evidence that the harms of screening differ for the various screening tests or by subgroups that may influence the underlying risk of colorectal cancer?

CONTEXTUAL QUESTIONS

1. What are the patient preferences and values for screening for colorectal cancer?
2. What is the evidence for a higher burden of disease, a differential treatment response, differential performance, or barriers to implementation of colorectal cancer screening in the Aboriginal population, other ethnic populations, rural or remote populations, women, or the elderly?

[i] Screening tests include colonoscopy, flexible sigmoidoscopy, CT colonography, gFOBT, FIT, fecal DNA testing, and other tests identified in the literature search

[ii] Populations at high risk of colorectal cancer (Table 1) will be excluded, such as those with prior colorectal cancer or polyps, signs/symptoms suggesting underlying colorectal cancer, familial adenomatous polyposis, or hereditary non-polyposis colorectal cancer.

[iii] Characteristics that may increase risk within the population covered by the guideline include older age, obesity, Ashkenazi Jewish ethnicity, high alcohol consumption, physical inactivity, smoking, and low fibre diet

[iv] Complications of the screening test or follow-up test, false positive, false negative, overdiagnosis

3. What risk assessment tools are identified in the literature to assess the risk of colorectal cancer?

4. What are the cost-effectiveness and resource implications of screening for colorectal cancer?

Search Strategy

For the key questions we searched Medline, Embase and Cochrane Central from January 2000 to November 21, 2013 (Appendix 1). The search dates were selected based on the last published CRC guideline by the CTFPHC in 2001. This search was peer reviewed using the peer review of electronic search strategies (PRESS) method.[18] Reference lists of included studies and on topic systematic reviews were checked for possible citations missed by the search. We also did a google search for grey literature for Canadian sources of CRC data. For contextual questions we searched Medline for on topic papers published after 2007.

Study Selection

The titles and abstracts of papers considered for the key question and sub questions were reviewed in duplicate by members of the synthesis team; any article marked for inclusion by either team member went on to full text rating. Full text inclusion was done independently by two people. All disagreements were resolved through discussions rather than relying on a particular level of kappa score to indicate when discussions were no longer necessary. The inclusion results were reviewed by a third person. For papers located in the contextual questions search, title and abstract screening was completed by one person.

Inclusion and Exclusion Criteria

Language

The published results of studies had to be available in either English or French.

Population

The population of interest for this review was asymptomatic adults 18 years and older who were not at high risk of colorectal cancer. Excluded from this review were adults who were at high risk, defined as those with Familial Adenomatous Polyposis (FAP), Hereditary Nonpolyposis Colorectal Cancer (HNPCC), history of Inflammatory Bowel Disorder (IBD), personal history of polyps (any polyp) or colorectal cancer; patients with symptoms suggesting underlying colorectal cancer (such as rectal bleeding or iron deficiency anemia), or those with known genetic mutations associated with increased colorectal cancer risk.

Interventions

Screening with colonoscopy, computed tomography (CT) colonoscopy, guaiac fecal occult blood testing (gFOBT), immunochemical fecal occult blood testing (iFOBT), Flexible Sigmoidoscopy (FS), Barium Enema (BE), Digital Rectal exam (DRE), fecal deoxyribonucleic acid (DNA), and other identified tests. Excluded were case-finding or surveillance tests. Follow-up tests were excluded except for the outcome of harms.

Settings

Settings were limited to primary care or settings to which a primary care physician could refer as in the case of colonoscopy, CT colonoscopy and flexible sigmoidoscopy.

Study Design and Comparison Groups

To answer the questions about the benefits of screening, only randomized controlled trials (RCTs) with comparison groups of no screening or comparison between tests were eligible for inclusion. For the question on test properties, acceptable study designs included RCTs, cohort (with a comparison) and case control studies. Any study design (with or without comparison groups) was considered acceptable to answer the questions about adverse events and the contextual questions.

Outcomes

To answer the question of benefits of screening, the outcomes of interest included CRC mortality, all-cause mortality and incidence of late stage CRC. Late stage CRC has been defined as stage III or IV; or Duke's C or D. The outcome of interest for the harms of screening included complications (bleeding or perforation) of the test or the follow-up test, false positive, false negative, and over-diagnosis. To answer the test properties question the outcome of interest was any stage CRC.

Timeframe

There was no minimum follow-up time necessary for inclusion in our evidence summary.

Contextual Questions

The purpose of the contextual questions was to help the guideline panel decide if there are subgroups of the Canadian population for whom there is a great burden of the disease or for whom there might be reasons that screening does not work well. The CTFPHC was also interested in understanding patient preferences and values regarding screening. As such a targeted search was undertaken and selected articles were incorporated in the evidence review.

Data Abstraction

For each study used to answer any KQ, review team members extracted data about the population, the study design, the intervention, the analysis and the results for outcomes of interest. For each study, one team member completed full abstraction (study characteristics, risk of bias assessment, outcome data) using electronic forms housed in a web-based systematic review software program.[19] A second team member then verified all extracted data and ratings; disagreements were resolved through discussion and/or third party consultation when consensus could not be reached. Prior to performing meta-analyses, tables were produced for each outcome and all data were checked in a third round of verification.

Assessing Risk of Bias

Arriving at a GRADE rating for a body of evidence (see next section) requires a preliminary assessment of the risk of bias or study limitations for the individual studies. All RCTs included to answer the effectiveness of screening question were assessed using the Cochrane Risk of Bias tool.[20] This rating tool covers six domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome reporting; selective outcome reporting; and other risk of bias. Information to determine risk of bias was abstracted from the primary methodology paper for each study and any other relevant published papers. For each study, one team member completed the initial ratings which were then verified by a second person; disagreements were resolved through discussion and/or third party consultation when consensus could not be reached. To assign a high or low risk of bias rating for a particular domain we looked for explicit statements or other clear indications that the relevant methodological procedures were or were not followed. In the absence of such details we assigned unclear ratings to the applicable risk of bias domains. To determine the overall risk of bias rating for an outcome we considered all domains, however when the level of bias between domains was not consistent greater emphasis was placed on randomization, allocation concealment and blinding because those represented most significant sources of introducing bias to a randomized controlled trial and hence could lead to biased estimates of outcome findings and conclusions.[21, 22] Table 1 summarizes the risk of bias ratings applied to the RCTs included in this review.

Assessing Strength or Quality of the Evidence

The strength of the evidence was determined based on the GRADE system of rating the quality of evidence using GRADEPro software.[22, 23] This system of assessing evidence is widely used and is endorsed by over 40 major organizations including the World Health Organization, Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.[21] The GRADE system rates the quality of a body of evidence as high, moderate, low or very low; each of the four levels reflects a different assessment of the likelihood that further research will impact the estimate of effect (i.e., high quality: further research is unlikely to

change confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; very low quality: the estimate of effect is very uncertain).[21]

A GRADE quality rating is based on an assessment of five conditions: (1) risk of bias (limitations in study designs), (2) inconsistency (heterogeneity) in the direction and/or size of the estimates of

effect, (3) indirectness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, (4) imprecision of results (few participants/events/observations, wide confidence intervals), and (5) indications of reporting or publication bias. Grouped RCTs begin with a high quality rating which may be downgraded if there are serious or very serious concerns across the studies related to one or more of the five conditions. For this review, key data were entered into the GRADEPro software along with the quality assessment ratings to produce two analytic products for each outcome and the comparisons of interest: (1) a GRADE Evidence Profile Table and (2) a GRADE Summary of Findings Table (presented in Evidence Sets 1 and 2). There was no assessment of the quality of the evidence for contextual questions.

Data Analysis

To perform meta-analysis for the benefits of CRC screening we utilized the number of events; proportion or percentage data from included RCTs to generate the summary measures of effect in the form of risk ratio (RR) using the DerSimonian and Laird random effects models with inverse variance method.[24] The subgrouping in meta-analysis was based on the type of screening method used such as gFOBT, iFOBT and FS. We found no RCTs that met our inclusion criteria for the benefits of CRC screening using colonoscopy and CT colonography. The Cochrane's Q (α=0.10) and I^2 statistic was employed to quantify the statistical heterogeneity between studies, where $p<0.05$ indicates a high level of statistical heterogeneity between studies.

For benefits of CRC screening (outcomes of colorectal cancer-specific mortality, all-cause mortality and incidence of late stage colorectal cancer) we calculated absolute risk reduction (ARR) and number needed to screen (NNS) for studies which should have a beneficial effect on mortality and incidence of late stage CRC. NNS was calculated using the absolute numbers presented in the GRADE tables. GRADE estimates the absolute number per million using the control group event rate and risk ratio with the 95% confidence interval obtained from the meta-analysis.[22]

For harms of CRC screening and follow-up tests we used the rates / proportions along with 95% confidence intervals across the studies and pooled them using the DerSimonian and Laird random effects models with inverse variance method to generate the summary measures of effect. The binomial confidence interval for each proportion/rate was calculated using "Wilson score interval" method to allow for inclusion of studies reporting zero events in to meta-

analysis.[25] The primary grouping in meta-analyses was based on the type of screening method used such as gFOBT, iFOBT, FS, screening colonoscopy, follow-up colonoscopy and CT colonography. The harms analyses for FS and colonoscopy were further sub grouped depending on base population i.e. whether the reported events were based on number of patients in study or number of colonoscopies performed.

The data for diagnostic test accuracy such as positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and likelihood ratios was pooled descriptively using median

with range approach. The studies were primarily sub-grouped based on screening test type such as gFOBT, iFOBT and FS. The test properties data for iFOBT was further sub grouped based on test type and cut points of 50 ng/ml, 70 to 75 ng/ml and 100 ng/ml. Guaiac FOBT does not have a cut point so there was no subgrouping of these data.

The analyses were performed using Review Manager ver. 5.1 software and STATA ver. 12.[20, 26] The studies not included in the meta-analyses were described narratively.

Chapter 3: Results

Summary of the Literature Search for Key Questions

The search for the key questions located 13,257 unique citations that were screened at title and abstract (Figure 2). Seventy-one systematic reviews were identified by our team. The reference lists of on-topic systematic reviews were also searched; three papers were added to our database as a result.

Summary of the Included Studies

A total of 87 studies were identified to answer the key questions that met the inclusion criteria for this review; nine RCTs for the benefits of screening; 40 studies for test properties; and 46 studies for harms of screening or harms of follow-up tests after screening. (Search Results: Figure 2) The screening tests of interest are colonoscopy, CT colonography, gFOBT, iFOBT, FS, BE, DRE, fecal DNA, and other identified tests.

Results for Key Questions

KQ1: What is the effectiveness of each colorectal screening test to reduce colorectal cancer-specific mortality, all-cause mortality, or incidence of late stage colorectal cancer in asymptomatic adults who are not at high risk for colorectal cancer?

a. What is the optimal age to start and stop screening and the optimal screening interval of asymptomatic adults not at high risk for colorectal cancer?

b. What is the evidence that the clinical benefits of screening differ for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancer?

Mortality – CRC

Nine RCTs were identified to help answer this question. Of these nine, four papers reported results for gFOBT[27-30]; one for iFOBT[31] or FIT and four for FS[32-35]. For characteristics of these included studies please see Table 3: Characteristics of Included Studies. Our search and selection process did not locate any RCTs meeting our inclusion criteria for colonoscopy, CT colonography, BE, DRE or fecal DNA. For the outcomes of CRC mortality the quality of the body of evidence was MODERATE with downgrades on Risk of Bias (RoB) for unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening.Detailed statistical analysis and GRADE evidence profile and summary of findings (SoF) and forest plots for these questions can be found in Evidence Set 1 KQ1.

gFOBT

Four RCTs[27-30] provided the data for the outcome of CRC specific mortality with primary screening of gFOBT. All of the studies included mixed gender population. Two studies included participants with ages ranging from 45 to 75 years, one study included participants ages 50 to 80 years and one study included participants ages 60 to 64 years. The screening arm across all studies received Hemoccult-II. A Swedish study offered two to three rounds of screening with 21 to 24 month intervals (follow-up 9 years).[30] One Danish study offered nine biennial FOBT screens with a follow-up 17 years.[27] One British study offered biennial screening, participants had on average 4-6 screens by the end of the screening period (follow-up 19.5 years).[29] A study conducted in the United States offered annual or biennial screening with follow-up 30 years.[30] The control group across all studies was a no screen group. One study was published in 2004 while the other three studies were published between 2008 and 2013. These four studies have a combined sample of 313,180 (156,737 [I -intervention]; 156,443[C - control]). For colorectal specific mortality, the meta-analysis for screening with gFOBT compared to no screening found RR 0.82 (95%CI, 0.73, 0.92, I^2=67%), with an ARR 2,654/ million (1,128-4,010 fewer). The number needed to screen (NNS) was 377 (95%CI, 249-887). This body of evidence received a GRADE rating of MODERATE quality and was downgraded on Risk of Bias (RoB) for unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening.

iFOBT

Colorectal cancer mortality was the outcome of interest for iFOBT screening in one RCT.[31] The sample included a mixed gender population ages 30 years and older. The screening arm received RPHA-FOBT (FIT) test using single screen method. The control group was no screening. The study was conducted in China and was published in 2003. The length of follow-up was eight years. The sample size was 192,261 (94,423 [I]; 97,838 [C]). The effect of iFOBT on CRC mortality was RR 0.88 (95%CI, 0.72, 1.07, I^2=*NA*); ARR 277/million (631 fewer to 151 more). This single study received a GRADE rating of MODERATE quality and was downgraded on the domain of imprecision.

Flexible Sigmoidoscopy (FS)

Four RCTs[32-35] were analyzed for the outcome of CRC specific mortality with a primary screening of flexible sigmoidoscopy. All studies included a mixed gender population. Three studies included participants with ages ranging from 55 to 64 years and one study included participants with ages 55 to 74 years. The screening arm across all studies received FS. Three studies offered once only screen with FS.[33, 35, 36] One study offered one screening at baseline then one at three or five years.[36] The control group across all studies was defined as a no screening group. One study was conducted in the US, one in the UK, one in Italy and one study in Norway. All studies were published between 2009 and 2013. The length of follow-up across four studies ranged from six years to 11.9 years. These four studies have a combined sample of 413,955

(165,333 [I]; 248,622 [C]). The RR for screening with FS compared to no screen was 0.72 (95%CI, 0.65, 0.81, I^2=0%); the ARR was 1,176/million (830-1,486 fewer). The NNS for the outcome of CRC mortality was 850 (95%CI, 673-1205). This body of evidence received a GRADE rating of MODERATE quality and has been downgraded on ROB due to unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening.

Mortality – All-Cause

Four RCTs reported on the outcomes of all-cause mortality with primary screening tests of gFOBT[27-30] and four RCTs with a primary screening test of FS.[32-35] This body of evidence received a GRADE rating of LOW quality and was downgraded on ROB (unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening) and imprecision.There were no other studies for tests of interest which met the inclusion criteria for this review which could be included for the outcome of all-cause mortality.

gFOBT

Four RCTs[27-30] provided data for the outcome of all-cause mortality. All of the studies included mixed gender population. Two studies included participants aged 45 to 75 years, one study included participants aged 50 to 80 years and one study included participants aged 60 to 64 years. The screening arm across all studies received guaiac Hemoccult-II. One study offered biennial FOBT screening, one study offered two to three rounds of screening with 21 to 24 month interval, one study offered seven rounds of screening and one study offered annual screening. The control group across all studies was defined as no screening group. One study was conducted in the UK, one in Sweden, one in Denmark and one study in the US. One study was published in 2004 while the other three studies were published between 2008 and 2013. The length of follow-up across four studies ranged from nine years to 30 years. These four studies have a combined sample of 313,180 (156,737 [I]; 156,443 [C]). For the outcome of all-cause mortality, screening with gFOBT compared to no screen had a RR of 1.00 (95%CI, 1.00, 1.01, I^2=0%). This body of evidence received a GRADE rating of LOW quality and was downgraded on ROB (unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening) and imprecision.

Flexible Sigmoidoscopy (FS)

For the outcome of all-cause mortality with a primary screening of FS four RCTs[32-35] were analyzed. All studies included mixed gender population while three studies included participants with an age range from 55 to 64 years and one study with ages 55 to 74 years. The screening arm across all studies received FS. Three studies offered once only screen with FS and one study offered one screening at baseline and one at three or five years. All studies had a no screen control group. The studies were conducted in the US, the UK, Italy and Norway and published between

2009 and 2013. The length of follow-up across studies ranged from six years to 11.9 years. The combined sample was 413,955 (165,333 (I); 248,622 [C]). Screening with FS compared to no screen had a pooled effect of RR 0.99 (95%CI, 0.97, 1.01, I^2=35%). This body of evidence received a GRADE rating of LOW quality and was downgraded on ROB (unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening) and imprecision.

Incidence of Late Stage CRC

Five RCTs[28, 29, 33-35] provided data on incidence of late stage CRC; two papers reported incidence for gFOBT[28, 29] and three for FS.[33-35] This body of evidence received a GRADE rating of MODERATE quality and was downgraded on ROB due to unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening. There were no other studies for tests of interest which met the inclusion criteria for this review which could be included for the outcome of incidence of late stage CRC (stage III or IV; Duke C or D).

gFOBT

Two RCTs provided data for the outcome of incidence of late stage CRC.[28, 37] These mixed gender studies included in one study participants aged 45 to 74 years and the other study aged 60 to 64 years. The screening arm across both studies received guaiac Hemoccult-II. One study offered biennial FOBT screen and one study offered two to three rounds of screening with 21 to 24 months interval. The control group across both studies was defined as no screening group. One study was conducted in the UK and the other in Sweden. The studies were published between 2008 and 2013. The length of follow-up across both studies ranged from 9 years to 19.5 years. These studies have a combined sample of 220,283 (110,200 [I]; 110,083[C]). Screening with gFOBT compared to no screen had a pooled effect of RR 0.92 (95%CI, 0.85, 0.99, I^2=0%); the ARR was 1,141/million (198 fewer to 2,017 fewer). The NNS is 876 (95%CI, 496-5051) for the outcome of incidence of late stage CRC. This body of evidence received a GRADE rating of MODERATE quality and was downgraded on ROB due to unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening.

Flexible Sigmoidoscopy (FS)

Three RCTs[33-35] provided data for this outcome. All studies included a mixed gender population. Two studies included participants with age ranging from 55 to 64 years and one study with age ranging from 55 to 74 years. Two studies offered once only screen with FS and one study offered one screening at baseline and one at three or five years. All studies had a no screen control group. One study was conducted in the US, one in Italy and one study in Norway. All studies were published between 2009 and 2013. The length of follow-up across four studies ranged from seven years to 11.9 years. These studies have a combined sample of 243,917 (108,234 [I]; 135,683 [C]). There was a reduction in late stage CRC using screening with FS compared to no

screen RR 0.75 (95%CI, 0.66, 0.86, I^2=23%); ARR 1,733/million (1,011-2,368 fewer, NNS = 577 (95%CI, 422-989)). This body of evidence received a GRADE rating of MODERATE quality and was downgraded on ROB (unclear allocation concealment, incomplete reporting and other bias such as information on funding sources or possible control group contamination through opportunistic screening).

KQ1a: What is the optimal age to start and stop screening and the optimal screening interval of asymptomatic adults not at high risk for colorectal cancer?

For the screening method of gFOBT two included studies separated their results by ages. Scholefield et al.[31] provided binary analysis of their sample by those under or over 60. There is benefit for those over 60 Mortality Rate (MR) 0.87 (95%CI, 0.79, 0.97). The sample included people 45-74 but the mean age of the sample was not reported. Shaukat et al.[30] analyzed data for 3 age groupings with a 30 year follow-up, those under 60, 60-69 and those over 70. The benefit of screening was in the age group of 60-69 RR 0.63 (95%CI, 0.49, 0.79). The mean age of this sample at randomization was 62.3 SD 7.8. One study offered annual or biennial screening and provided age and interval data.[30] These data showed no impact on mortality for people under the age of 60 with either annual (a) RR 0.82 (95%CI, 0.59, 1.14) or biennial (b) RR 0.90 (95%CI, 0.65-1.24) screening. For ages 60-69 both intervals showed a benefit of screening (a) RR 0.58 (95%CI, 0.43, 0.78); (b) RR 0.67 (95%CI, 0.51, 0.89) and for those 70 plus screening was most effective on an annual basis RR 0.47 (95%CI, 0.26, 0.84).

One paper provide data by age for flexible sigmoidoscopy.[34] Schoen et al. showed that FS was an effective screening method for CRC mortality for age group 65-74 but not for 55-64. In participants aged 55-64 the RR 0.84 (95%CI, 0.67, 1.06) and aged 65-74 RR 0.65 (95%CI, 0.52, 0.82). It is important to note that evidence for age group 55-64 is limited by lack of statistical power to detect an effect as shown in post-hoc power analysis (see Evidence Set 1 for Summary). The single RCT on screening with iFOBT[31] did not provide age analysis. The RCT on iFOBT offered one time only screening and none of the FS studies provided interval data.

KQ1b: What is the evidence that the clinical benefits of screening differ for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancer?

There was insufficient data in our included studies to be able to answer this question.

KQ2: What is the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the colorectal cancer screening tests to detect colorectal cancer?

Tests of interest in this key question were tests that showed a positive impact on at least one of the outcomes in key question 1. Therefore test properties were extracted for iFOBT, gFOBT and

FS. Median with range are provided for each test and for iFOBT for the most common cutpoints used in clinical practice. There are a total of 40 studies (38 cohorts and two case controls) included in this section.[28, 38-76] For a more detailed overview of the data on these tests see Evidence Set 2 KQ2, Findings Summary Tables 5.1 and 5.2. We assessed these papers with QUADAS II (Table 2)[77] which demonstrated that the studies of interest had unclear or high risk of bias across domains with the exception of the domain of the reference standard. The reference standard was primarily standard colonoscopy with only one study using FS as the reference standard. Overall these studies provide low quality evidence for this question.

These data were not pooled, rather result are reported in median with range. The overall sensitivity for iFOBT was 81.5% (53.3%-100%) and a specificity of 95.0% (87.2%-96.9%) with median PPV 7.35% (4.0%-10.8%), NPV 100% (99.7%-100%) and NNS 209 (41-430). The overall sensitivity of gFOBT is 47.1% (12.9%-75.0%) and median specificity of 96.1% (90.1%-98.1%) with PPV of 7.5 (1.5%-15%), NPV of 99.55% (99.5%-99.6%) and NNS 597 (239-936). The sensitivity of Hemoccult or Hemoccult II gFOBT is 38.1% (12.9%-61.0%) and specificity of 96.4% (92.4%-98.1%) with PPV of 7.4 (4.5%-15%), NPV of 99.5% (99.5%-99.6%) and NNS 597 (239-936). For Hemoccult Sensa the sensitivity is 64.3% (47.1%-75.0%) and specificity of 90.1% (89.3%- 90.8%), PPV of 5.3 (1.5%-9.1%), NPV and NNS were not reported.

The search did not locate any papers which reported on the specific test properties with the outcome of CRC for FS.

KQ3: What are the harms of screening for colorectal cancer in adults not at high risk for colorectal cancer? What is the evidence that the harms of screening differ for the various screening tests or by subgroups that may influence the underlying risk of colorectal cancer?

The harms of interest for this review include: death, perforation, bleeding (with or without hospitalization), false-positive, false-negative and over-diagnosis. Our search located 46 studies that provided evidence of harms from CRC screening or from the subsequent testing. Where possible, data are presented for the harms by number of tests (e.g. colonoscopy) and/or number of patients. These uncontrolled observational studies were rated as VERY LOW quality in GRADE. Summary statistics are available in Evidence Set 3 KQ3 Findings Summary Tables 6.1-6.7.

Death

Screening Colonoscopy Death as a result of colonoscopy screening was reported in one study by number of colonoscopies[78]; total events were 12 deaths for 38,472 colonoscopies 0.31/1,000 (95%CI, 0.18-0.55). For the two studies reporting this outcome by number of patients, total events were 2/70,828, resulting in a proportion of 0.02/1,000 (95%CI, 0.0-0.06).[79, 80]

Follow-up Colonoscopy Death as a result of a follow-up colonoscopy was reported in three uncontrolled studies by number of colonoscopy[47, 78, 81]. In these papers the total event rate was

3/22,674 with a proportion of 0.03/1,000 (95%CI, 0.0-0.19). Two papers reported this outcome by number of patients[36, 82]. The total events were 7/19,569 with a proportion of 0.35/1,000 (95%CI, 0.06-0.64).

Flexible Sigmoidoscopy (FS) Death resulting from screening with FS was reported in one study by the number of patients. There were 6 deaths in 40,332 patients 0.15/1,000 (95%CI, 0.07-0.32).

Perforation

Screening Colonoscopy Eight uncontrolled observational studies reported perforation data for screening colonoscopy; three of those by number of colonoscopies[78, 83, 84]. There were a total of 16 events for 39,235 colonoscopies 0.41/1,000 (95%CI 0.19-0.62). For the five papers that reported by number of patients, there were 45 events in 84,850 patients 0.53/1,000 (95%CI 0.37-0.69).[79, 80, 85-87]

Follow-up Colonoscopy Fifteen uncontrolled observational studies reported perforation data for follow-up colonoscopy following an iFOBT, gFOBT or FS. For the five papers that reported by the number of colonoscopies there were 41 perforations for 37,035 colonoscopies with the proportion of perforations being 1.04/1,000 (95%CI, 0.69-1.39).[34, 56, 78, 81, 88] For the 10 papers that reported proportion of perforation by number of patients, there were 31 events for 51,741 patients with the proportion of 0.61/1,000 (95%CI, 0.10-1.11).[36, 41, 55, 62, 65, 71, 82, 89-91]

Flexible Sigmoidoscopy (FS) Seven uncontrolled observational studies reported perforation for screening with FS. For the three papers that reported number of sigmoidoscopies, there were three perforations for 116,680 sigmoidoscopies, with the proportion of perforations being 0.03/1,000 (95%CI, 0.0-0.07).[34, 92, 93] Four papers reported perforations by number of patients[36, 90, 94, 95]; this event rate was 4 for 277,421 patients with the proportion 0.01/1,000 (95%CI, 0.0-0.03).

Screening CT colonography One paper[96] reported no perforations for screening with CT colonography with 0 events for 11,707 tests 0.0/1,000 (95%CI, 0.0- 0.33).

Follow-up CT colonography One paper[96] reported rates of perforation by number of patients. Two of 10,216 patients receiving a follow-up CTC test had a perforation representing a proportion of 0.02/1,000 (95%CI, 0.05-0.71).

Bleeding Requiring hospitalization

Screening Colonoscopy One uncontrolled study reported no cases of bleeding that resulted in hospitalization by number of colonoscopies (0/324 events; proportion of 0.0/1,000 (95%CI, 0.0-11.72).[83] Reported by number of patients, bleeding that required hospitalization occurred in 94 of 79,486 patients 1.08/1,000 (0.85-1.32).[79, 80, 86]

Follow-up Colonoscopy Three uncontrolled observational studies reported bleeding requiring hospitalization by number of colonoscopies[56, 81, 88]. The total events were 68/14,379 4.73/1,000 (95%CI, 3.59-5.87). Seven papers reported this outcome by number of patients[36, 53, 65, 82, 90, 91, 97] finding 28 bleeds requiring hospitalization for 25,178 patients 1.11/1,000 (95%CI, 0.62-1.57).

Flexible Sigmoidoscopy (FS) Major bleeding requiring hospitalization from primary screening with FS was reported by number of patients in two papers. The total events were 14/149,866, 0.00/1,000 (95%CI, 0.0.04-0.15).[36, 95]

Bleeding (not requiring hospitalization)

Screening Colonoscopy One uncontrolled observational study reported minor bleeding as a result of screening with colonoscopy by number of colonoscopies.[78] The event rate per test was 103/38,472 with a proportion of 2.68/1,000 (95%CI, 2.21-3.25). Four papers reported minor bleeding by number of patients.[80, 85, 87, 98] Nine incidences of minor bleeding were reported in 8,974 screening colonoscopies, representing a proportion of 0.84/1,000 (95%CI, 0.0-1.98).

Follow-up Colonoscopy Two uncontrolled observation studies reported on minor bleeding after a follow-up colonoscopy by number of colonoscopies.[78, 81] The event rate per test was 47/15,261 with a proportion of 3.02/1,000 (95%CI, 2.07-3.98). For the eight papers that reported with number of patients, the total events were 67 minor bleeds in 25,188 patients 2.75/1,000 (95%CI, 1.01-4.50).[36, 41, 53, 62, 65, 82, 90, 99]

Flexible Sigmoidoscopy (FS) Minor bleeding was reported in two papers with screening with FS by the number of sigmoidoscopies.[92, 93] No events were reported in 9,444 FS procedures. Five papers reported this outcome by number of patients, finding 101 events for 281,887 patients, representing a proportion of 0.5/1,000 (95%CI, 0.25-0.74).[36, 53, 90, 94, 95]

False –positive

iFOBT

Data were extracted on false-positive proportions for the 3 most common cut-points used in clinical practice 50 ng/ml; 70-75 ng/ml, and 100 ng/ml. Two papers reported on the cut-points of 50 ng/ml and 70-75 ng/ml.[64, 74] The total events were 3,022 / 23,442; the proportion of false-positives for 50ng/ml was 12.89% (95%CI, 12.46% to 13.32%) or 128.9/1,000; and for 70-75 ng/ml the events were 2,010 / 23,442 with a proportion of 9.37% (95%CI, 7.20% to 11.54%) or 93.7/1,000. When the cutpoint was 100ng/ml the false positive events were 1,707 / 43,239; with the proportion of 5.55% (95%CI, 2.21% to 8.89%) or 55.52/1,000.[59, 64, 74] It is important to note that the one RCT for screening benefits with iFOBT[33] included in this review did not report the cutpoint used to determine CRC.

gFOBT

Two papers provided false-positive data for gFOBT.[59, 74] The false-positive events were 251/20,567, with the proportion of 1.22% (95%CI, 1.07% to 1.37%) or 12.2/1,000.

Follow-up Colonoscopy

One paper reported false-positives for follow-up colonoscopies by number of tests.[96] The total events were 288/10,277 representing 28/1,000 (95%CI, 25.0-31.4).

False-Negative

iFOBT

We have extracted and reported false-negative rates for the three cutpoints most commonly used in clinical practice. One study reported false negative rates for the cutpoint of 50ng/ml.[74] The events were 1/770 with a proportion of 0.0013 (95%CI, -0.00 2%, 0.73%) or 1.30/1,000. Two papers provided data for the cutpoint of 70-75ng/ml[43, 74] with false negative event rates of 1/1,994 representing a proportion of 0.02% (95%CI, 0.01% to 0.02%) or 0.21/1,000. Two papers reported data for 100ng/ml.[74, 100] The total events are 5 /5,793 representing a proportion of 0.08% (95%CI, 0.0% to 0.17%) or 0.83/1,000.

gFOBT

Three uncontrolled observational studies provide FN data.[43, 57, 74] The total events are 18 false negatives/3,270 with a proportion of 0.55% (95%CI, 0.28%, 0.82%) or 5.51/1,000.

Overdiagnosis

Our search did not locate any papers that presented data on overdiagnosis with any screening test of interest in this review.

Results for Contextual Questions

1. What are the patient preferences and values for screening for colorectal cancer?

We found 3 reviews and 20 primary studies that examined this question. The screening tests for which these studies included data were fecal occult blood test (FOBT), computed tomography (CT) colonoscopy, and flexible sigmoidoscopy.

In 2009, the Canadian Partnership Against Cancer conducted a survey with Canadians aged 45-74 years in order to gather baseline data on the awareness and understand of screening for CRC in Canada. The vast majority of respondents agreed that CRC and early treatment is important. That survey showed that people were aware, in general terms, of CRC screening but less aware of the particulars of screening. In fact, most people reported colonoscopy as being the primary

test for CRC screening and only a minority of respondents knew about FOBT.[15] These data suggest that perhaps, the greatest barrier to Canadians being screened is lack of education on the FOBTs and not embarrassment or a lack of appreciation for the importance of screening.

A Canadian study mailed preference surveys to a random sample of adults aged 40 to 60 years from a primary care network.[101] Results from the returned surveys (N=1047) showed the 29% of the respondents preferred no screening. Preferred test attributes included non-invasive procedures; no preparation; no pain; 100% specificity and 90% sensitivity. It is important to note that this survey did not include the attributes of screening intervals or the impact on cancer specific mortality.

A US study with participants at average risk of colorectal cancer used an Analytic Hierarchy Process to determine decision priorities for patients in primary care settings. The study (N=484) concluded that the highest priority in screening decision making were (in order of preference) preventing cancer (55%); avoiding test side effects (17%); minimizing false positives (15%) and the combined priority of screening frequency, test preparation, and test procedure(s) (14%).[102]

Advantages and Disadvantages of Screening Tests

Disadvantages that affected screening rates included discomfort associated with the laxative bowel preparation, worry about perforation and bleeding, concerns about embarrassment, concerns about modesty and dignity, and the cumbersome cleansing preparation for the test.[103, 104] The most common negative was fear of pain and discomfort related to insertion of the endoscope.[103]

Individuals who had or were having an FOBT mentioned a few different advantages and disadvantages. The disadvantages included confusing instructions[105], discomfort, and adverse effects associated with the FOBT.[103, 104, 106-113] The features that individuals liked about the test were simplicity[114], comfort/lack of invasiveness[115, 116], ease/convenience/time,[114, 116] cost,[116] and privacy.[116]

Abdominal pain and discomfort were the most common disadvantages of CT colonography.[107-109] There were several other less common disadvantages that included diarrhea, flatulence, CO^2 insufflation, the breath hold, loss of dignity, pain, feelings of disrespect, mild bloating and moderate cramping. .[107-110] The facilitators that led people to have or want a CT colonography were non-invasiveness, avoidance of sedation/anesthesia, ability to drive after the test, avoidance of normal colonoscopy, risks, identifying abnormalities outside the colon, and mild or no discomfort.[107, 110, 117, 118]

Many negatives and positive features were found for colonoscopy. The most common negative was inconvenience.[103, 111] The other disadvantages mentioned were physical discomfort, embarrassment, danger, perforation anxiety, movement of the scope, CO^2 insufflation, competing health concerns or needing other medical investigations, difficulties with transportation and

scheduling of appointments and financial cost and access to endoscopic procedures.[103, 107, 111, 119, 120] The most common reasons for uptake were accuracy and physician recommendation. Other reasons were greater screening readiness, confidence in completing a test, greater colorectal cancer worry, perceived pros of screening, an accurate test, frequency of testing, mild or no discomfort, a good doctor-patient relationship, and adequate communication.[103, 104, 115, 116, 118, 121]

Flexible sigmoidoscopy had only one reported negative and a few reasons for uptake. The one negative was perforation anxiety.[120] Having a physician recommendation, greater screening readiness, confidence in completing a test, and perceived pros of screening were reasons for preferring flexible sigmoidoscopy over FOBT.[121]

2. What is the evidence for a higher burden of disease, a differential treatment response, differential performance, or barriers to implementation of colorectal cancer screening in the Aboriginal population, other ethnic populations, rural or remote populations, women, or the elderly?

Burden of the Disease

Ethnic Subgroups

Information on ethnicity and cancer in Canada is limited by the fact that most health information databases do not track ethnicity. The Aboriginal population, in Canada has historically had lower rates of most cancers but this has been changing rapidly. A 2009 report on First Nations access to cancer screening found that colorectal cancer rates have reached the same level as the non-Aboriginal population in Ontario (actually higher for men and slightly lower for women). Similar increases in CRC rates have been reported in Saskatchewan, the Northwest Territories and Nunavut.[122] Among Inuit age standardized incidence rates are higher among both men and women than for the general population of Ontario.[123]

A 2010 study looked at the incidence of CRC in Caucasian (C), Chinese (CC) and South Asian Canadians (SAC) in British Columbia**.** Caucasians in B.C. were 1.9 times more likely to develop CRC than Chinese B.C. residents and 7.9 times more likely than South Asian Canadians in the province. (C versus CC (RR1.9; 95% CI 1.58 to 2.31), C versus SAC (RR 7.1; 95% CI 4.20 to 12.0) and CC versus SAC (RR 3.7; 95% CI 2.14 to 6.5).[124]

Rural/Urban

A recent report (2014) using data from 2007 found that Canadians living in rural areas have slightly higher age-standardized incidence rate (per 100,000) for CRC than those in urban areas: Urban 49.3; Rural 52.7; Rural-Remote 52.9 Rural-Very Remote 54.3.[125]

Women/Age

According to a 2012 report on cancer system performance, women were more likely than men to be up to date with recommended CRC screening (45% versus 41%) and the percentage up to date for both sexes increased with age, ranging from 35% of those 50-59 to 56% aged 70-74.[126]

3. What risk assessment tools are identified in the literature to assess the risk of colorectal cancer?

Our search did not locate any studies that addressed the question of risk assessment tools for Colorectal Cancer.

4. What are the cost-effectiveness and resource implications of screening for colorectal cancer?

Two Canadian studies were found.[127, 128] One compared 10 different screening strategies, using Markov modeling to estimate costs and quality adjusted life expectancy of 50 year old average risk Canadians without screening and with screening by each test. Costs were calculated in 2007 Can$. Three strategies in particular were analyzed as they were most often used or considered for use in Canada: low –sensitivity gFOBT performed annually, iFOBT performed annually; or colonoscopy performed every 10 years. The incremental cost-effectiveness ratios were $9159, $611 and $6,133 respectively. The number of cancers was decreased by 44%, 65% and 81% respectively; and mortality was decreased by 55%, 74% and 83% respectively. The authors concluded that annual screening with iFOBT or colonoscopy every 10 years offers the best value for money in Canada.[128]

Heitman and colleagues (2010) performed an economic evaluation of CRC screening in average risk North American individuals, considering gFOBT or iFOBT annually, fecal DNA every 3 years, flexible sigmoidoscopy or CTC every 5 years, and colonoscopy every 10 years. CRC treatment costs were calculated in 2008 CAN$ and were based on local estimates derived from the Calgary Health Region costing database. An incremental cost utility analysis using Markov modeling was done. Annual iFOBT with mid-range test characteristics (iFOBT-mid) (sensitivity 0.81; specificity 0.96) was more effective and less costly compared to all strategies across all models, including no screening, except for iFOBT with high test performance characteristics (sensitivity 0.94; specificity 0.91; quality adjusted life years 11.3). With iFOBT–mid, the number of cancers could be reduced in the lifetimes of 100,000 average-risk patients by 71% and the number of CRC deaths by 74% while saving $68 (CAN) per person.[127]

Both studies modeled higher CRC incidence and mortality than were found in the trials in this review. They acknowledged that the actual time for adenoma progression to carcinoma is not well known.

Chapter 4: Discussion, Limitations and Conclusion

Discussion

No trials were found for the benefits of primary screening for CRC with CT colonography, fecal DNA, barium enema, or digital rectal examination. The discussion below is organized by screening methods rather than by key question for easier comparisons between tests.

gFOBT

Guaiac screening resulted in an 18% reduction in CRC mortality when study participants were followed between 9-30 years, although there was a moderate level of heterogeneity. Those same studies showed that gFOBT screening did not impact all-cause mortality or incidence of late stage cancer. There are few harms associated with gFOBT given it is a non-invasive procedure. False-positive proportions are low and there are few false-negatives.

iFOBT (FIT)

Only one RCT provided the evidence for the effectiveness of iFOBT on the outcome of CRC mortality. That study showed no benefit of screening with iFOBT on mortality or incidence of late stage CRC. There is little harm associated with iFOBT. False-positives are highest (12.89%) when the cutpoint is lowest 50ng/ml and lowest 5.52% when the cutpoint is 100ng/ml. Screening adults without obvious signs of, or who are not at high risk for CRC with iFOBT is common practice. Modeling studies suggests that annual FIT with mid-range test characteristics is effective and cost-effective compared to other tests; specifically colonoscopy. We did not meta-analyze test properties. Lee and colleagues performed a meta-analysis on FIT test properties data using a bivariate random-effects model. [129] Their primary approach of grouping FIT studies is similar to this current systematic review, which is, first looking overall, then for sub-groups by FIT test type and cut-points. However, they included studies even if the study used a cut-point different from the manufacturer's cut-point; the self-selected cut-point was used to maximize specificity or sensitivity. We selected studies which used only manufacturer's cut-point for a particular FIT test. Since our results are based on descriptive pooling, we have a wider range of values, but the direction and magnitude of effect is fairly consistent.[129]

FOBT is reported as the preferred test by patients although there are some barriers particularly due to embarrassment. However the specifically Canadian data suggests that it is actually lack of awareness of the simplicity of FOBT that is the real barrier to more Canadians being screened. There is little harm associated with these tests; however, false positives can lead to unnecessary additional follow-up tests, such as colonoscopy, which do have harms such as bleeding, infection and the rare occasion death.

Flexible Sigmoidoscopy

Screening for CRC with flexible sigmoidoscopy is effective at decreasing CRC mortality and incidence of late stage CRC but not all-cause mortality. However, there are also greater potential for harms such as perforation, bleeding (both major and minor) and death.

Colonoscopy

There is no RCT evidence of effectiveness of colonoscopy for screening patients who do not have symptoms of or are not at high risk for CRC. There are important harms associated with colonoscopy including perforation, bleeding (both minor and major requiring hospitalization) and in rare cases, death. The ability to make screening recommendations is limited by the absence of any trials related to colonoscopy effectiveness, although colonoscopy is the usual gold standard test for comparison of other screening methods. Some modeling studies have assessed the benefits of colonoscopy as a screening strategy compared with no screening for colorectal cancer. One Canadian study used Markov modeling and predicted a decrease of 81% in CRC incidence and an 83% reduction in CRC mortality for 50-year-old individuals at average risk for colorectal cancer. This compared to a 44% and 65% reduction in incidence of colorectal cancer and 55% and 74% reduction in CRC mortality with low-sensitivity gFOBT and iFOBT respectively. Colonoscopy every 10 years yielded the greatest net health benefit compared to annual screening with iFOBT or low sensitivity guaiac tests.[128] The second study was done for the USPSTF review, and used two micro simulation models and predicted a decrease of 29.6% in CRC incidence and 51.9% reduction in CRC mortality using a MISCAN model; and a decrease of 34.7% in CRC incidence and 80.6% reduction in CRC mortality using SimCRC model for 50 to 75 year-old asymptomatic general population.[130] Caution should be given when interpreting results of modeling studies given there is no RCT data to corroborate their findings.

Other Screening Tests

No evidence was found on the effectiveness of screening with CT colonography as a first screen. Although there are few harms reported with CT colonography there have been perforations reported when this test is used as a follow-up test following screening.

In addition, no RCTs were found on effectiveness or harms of barium enema or fecal DNA tests for the outcomes of mortality or incidence of late-stage colorectal cancer.

Ages and intervals to screen

Two studies showed that the largest benefit of screening with gFOBT was in people over the age of 60 but these studies did not provide data on when to end screening. One study provided analysis of ages and intervals for screening. These data indicates that screening those under the age of 60 was not beneficial; screening those 60-69 was effective whether done annually or biennially and for those over the age of 70 annual screening was effective. One trial of flexible

sigmoidoscopy provided data on effective on mortality for people aged 65-74. However, in the studies which provided analysis by age the post-hoc analysis indicates that those studies were not sufficiently powered to determine an effect for ages below 60 or above 69 for gFOBT or the age of 55-64 in flexible sigmoidoscopy. This limits the conclusions which can be drawn from these data. There is no data in our included studies for any of the screening tests to help answer the question of when to end screening. A recent modelling study conducted by the USPSTF suggests that the ideal age to begin screening is 50 years and to stop screening by age 75.[130] That same report suggested a high sensitivity FOBT annually, 10-yearly colonoscopy, or high sensitivity FOBT every 2 to 3 years with a 5 yearly flexible sigmoidoscopy would provide similar life years gained.[130]

Implications for future research

More research is needed on the effectiveness of iFOBT for the outcome of CRC morality, all-cause mortality and incidence of late stage CRC. Longer follow-up studies would also help provide more conclusive results on CRC mortality with annual iFOBT screening given that the current evidence shows a non-significant benefit with one time screening and 8 years follow-up. There are a number of questions of interest for this review which could not be answered due to a lack of evidence. More research is needed to help answer the questions of when to start and stop screening and what intervals are most effective and result in the least harm. Head to head studies of the FOBT tests and/or between the high and low sensitivity guaiac tests would help us better understand the clinical benefits of those. A risk assessment tool could be developed and validated to help clinicians to identify patients at greater risk of colorectal cancer.

Limitations

The literature search was limited to English and French language papers only. While the search was comprehensive it is possible that potentially relevant studies could have been missed. Publication bias could not be assessed given the low number of included studies. There was insufficient evidence to answer several questions of interest including how clinical benefits of screening differ for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancer, and we did not locate any effective risk assessment tools. The single iFOBT trial had only 8 year follow-up, and was conducted in China where the health care system and health care behaviours are markedly different from Canada thus impacting generalizability. Due to the fact that iFOBT is a relatively new test there was not sufficient follow-up to determine the impact on long-term outcomes. No significant reduction was found in overall mortality in the clinical trials. This may be because the studies were not powered to detect such differences. It is important to note that there was no signal for increase in overall mortality, which would have suggested that screening decreases death from CRC, but increases death due to other causes. The section of this review on test properties was limited to papers which had reported data, we did not calculate any components of test properties. Test property data were also not meta-analyzed which would have provided more precise estimates than what appear in our review.

Conclusion

Screening for CRC with fecal occult blood testing and flexible sigmoidoscopy are effective at reducing CRC mortality and incidence of CRC. Trials of effects of colonoscopy and CT colonography screening on mortality or incidence of late stage cancer do not exist and have not been directly compared to screening with FOBT. Although there is a lack of data on the impact of iFOBT on mortality the test properties indicate that it is both sensitive and specific. However, these tests can only be effective for those who use them. It has been suggested that screening could be increased through better education about what is involved with the home-based fecal tests.

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Figures

Figure 1: Analytic Framework

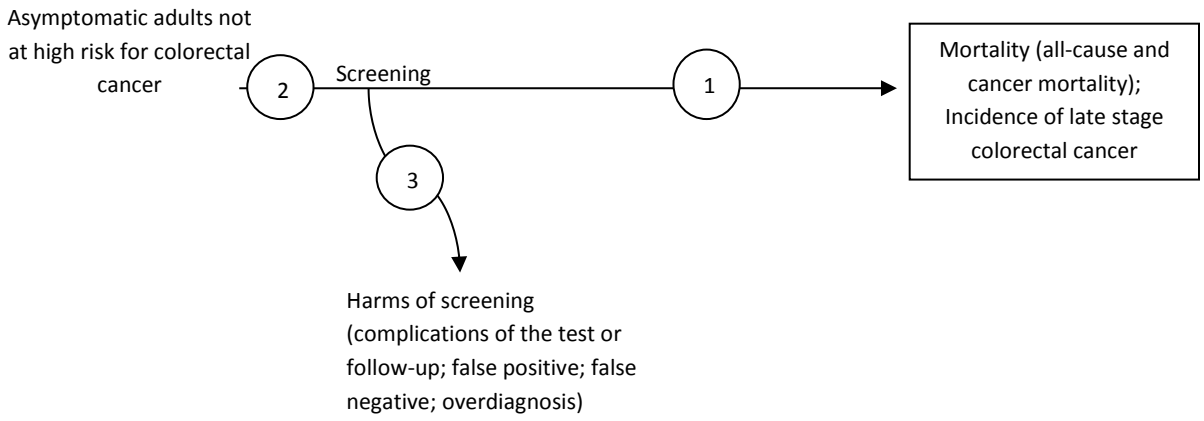
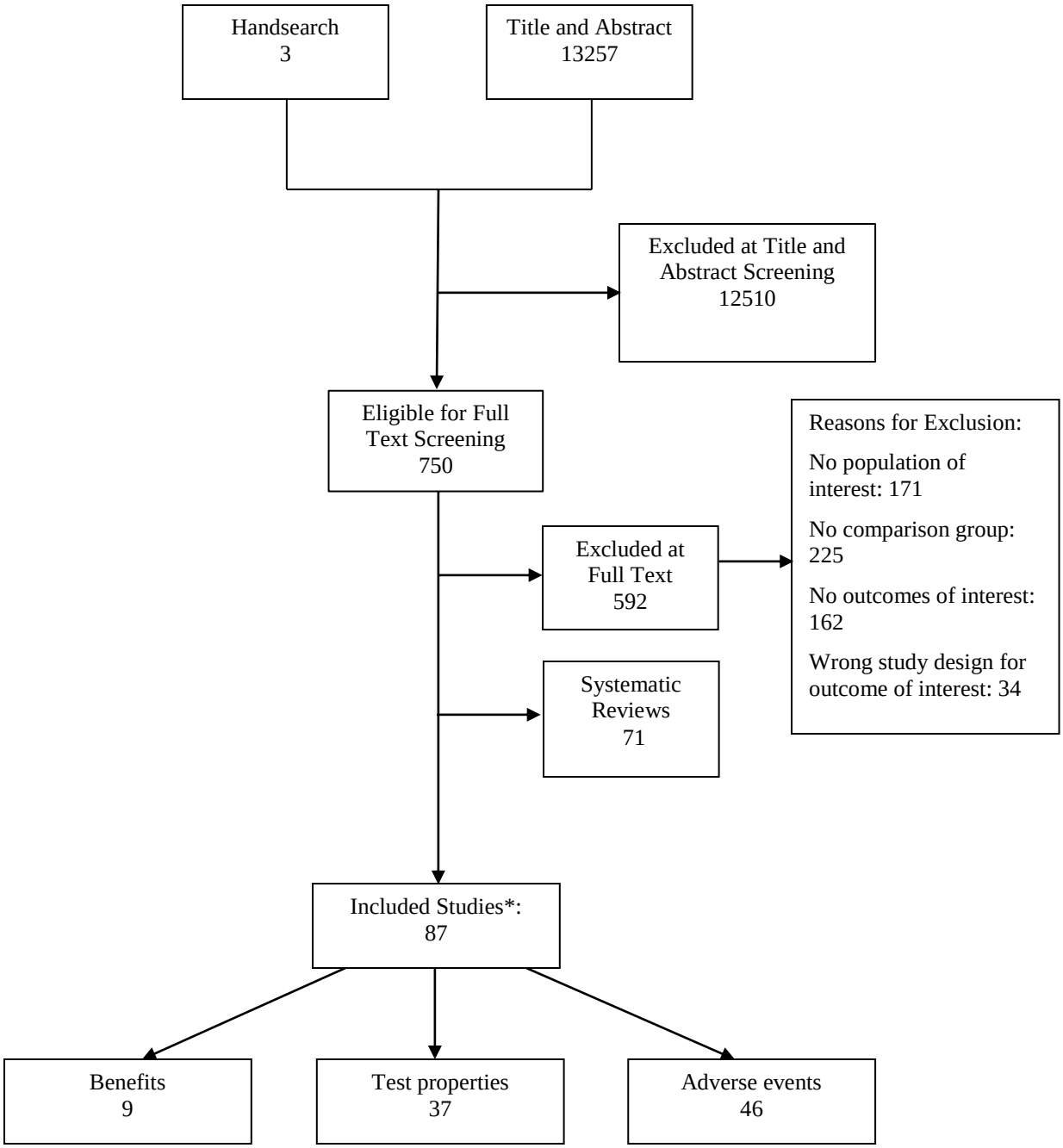


Figure 2: Colorectal Cancer Screening Search Results



*There are 87 included studies in total; a number of studies appear in more than one KQ

Tables

Table 1: Summary of Risk of Bias Assessment of Included RCTs Using Cochrane's Risk of Bias Tool[19]

Study	Sequence Generation	Allocation Concealment	Blinding of Outcome Assessors	Incomplete Reporting	Selective Reporting	Other Bias*
Scholefield 2012[31]	U	U	L	L	L	U
Schoen 2012[36]	L	U	U	U	L	H
Segnan 2011[37]	L	U	L	H	L	U
Atkin 2010[34]	L	U	L	L	L	U
Hoff 2009[35]	L	U	L	L	L	L
Lindholm 2008[30]	U	U	L	H	L	U
Kronborg 2004[29]	L	U	L	H	L	U
Zheng 2003[33]	L	U	L	U	L	U
Shaukat 2013[32]	U	U	L	U	L	U

L (green) = Low Risk; U (yellow) = Unclear Risk; H (red) = High Risk

*other potential sources of bias were industry funding; lack of a power calculation; control group contamination through opportunistic screening

Table 2: QUADAS II ratings summary

Author	CRC test assessed	Frequency	Reference Standard	Domain 1: ROB Patient Selection	Domain 1: Applicability Patient Selection	Domain 2: ROB Index Test	Domain 2: Applicability Index Test	Domain 3: ROB Ref. Standard	Domain 3: Applicability Ref. Standard	Domain 4: ROB Flow and Timing
Ahlquist[49]	gFOBT	Single	Colonoscopy	High	Low	Low	Low	High	Low	Low
Allison[63]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	High	Low	Low	Low	High	Low	High
Brenner[75]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Unclear	Low	Low	Low	Low	Low	Low
Castiglione[68]	iFOBT (FIT)	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Chen[64]	iFOBT (FIT)	Annual	Colonoscopy	Low	Low	Low	Low	High	Low	High
Cheng[71]	gFOBT	Single	Colonoscopy	High	Low	Low	Low	High	Low	Low
Collins[54]	gFOBT	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Crotta[41]	iFOBT (FIT)	Biennial	Colonoscopy	High	Low	Low	Low	High	Low	High
Dancourt[62]	iFOBT (FIT) +gFOBT	Biennial	Colonoscopy	Unclear	Low	Low	Low	Low	Low	High
Denis[65]	gFOBT	Biennial	Colonoscopy	High	Low	Low	Low	High	Low	High
Denters[42]	iFOBT (FIT) +gFOBT	Multiple	Colonoscopy	Low	Low	Low	Low	High	Low	High
De Wijkerslooth[40]	iFOBT(FIT)	Single	Colonoscopy	High	Low	Low	Low	Low	Low	Unclear
Faivre[56]	gFOBT	Biennial	Colonoscopy	Low	Low	Low	Low	High	Low	High
Faivre[60]	iFOBT (FIT) +gFOBT	Biennial	Colonoscopy	High	Low	Low	Low	Low	Low	High
Fenocchi[69]	iFOBT (FIT)	Single	Virtual Colonoscopy	Low	Low	Low	Low	High	Low	High
Guittet[61]	iFOBT (FIT) +gFOBT	Multiple	Colonoscopy	High	Low	Low	High	Low	Low	High
Hamza[58]	iFOBT (FIT)	Multiple	Colonoscopy	Unclear	Low	Low	Low	Low	Low	High

	+gFOBT									
Hol[47]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Imperiale[55]	gFOBT	Single	Colonoscopy	High	High	Low	Low	High	Low	Low
Jouve[72]	gFOBT	Biennial	Colonoscopy	Low	Low	Low	Low	High	Low	High
Kristinsson[57]	gFOBT	Single	Colonoscopy	High	Low	Low	Low	High	Low	Low
Levi[44]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Lindholm[30]	gFOBT	Multiple	Other	Low	Low	Low	Low	High	Low	High
Lohsiriwat[51]	iFOBT (FIT)	Single	Colonoscopy	High	High	High	High	High	High	High
Malila[43]	gFOBT	Biennial	Colonoscopy	High	Low	Unclear	Unclear	High	Unclear	High
Paimela[46]	gFOBT	Biennial	Colonoscopy	Low	Low	Low	Low	High	Low	High
Park[73]	iFOBT (FIT)	Single	Colonoscopy	Low	Low	Low	Low	High	Low	Low
Parro-Blanco[45]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Low	Low	Low	Low	Low	Low	High
Peris[66]	gFOBT	Biennial	Colonoscopy	Low	Low	Unclear	Low	High	Low	High
Raginel[59]	iFOBT (FIT) +gFOBT	Biennial	Colonoscopy	Low	Low	Low	Low	High	Low	High
Rubeca[53]	iFOBT (FIT)	Biennial	Colonoscopy	Unclear	Low	Low	Low	High	Low	High
Smith[52]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Steele[48]	gFOBT	Biennial	Colonoscopy	Low	Low	Low	Low	High	Low	High
Steele[70]	gFOBT	Single	Colonoscopy	Unclear	Low	Low	Low	High	Low	High
Van Rossum[50]	iFOBT (FIT) +gFOBT	Single	Colonoscopy	Low	Low	Low	Low	High	Low	High
Weller[67]	gFOBT	Single	Colonoscopy	Unclear	Low	High	Unclear	High	Low	High
Zorzi[74]	iFOBT (FIT)	Multiple	Colonoscopy	High	Low	Low	Low	High	Low	High

Table 3: Characteristics of Included Studies

gFOBT

Study/Location Kronborg 2004[29] Denmark	
Objective	To evaluate reduction in mortality and the possible influence of compliance on mortality from CRC
Methods	Design: RCT Selection: invitations sent out by mail from the screening office; two reminders during the initial screening round, one during the following rounds; only those participating in previous rounds and without CRC or adenomas were re-invited. Exlcusion Criteria: subjects with known CRC, colorectal adenomas, or distant spread of all types of malignant disease
Participants	Sample: n=61,933 Intervention n= 30,762 ; Control n= 30,966 Mean age (I): 58.8 years; Mean age (C): 59.8 years (recruited ages: 45-75 years) Gender [Female n(%)]: NR Loss to follow-up: (I) n= 11,108; (C) n= 11,356
Intervention	Description of Intervention: biennial screening with Hemoccult-II Description of Control group: no screening Duration of intervention: 9 rounds of screening Length of follow-up: 17 years
Study/Location Lindholm 2008[30] Sweden	
Objective	To evaluate the effect of FOBT screening on colorectal cancer mortality in a Swedish population
Methods	Design: RCT Selection: recruitment through local population register Inclusion Criteria: ages 60-64 years

Participants	Sample: n=68,308 Intervention n= 34,144; Control n = 34,164 Mean age overall: NR (recruited ages: 60-64 years) Gender [Female n (%)]: NR Loss to follow-up: (I) n= 170; (C) n= 821
Intervention	Description of Intervention: screening with FOBT Description of Control group: no screening Duration of intervention: 3 screens; 21-24 months between screens Length of follow-up: 9 years (mean)
Study/Location	Scholefield 2012[31] UK
Objective	To compare the CRC mortality and incidence in the intervention arm with the control arm after long-term follow-up
Methods	Design: RCT Selection: Subjects were recruited from 92 general practice areas in and near the city of Nottingham Inclusion Criteria: 45-74 years of age; living in the Nottingham area Exlcusion Criteria: serious illness, including a diagnosis of CRC within the previous 5 years
Participants	Sample: n=152,850 Intervention n= 76,466; Control n= 76,384 Mean age overall: NR (recruited ages: 45-74 years) Gender [Female n(%)]: NR Loss to follow-up: 0
Intervention	Description of Intervention 1: biennial screening by FOBT, the majority being offered between three and five tests according to their date of entry Description of Control: usual care Duration of Intervention: biennial screening; between three and five screens

	according to date of entry into study Length of follow-up: 19.5 years (median)

Study/Location	Shaukat 2013[32] US
Objective	To determine the duration of the benefit of fecal occult-blood testing and whether the effects are specific to age and sex
Methods	Design: RCT Selection: the Minnesota Colon Cancer Control Study randomly assigned healthy volunteers
Participants	Sample: n=46,551 Intervention 1 n= 15,570; Intervention 2 n= 15,587; Control n= 15,394 Mean age (SD) (I1): 62.3 (7.8) years; Mean (SD) (I2): 62.3 (7.8) years; Mean age (SD) (C): 62.3 (7.7) years; (recruited ages: 50-80 years) Gender [Female n(%)]: (I1): n= 8,081 (51.9%); (I2): n=8,143 (52.2%); (C): n=7,960 (51.7%)
Intervention	Description of Intervention: I1: 11 screenings were offered to participants in the annual-screening group; I2: 6 screenings were offered to those in the biennial-screening group Description of Control group: usual care Duration of intervention: 11 screens in annual group; 6 screens in biennial group Length of follow-up: 30 years

iFOBT (FIT)

Study/Location	Zheng 2003[33] China
Objective	The objectives of this study first were to develop a mass screening program for the people of China; the population may also need an intervention program

	early in the history of this disease; Second, we aimed to optimize the mass screening protocol and evaluate its efficacy in low-incidence areas
Methods	Design: RCT Selection: All residents could be identified from the complete housing-book registry system Inclusion Criteria: over 30 years of age residing in Jiashan County in 1989; identified as having at least 5 years of residence in the county Exclusion Criteria: individuals with a previous diagnosed malignancy or severe physiologic or mental disabilities were also excluded
Participants	Sample: n=192,261 Intervention n= 94,423; Control n= 97,838 Mean age overall: NR (recruited ages: >30 years) Gender [Female n(%)]: I: n= 46,243 (49%); C: n=47,917 (49%)
Intervention	Description of Intervention: screening with FIT Description of Control group: no screening Duration of intervention: one screen Length of follow-up: 5-6 years

Flexible Sigmoidoscopy

Study/Location	Atkin 2010[34] UK
Objective	To test the hypothesis that only one FS screening between 55 and 64 years of age can substantially reduce colorectal cancer incidence and mortality
Methods	Design: RCT Selection: all men and women aged between 55 and 64 years and registered with participating general practices were eligible Exclusion criteria: inability to provide informed consent; history of colorectal cancer, adenomas, or inflammatory bowel disease; severe or terminal disease; life expectancy less than 5 years; or sigmoidoscopy or colonoscopy within the previous 3 years

Participants	Sample: n=170,432 Intervention n= 57,237; Control n = 113,195 Mean age overall (SD): 60 (2.9) years (recruited ages: 55-64 years) Gender [Female n(%)]: I: 51%; C: 51% Loss to follow-up: (I) n= 138; (C) n= 256
Intervention	Description of Intervention: flexible sigmoidoscopy screening Description of Control group: no intervention Duration of intervention: one time screen Length of follow-up: 11.2 years (median)
Study/Location	Hoff 2011[35] Norway
Objective	To determine the risk of colorectal cancer after screening with FS
Methods	Design: RCT Selection: drawn by individual randomization from the population registry and invited directly to once only flexible sigmoidoscopy screening Inclusion Criteria: residents aged 55-64 years living in the city of Oslo and Telemark County, Norway, who were registered and alive in the national population registry by November 1998 Exclusion criteria: previous open colorectal surgery, need for long term attention and nursing services (somatic or psychosocial reasons, mental retardation), ongoing cytotoxic treatment or radiotherapy for malignant disease, severe chronic cardiac or pulmonary disease, lifelong anti-coagulant treatment, admission to hospital for a coronary event during the previous three months, and residence abroad
Participants	Sample: n=55,736 Intervention n= 13,823 (FS only: 6915; combined FS and FOBT: 6098); Control n = 41,913 Mean age overall (SD): 59 years (recruited ages: 55-64 years) Gender [Female n(%)]: (I): 50%; (C): 50% Loss to follow-up: (I) n= 170; (C) n= 821

Intervention	Description of Intervention 1: FS or FS with FOBT Description of Control group: no screening Duration of intervention: one time screen Length of follow-up: 7 years
Study/Location	Schoen 2012[36] US
Objective	To evaluate the effect of screening with flexible sigmoidoscopy on colorectal cancer incidence and mortality
Methods	Design: RCT Selection: subjects were recruited from 10 screening centers across the United States Exclusion Criteria: history of prostate, lung, colorectal, or ovarian cancer; ongoing treatment for any type of cancer except basal-cell or squamous cell skin cancer; and, beginning in 1995, assessment by means of a lower endoscopic procedure (flexible sigmoidoscopy, colonoscopy, or barium enema examination)
Participants	Sample: n=154,900 Intervention n= 77,445; Control n = 77,455 Mean age overall: NR (recruited ages: 55-74 years) Gender [Female n(%)]: (I): n= 39,105 (50.5%); (C): n= 39,111 (50.5%) Loss to follow-up: (I) n= 35,587; (C) n= not reported
Intervention	Description of Intervention: screening with FS Description of Control group: usual care Duration of intervention: 2 screens (1 at baseline, one at 3 or 5 years) Length of follow-up: 11.9 years (median)
Study/Location	Segnan 2011[37] Italy
Objective	To evaluate the effect of FS screening on CRC incidence and mortality
Methods	Design: RCT

	Selection: In Arezzo, Rimini, and Turin, all patients enrolled in the rosters of a random sample of National Health Service general practitioners (GPs) were targeted for recruitment; in Milan, all patients of the GPs who volunteered to cooperate in the trial were included in the population targeted for enrollment; In Genoa and Biella, a random sample of individuals in the target age range was drawn from the National Health Service register Exclusion Criteria: personal history of CRC, colorectal adenomas, or inflammatory bowel disease; having had a colorectal endoscopy within the previous 2 years; having two or more first-degree relatives with CRC; and having a medical condition that would preclude a benefit from screening
Participants	Sample: n=34,292 Intervention n= 17,148; Control n = 17,144 Mean age (I): 59.7 (55.5-64.3) years; Mean age (C): 59.6 (55.5-64.4) (recruited ages: 55-64 years) Gender [Female n(%)]: (I): 50%; (C): 49.5% Loss to follow-up: (I) n= 12; (C) n= 8
Intervention	Description of Intervention 1: Screening with FS Description of Control group: no screening Duration of intervention: one time screen Length of follow-up: Incidence: 10.5 years (median); Mortality: 11.4 years (median)

Evidence Set 1 KQ1: Benefits of Screening

- Findings Summary Table 4.1
- GRADE Evidence Profile Table 4.2: Effect of colorectal screening on CRC-Specific Mortality, All-cause Mortality and Incidence of late stage cancer
- GRADE Summary of Findings Table 4.3: Effect of colorectal cancer screening on CRC-Specific Mortality, All-cause Mortality and Incidence of late stage cancer
- Forest Plots 1.1 to 1.3
    - 1.1: CRC-Specific Mortality
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    - 1.3: Incidence of late stage CRC
- POST-HOC Statistical Power Calculations Summary

Findings Summary Table 4.1

Number of Studies	Number needed to screen	Risk Reduction	Absolute Risk Reduction per million
CRC-specific Mortality - Guaiac FOBT (follow-up 9 - 30 years; assessed with: Objective)			
4[29-32]	337	RR 0.8215 (0.7303 to 0.9241)	2,654 (1,128 fewer to 4010 fewer)
CRC-specific Mortality - FIT (I-FOBT) (follow-up mean 8 years; assessed with: Objective)			
1[137]	NA	RR 0.8789 (0.7246 to 1.0661)	277 (631 fewer to 151 more)
CRC-specific Mortality - Flex Sigmoidoscopy (follow-up 6 - 11.9 years; assessed with: Objective)			
4[34-37]	850	RR 0.7245 (0.6517 to 0.8056)	1,176 (830 fewer to 1486 fewer)
All-cause Mortality - Guaiac FOBT (follow-up 9 - 30 years; assessed with: Objective)			
4[29-32]	NA	RR 1.0019 (0.995 to 1.0088)	901 (2,371 fewer to 4172 more)
All-cause Mortality - Flex Sigmoidoscopy (follow-up 6 - 11.9 years; assessed with: Objective)			
4[34-37]	NA	RR 0.9864 (0.9652 to 1.0081)	1,838 (4,704 fewer to 1,095 more)
Late Stage CRC Incidence - Guaiac FOBT (follow-up 9 - 19.5 years; assessed with: Objective)			
2[30,39]	876	RR 0.9164 (0.8523 to 0.9855)	1,141 (198 fewer to 2,017 fewer)
Late Stage CRC Incidence - Flex Sigmoidoscopy (follow-up 7 - 11.9 years; assessed with: Objective)			
3[35-37]	577	RR 0.7528 (0.6622 to 0.8558)	1,733 (1,011 fewer to 2,368 fewer)

GRADE Evidence Profile Table 4.2: Effect of screening of CRC-specific mortality, All-cause mortality and Incidence of late stage CRC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benefits of Screening for Colorectal Cancer	Control	Relative (95% CI)	Absolute		
CRC-specific Mortality - Guaiac FOBT (follow-up 9 - 30 years; assessed with: Objective)												
4	randomised trials[1]	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	1,990/156,737 (1.3%)	2,326/156,443 (1.5%)	RR 0.8215 (0.7303 to 0.9241)	2,654 fewer per 1,000,000 (from 1,128 fewer to 4,010 fewer)	⊕⊕⊕O MODERATE	CRITICAL
CRC-specific Mortality - FIT (I-FOBT) (follow-up mean 8 years; assessed with: Objective)												
1	randomised trials[7]	no serious risk of bias[8]	no serious inconsistency[9]	no serious indirectness[10]	serious[11]	none[6]	190/94,423 (0.2%)	224/97,838 (0.23%)	RR 0.8789 (0.7246 to 1.0661)	277 fewer per 1,000,000 (from 631 fewer to 151 more)	⊕⊕⊕O MODERATE	CRITICAL
CRC-specific Mortality - Flex Sigmoidoscopy (follow-up 6 - 11.9 years; assessed with: Objective)												
4	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	no serious imprecision[16]	none[6]	530/165,333 (0.32%)	1061/248,622 (0.43%)	RR 0.7245 (0.6517 to 0.8056)	1,176 fewer per 1,000,000 (from 830 fewer to 1,486 fewer)	⊕⊕⊕O MODERATE	CRITICAL
All-cause Mortality - Guaiac FOBT (follow-up 9 - 30 years; assessed with: Objective)												
4	randomised trials[1]	serious[2]	no serious inconsistency[17]	no serious indirectness[4]	serious[18]	none[6]	74,549/156,737 (47.6%)	741,74/156,443 (47.4%)	RR 1.0019 (0.995 to 1.0088)	901 more per 1,000,000 (from 2,371 fewer to 4,172 more)	⊕⊕OO LOW	CRITICAL

All-cause Mortality - Flex Sigmoidoscopy (follow-up 6 - 11.9 years; assessed with: Objective)												
4	randomised trials[12]	serious[13]	no serious inconsistency[19]	no serious indirectness[15]	serious[20]	none[6]	21,411/165,333 (13%)	33,608/248,622 (13.5%)	RR 0.9864 (0.9652 to 1.0081)	1,838 fewer per 1,000,000 (from 4,704 fewer to 1,095 more)	⊕⊕OO LOW	CRITICAL
Late Stage CRC Incidence - Guaiac FOBT (follow-up 9 - 19.5 years; assessed with: Objective)												
2	randomised trials[21]	serious[22]	no serious inconsistency[23]	no serious indirectness[24]	no serious imprecision[25]	none[6]	1,379/110,200 (1.3%)	1,503/110,083 (1.4%)	RR 0.9164 (0.8523 to 0.9855)	1,141 fewer per 1,000,000 (from 198 fewer to 2,017 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Late Stage CRC Incidence - Flex Sigmoidoscopy (follow-up 7 - 11.9 years; assessed with: Objective)												
3	randomised trials[12]	serious[26]	no serious inconsistency[27]	no serious indirectness[28]	no serious imprecision[29]	none[6]	571/108,234 (0.53%)	951/135,683 (0.7%)	RR 0.7528 (0.6622 to 0.8558)	1,733 fewer per 1,000,000 (from 1,011 fewer to 2,368 fewer)	⊕⊕⊕O MODERATE	CRITICAL

GRADE Summary of Findings Table 4.3: Effect of colorectal screening on CRC-Specific Mortality, All-cause mortality and incidence of late stage cancer

Benefits of Screening for Colorectal Cancer for Colorectal Cancer

Patient or population: patients with Colorectal Cancer

Intervention: Benefits of Screening for Colorectal Cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Benefits of Screening for Colorectal Cancer				
CRC-specific Mortality - Guaiac FOBT Objective Follow-up: 9 - 30 years	**Study population**		**RR 0.8215** (0.7303 to 0.9241)	313,180 (4 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]	
	14,868 per 1,000,000	**12,214 per 1,000,000** (10,858 to 13,740)				
	Moderate					
	14,000 per 1,000,000	**11,501 per 1,000,000** (10,224 to 12,937)				
CRC-specific Mortality - FIT (I-FOBT) Objective Follow-up: mean 8 years	**Study population**		**RR 0.8789** (0.7246 to 1.0661)	192,261 (1 study[7])	⊕⊕⊕⊖ **moderate**[6,8,9,10,11]	
	2,289 per 1,000,000	**2,012 per 1,000,000** (1,659 to 2,441)				
	Moderate					
	2,000 per 1,000,000	**1,758 per 1,000,000** (1,449 to 2,132)				
CRC-specific Mortality - Flex Sigmoidoscopy Objective Follow-up: 6 - 11.9 years	**Study population**		**RR 0.7245** (0.6517 to 0.8056)	413,955 (4 studies[12])	⊕⊕⊕⊖ **moderate**[6,13,14,15,16]	
	4,268 per 1,000,000	**3,092 per 1,000,000** (2,781 to 3,438)				
	Moderate					
	4,000 per 1,000,000	**2,898 per 1,000,000** (2,607 to 3,222)				
All-cause Mortality - Guaiac FOBT Objective Follow-up: 9 - 30 years	**Study population**		**RR 1.0019** (0.995 to 1.0088)	313,180 (4 studies[1])	⊕⊕⊖⊖ **low**[2,4,6,17,18]	
	474,128 per 1,000,000	**475,029 per 1,000,000** (471,757 to 478,300)				
	Moderate					
	420,000 per	**420,798 per 1,000,000**				

	1,000,000	(417,900 to 423,696)			
All-cause Mortality - Flex Sigmoidoscopy Objective Follow-up: 6 - 11.9 years	**Study population**		**RR 0.9864** (0.9652 to 1.0081)	413,955 (4 studies[12])	⊕⊕⊖⊖ **low**[6,13,15,19,20]
	135,177 per 1,000,000	**133,339 per 1,000,000** (130,473 to 136,272)			
	Moderate				
	143,000 per 1,000,000	**141,055 per 1,000,000** (138,024 to 144,158)			
Late Stage CRC Incidence - Guaiac FOBT Objective Follow-up: 9 - 19.5 years	**Study population**		**RR 0.9164** (0.8523 to 0.9855)	220,283 (2 studies[21])	⊕⊕⊕⊖ **moderate**[6,22,23,24,25]
	13,653 per 1,000,000	**12,512 per 1,000,000** (11,637 to 13,455)			
	Moderate				
	13000 per 1,000,000	**11,913 per 1,000,000** (11,080 to 12,811)			
Late Stage CRC Incidence - Flex Sigmoidoscopy Objective Follow-up: 7 - 11.9 years	**Study population**		**RR 0.7528** (0.6622 to 0.8558)	243,917 (3 studies[12])	⊕⊕⊕⊖ **moderate**[6,26,27,28,29]
	7,009 per 1,000,000	**5,276 per 1,000,000** (4,641 to 5,998)			
	Moderate				
	7,000 per 1,000,000	**5,270 per 1,000,000** (4,635 to 5,991)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 1) Scholefield et. al, 2012; 2) Lindholm et. al, 2008; 3) Kronborg et. al, 2004; 4) Shaukat et. al, 2013.
[2] Using Cochrane's Risk of Bias tool, for this outcome all 4 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (75%), allocation concealment (100%) and other sources of bias (100%; studies not providing information on contamination/opportunist screening in control group), and high risk of bias associated with incomplete outcome reporting (75%). Given that most of the information is from studies with serious concerns regarding risk of bias, this body of evidence was downgraded for serious study limitations.
[3] The statistical heterogeneity is moderate [Chi^2=9.14, df=3 (P=0.03); I^2=67%] but the direction of the effect is consistent across studies and the confidence intervals overlap across most studies. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency
[4] Four RCTs provided data for this outcome. All studies included mixed gender population. Two studies included participants with age ranged from 45 to 75 years, one study included participants with age 50 to 80 years and one study with age ranged from 60 to 64 years. The screening arm across all studies received guaiac FOBT (Hemoccult-II). One study offered Biennial FOBT screen, one study offered 2-3 rounds of screening with 21 to 24 months interval, one study offered 7 rounds of screening and one study offered annual screening. The

control group across all studies was defined as no screening group. One study was conducted in UK, one in Sweden, one in Denmark and one study in US. One study was published in 2004 while the other three studies were published from 2008 to 2013. The length of follow-up across four studies ranged from 9 years to 30 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[5] The sample size is adequate (156,737 screening arm, 156,443 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.8215 (0.7303, 0.9241)]. This body of evidence was not downgraded for imprecision

[6] There were too few studies (n<10) to assess publication bias.

[7] Zheng et. al, 2003

[8] Using Cochrane's Risk of Bias tool, for this outcome the single study was rated as low risk. Across domains, there was a lack of certainty (unclear ratings) regarding allocation concealment, incomplete reporting and other other sources of bias (i.e. no information on contamination/opportunist screening in control group). Given that most of the information is from studies at low risk of bias, this body of evidence was not downgraded for serious study limitations.

[9] The consistency could not be assessed as only one study reported data for this outcome.

[10] One RCT provided data for this outcome. It included mixed gender population with age 30 years and above. The screening arm received RPHA-FOBT (FIT) test using single screen method. The control group in the study was defined as no screening group. The study was conducted in China. The study was published in 2003. The length of follow-up was 8 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[11] The sample size is adequate (94,423 screening arm, 97,838 control arm) but the effect estimate is imprecise with 95% CI including the no effect value of 1 (RR = 0.8789 (95% CI, 0.7246 to 1.0661). This body of evidence was downgraded for serious concerns regarding imprecision.

[12] 1) E. Schoen et. al, 2012; 2) Segnan et.al , 2011; 3) Hoff et. al, 2009; 4) S Atkin et.al , 2010.

[13] Using Cochrane's Risk of Bias tools for this outcome, two studies were rated as low risk and two studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding allocation concealment (100%), blinding of outcome assessment (25%) and other sources of bias (50%; studies not providing information on contamination/opportunist screening in control group), and high risk of bias associated with incomplete outcome reporting (25%) and other sources of bias associated with contamination/opportunist screening in control group (25%). Given that most of the information is from studies with serious concerns regarding risk of bias, this body of evidence was downgraded for serious study limitations.

[14] The statistical heterogeneity is minimal [Chi^2=0.53, df=3 (P=0.91); I^2=0%] and the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[15] Four RCTs provided data for this outcome. All studies included mixed gender population. Three studies included participants with age ranged from 55 to 64 years and one study with age ranged from 55 to 74 years. The screening arm across all studies received Flexible Sigmoidoscopy. Three studies offered once only screen with flexible Sigmoidoscopy and one study offered one screening at baseline and one at 3 or 5 years. The control group across all studies was defined as no screening group. One study was conducted in US, one in UK, one in Italy and one study in Norway. All studies were published from 2009 to 2013. The length of follow-up across four studies ranged from 6 years to 11.9 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[16] The sample size is adequate (165,333 screening arm, 248,622 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.7245 (0.6517, 0.8056)]. This body of evidence was not downgraded for imprecision.

[17] The statistical heterogeneity is minimal [Chi^2=1.81, df=3 (P=0.61); I^2=0%] and the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[18] The sample size is adequate (156,737 screening arm, 156,443 control arm) but the effect estimate is imprecise with 95% CI including the no effect value of 1 (RR = 1.0019 (95% CI, 0.9950 to 1.0088). This body of evidence was downgraded for serious concerns regarding imprecision.

[19] The statistical heterogeneity is minimal [Chi^2=4.61, df=3 (P=0.20); I^2=35%] and the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[20] The sample size is adequate (165,333 screening arm, 248,622 control arm) but the effect estimate is imprecise with 95% CI including the no effect value of 1 (RR = 0.9864 (95% CI, 0.9652 to 1.0081). This body of evidence was downgraded for serious concerns regarding imprecision.

[21] 1)Scholefield et. al, 2012; 2) Lindholm et. al, 2008;

[22] Using Cochrane's Risk of Bias tool, for this outcome both studies were rated as unclear risk. Across both studies, there was a lack of certainty (unclear ratings) regarding sequence generation, allocation concealment and other sources of bias (studies not providing information on contamination/opportunist screening in control group), and high risk of bias associated with incomplete outcome reporting (50%). Given that most of the information is from studies with serious concerns regarding risk of bias, this body of evidence was downgraded for serious study limitations.

[23] The statistical heterogeneity is minimal [Chi^2=0.39, df=1 (P=0.53); I^2=0%] and the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[24] Two RCTs provided data for this outcome. Both studies included mixed gender population. One study included participants with age ranged from 45 to 74 years and one study with age ranged from 60 to 64 years. The screening arm across bothl studies received guaiac FOBT (Hemoccult-II). One study offered Biennial FOBT screen and one study offered 2-3 rounds of screening with 21 to 24 months interval. The control group across both studies was defined as no screening group. One study was conducted in UK and the other study in Sweden. Both studies were published from 2008 to 2013. The length of follow-up across both studies ranged from 9 years to 19.5 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[25] The sample size is adequate (110,200 screening arm, 110,083 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.9164 (0.8523, 0.9855)]. This body of evidence was not downgraded for imprecision.

[26] Using Cochrane's Risk of Bias tool, for this outcome, one study was rated as low risk and two studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding allocation concealment (100%), blinding of outcome assessment (33%) and other sources of bias (33%; studies not providing information on contamination/opportunist screening in control group), and high risk of bias associated with incomplete outcome reporting (33%) and other sources of bias associated with contamination/opportunist screening in control group (33%). Given that most of the information is from studies with serious concerns regarding risk of bias, this body of evidence was downgraded for serious study limitations.

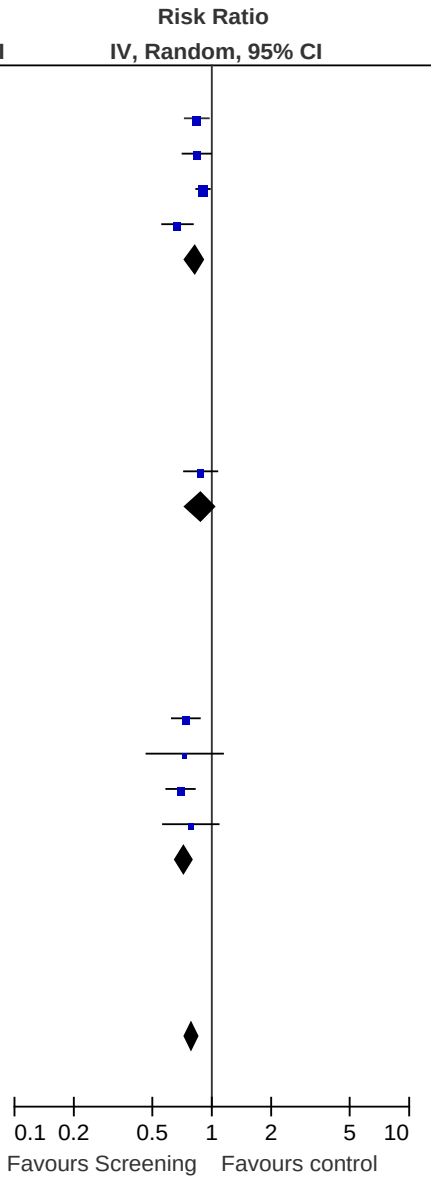
[27] The statistical heterogeneity is minimal [Chi^2=2.60, df=2 (P=0.27); I^2=23%] and the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[28] Three RCTs provided data for this outcome. All studies included mixed gender population. Two studies included participants with age ranged from 55 to 64 years and one study with age ranged from 55 to 74 years. The screening arm across all studies received Flexible Sigmoidoscopy. Two studies offered once only screen with flexible Sigmoidoscopy and one study offered two screenings, one at baseline and one at 3 or 5 years. The control group across all studies was defined as no screening group. One study was conducted in US, one in Italy and one study in Norway. All studies were published between 2009 and 2013. The length of follow-up across the three studies ranged from 7 years to 11.9 years. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded

[29] The sample size is adequate (108,234 screening arm, 135,683 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR= 0.7528 (0.6622, 0.8558)]. This body of evidence was not downgraded for imprecision.

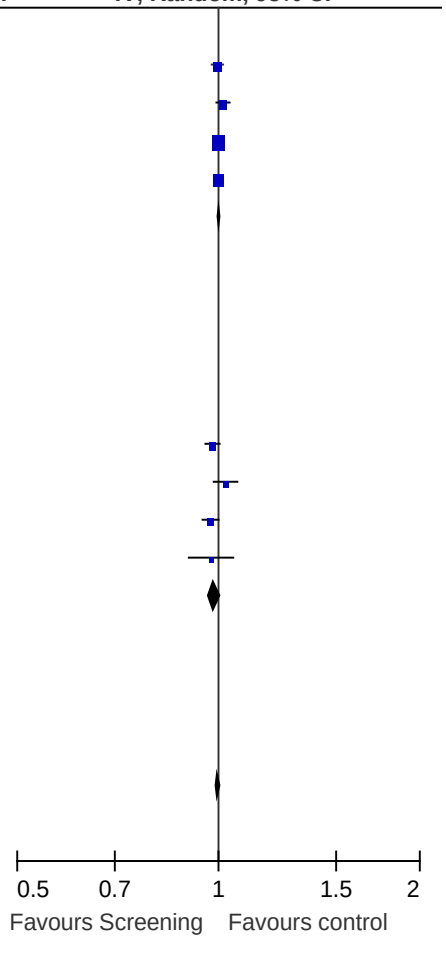
Forest Plot 1.1: Effect of colorectal cancer screening on CRC- Specific Mortality

Study or Subgroup	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Guaiac FOBT						
Kronborg, 2004	362	30967	431	30966	14.2%	0.8399 [0.7310, 0.9650]
Lindholm, 2008	252	34144	300	34164	12.1%	0.8405 [0.7114, 0.9931]
Scholefield, 2012	1176	76056	1300	75919	19.4%	0.9030 [0.8350, 0.9765]
Shaukat, 2013	200	15570	295	15394	11.3%	0.6703 [0.5609, 0.8010]
Subtotal (95% CI)		**156737**		**156443**	**56.9%**	**0.8215 [0.7303, 0.9241]**
Total events	1990		2326			
Heterogeneity: Tau² = 0.01; Chi² = 9.14, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 3.28 (P = 0.001)						
1.1.2 FIT (I-FOBT)						
Zheng, 2003	190	94423	224	97838	10.4%	0.8789 [0.7246, 1.0661]
Subtotal (95% CI)		**94423**		**97838**	**10.4%**	**0.8789 [0.7246, 1.0661]**
Total events	190		224			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.1.3 Flex Sigmoidoscopy						
E. Schoen, 2012	252	77445	341	77455	12.4%	0.7391 [0.6282, 0.8695]
Hoff, 2009	24	13653	99	41092	3.0%	0.7296 [0.4673, 1.1392]
S Atkin, 2010	189	57099	538	112939	12.2%	0.6949 [0.5889, 0.8199]
Segnan, 2011	65	17136	83	17136	5.1%	0.7831 [0.5664, 1.0827]
Subtotal (95% CI)		**165333**		**248622**	**32.7%**	**0.7245 [0.6517, 0.8056]**
Total events	530		1061			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 5.96 (P < 0.00001)						
Total (95% CI)		**416493**		**502903**	**100.0%**	**0.7962 [0.7327, 0.8653]**
Total events	2710		3611			
Heterogeneity: Tau² = 0.01; Chi² = 17.15, df = 8 (P = 0.03); I² = 53%						
Test for overall effect: Z = 5.37 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.07, df = 2 (P = 0.13), I² = 50.9%						

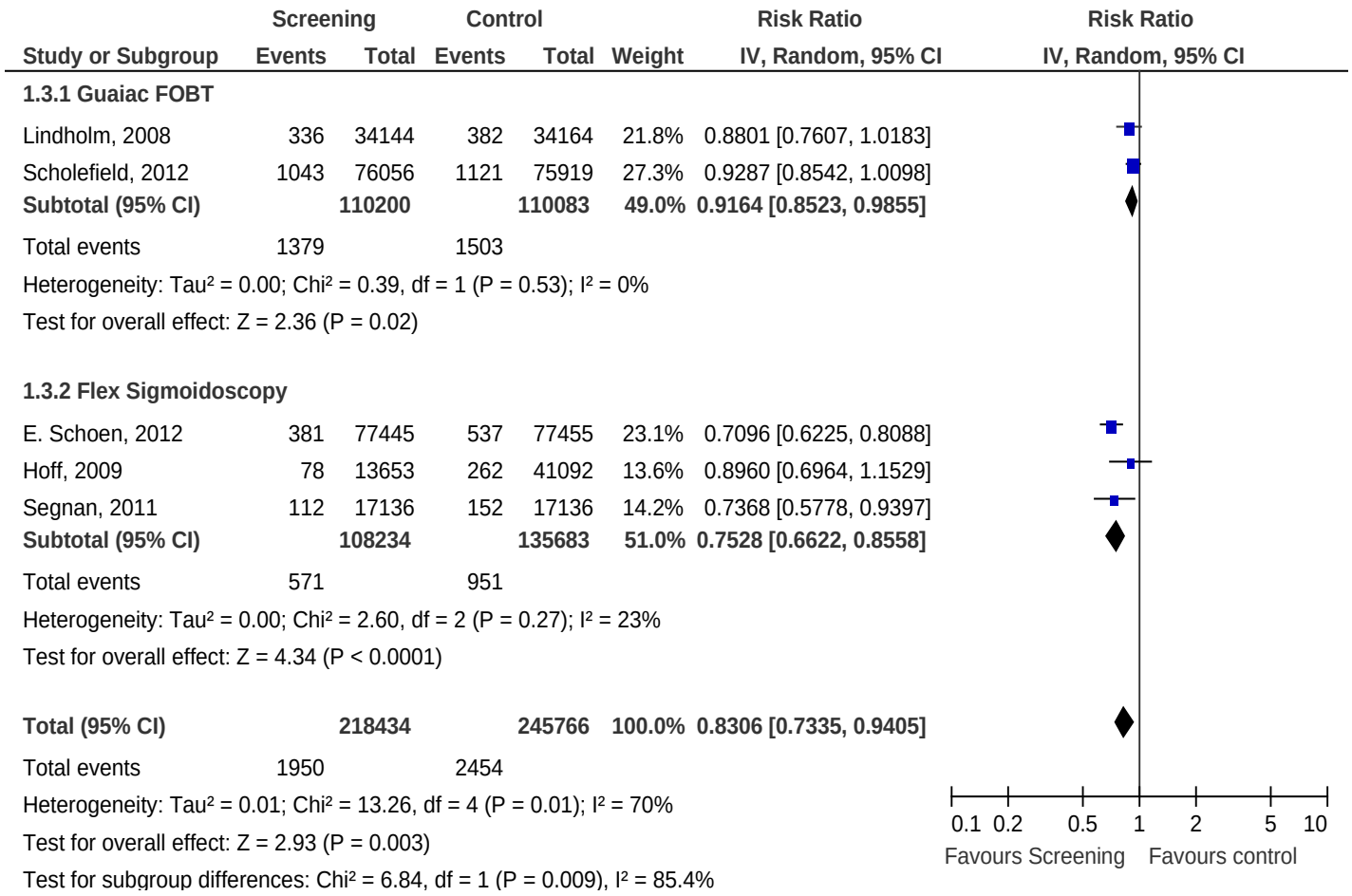


Forest Plot 1.2: Effect of colorectal cancer screening on All-cause Mortality:

Study or Subgroup	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Guaiac FOBT						
Kronborg, 2004	12205	30967	12248	30966	14.1%	0.9965 [0.9772, 1.0161]
Lindholm, 2008	10591	34144	10432	34164	11.5%	1.0158 [0.9932, 1.0389]
Scholefield, 2012	40681	76056	40550	75919	29.4%	1.0014 [0.9921, 1.0109]
Shaukat, 2013	11072	15570	10944	15394	20.7%	1.0003 [0.9862, 1.0146]
Subtotal (95% CI)		**156737**		**156443**	**75.7%**	**1.0019 [0.9950, 1.0088]**
Total events	74549		74174			
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 3 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
1.2.2 Flex Sigmoidoscopy						
E. Schoen, 2012	10879	77445	11102	77455	10.1%	0.9800 [0.9563, 1.0043]
Hoff, 2009	2555	13653	7505	41092	4.3%	1.0246 [0.9840, 1.0670]
S Atkin, 2010	6775	57099	13768	112939	8.5%	0.9733 [0.9471, 1.0002]
Segnan, 2011	1202	17136	1233	17136	1.3%	0.9749 [0.9030, 1.0524]
Subtotal (95% CI)		**165333**		**248622**	**24.3%**	**0.9864 [0.9652, 1.0081]**
Total events	21411		33608			
Heterogeneity: Tau² = 0.00; Chi² = 4.61, df = 3 (P = 0.20); I² = 35%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Total (95% CI)		**322070**		**405065**	**100.0%**	**0.9982 [0.9893, 1.0071]**
Total events	95960		107782			
Heterogeneity: Tau² = 0.00; Chi² = 10.22, df = 7 (P = 0.18); I² = 31%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² = 43.7%						



Forest Plot 1.3: Effect of colorectal cancer screening on incidence of late stage incidence of CRC



POST-HOC Statistical Power Calculations Summary

The estimation is based on reported number of events and sample size for each sub-group with a significance level of 5 % ($\alpha = 0.05$).

(Shaukat et al. 2013):

- Annual gFOBT screening vs. Control:
  Age < 60 years: RR = 0.82 (95% CI 0.59 to 1.14), Post-hoc power = 28.7 %
  Age 60 – 69 years: RR = 0.58 (95% CI 0.43 to 0.78), Post-hoc power = 98.8 %
  Age ≥ 70 years: RR = 0.47 (95% CI 0.26 to 0.84), Post-hoc power = 34.8 %
- Biennial gFOBT screening vs. Control:
  Age < 60 years: RR = 0.90 (95% CI 0.65 to 1.24), Post-hoc power = 11.6 %
  Age 60 – 69 years: RR = 0.67 (95% CI 0.51 to 0.89), Post-hoc power = 90.0 %
  Age ≥ 70 years: RR = 0.66 (95% CI 0.35 to 1.26), Post-hoc power = 2.9 %
- Combined gFOBT (annual & biennial) screening vs. Control:
  Age < 60 years: RR = 0.86 (95% CI 0.65 to 1.14), Post-hoc power = 24.8 %
  Age 60 – 69 years: RR = 0.63 (95% CI 0.49 to 0.79), Post-hoc power = 99.0 %
  Age ≥ 70 years: RR = 0.58 (95% CI 0.33 to 1.00), Post-hoc power = 15.5 %

(Scholefield et al. 2012):

- Biennial gFOBT screening vs. Control:
  Age < 60 years: RR = 0.96 (95% CI 0.85 to 1.10), Post-hoc power = 9.0 %
  Age 60 – 69 years: RR = 0.87 (95% CI 0.79 to 0.97), Post-hoc power = 80.0 %

(Schoen et al. 2012):

- Flex sigmoidoscopy screening vs. Control:
  Age 55 – 64 years: RR = 0.84 (95% CI 0.67 to 1.06), Post-hoc power = 29.3 %
  Age 65 – 74 years: RR = 0.65 (95% CI 0.52 to 0.82), Post-hoc power = 96.2 %

Evidence Set 2 KQ2: Test Properties

- Findings Summary Table 5.1 Test Properties iFOBT – Overall
- Findings Summary Table 5.2 Test Properties gFOBT – Overall
- Findings Summary Table 5.3 Test Properties iFOBT – OC Sensor
- Findings Summary Table 5.4 Test Properties iFOBT – OC Light
- Findings Summary Table 5.5 Test Properties iFOBT - Magstream
- Findings Summary Table 5.6 Test Properties iFOBT – FOB Gold
- Findings Summary Table 5.7 Test Properties iFOBT – Other tests
- Findings Summary Table 5.8 Test Properties gFOBT – Hemoccult II
- Findings Summary Table 5.9 Test Properties gFOBT – Hemoccult Sensa
- Findings Summary Table 5.10 Test Properties gFOBt – Hema Screen
- Findings Summary Table 5.11 Test Properties gFOBT – Hema FEC
- Findings Summary Table 5.12 Test Properties gFOBT – CFOBB

Findings Summary Table 5.1 Test Properties iFOBT – Overall:

Study Design	# of studies	Cut-point (Depending on test-type and units)	Sample Size	Results
PPV				
Prospective / Cohort	17 [39-41, 44, 46, 49, 52, 53, 58-63, 70, 75, 76]	20 to 100 ngHb/ml, 7.95 to 50 µgHb/g	524,396	7.35% (4.0% to 10.8%)*
NPV				
Prospective / Cohort	3 [39, 44, 76]	50 to 100 ngHb/ml, 7.95 to 24.5 µgHb/g	5,247	100% (99.7% to 100%)*
Sensitivity				
Prospective / Cohort	9 [39, 44, 51, 52, 63, 64, 69, 74, 76]	50 to 100 ngHb/ml, 7.95 to 24.5 µgHb/g	66,018	81.5% (53.3% to 100%)*
Specificity				
Prospective / Cohort	9 [39, 44, 46, 49, 58, 60, 63, 74, 76]	20 to 100 ngHb/ml, 7.95 to 24.5 µgHb/g	63,560	95.0% (87.2% to 96.9%)*
LR +ve				
Prospective / Cohort	4 [39, 63, 74, 76]	50 to 100 ngHb/ml, 7.95 to 24.5 µgHb/g	10,193	11.4 (7.2 to 26.7)*
LR –ve				
Prospective / Cohort	3 [39, 74, 76]	50 to 100 ngHb/ml, 7.95 to 24.5 µgHb/g	4,261	0.2 (0.10 to 0.49)*
NNS				
Prospective / Cohort	7 [39, 44, 46, 49, 58-60]	20 to 100 ngHb/ml	74,420	209 (41 to 430)*

Findings Summary Table 5.2 Test Properties gFOBT – Overall:

Study Design	# of studies	Sample Size	Results
PPV			
Prospective / Cohort	21 [28, 41-47, 49, 56, 58-63, 65, 67, 68, 71, 76]	946,851	7.5% (1.5% to 15%)*
NPV			
Prospective / Cohort	2 [44, 76]	3,991	99.55% (99.5% to 99.6%) £
Sensitivity			
Prospective / Cohort	12 [44, 45, 48, 51, 54, 55, 57, 63, 72-74, 76]	112,887	47.1% (12.9% to 75.0%)*
Specificity			
Prospective / Cohort	10 [44, 46, 49, 55, 57, 58, 60, 63, 74, 76]	128,892	96.05% (90.1% to 98.1%)*
LR +ve			
Prospective / Cohort	3 [63, 74, 76]	8,804	6.5 (4.0 to 6.98)*
LR –ve			
Prospective / Cohort	2 [74, 76]	3,005	0.75 (0.70 to 0.80) £
NNS			
Prospective / Cohort	4 [46, 49, 58, 59]	50,239	597 (239 to 936)*

Findings Summary Table 5.3 Test Properties iFOBT – OC SENSOR:

Study Design	# of studies	Cut-point (ngHb/ml)	Sample Size	Results
PPV				
Prospective / Cohort	3 [39, 41, 46]	50 ngHb/ml	7,106	6.0% (6.0% to 7.0%)*
Prospective / Cohort	3 [39, 41, 46]	70-75 ngHb/ml	7,106	8.0% (7.0% to 9.0%)*
Prospective / Cohort	9 [39-41, 46, 49, 52, 59, 70, 75]	100 ngHb/ml	426,167	8.0% (5.5% to 10.0%)*
NPV				
Prospective / Cohort	1 [39]	50 ngHb/ml	1,256	100% (99.0% to 100%) ¥
Prospective / Cohort	1 [39]	70-75 ngHb/ml	1,256	100% (99.0% to 100%) ¥
Prospective / Cohort	1 [39]	100 ngHb/ml	1,256	100% (99.0% to 100%) ¥
Sensitivity				
Prospective / Cohort	3 [39, 64, 74]	50 ngHb/ml	24,698	88.0% (81.5% to 92.3%)*
Prospective / Cohort	3 [39, 64, 74]	70-75 ngHb/ml	24,698	81.5% (75.0% to 92.3%)*
Prospective / Cohort	4 [39, 52, 64, 74]	100 ngHb/ml	28,831	86.9% (75.0% to 100%)*
Specificity				
Prospective / Cohort	3 [39, 46, 74]	50 ngHb/ml	5,005	91.0% (87.2% to 92.9%)*
Prospective / Cohort	3 [39, 46, 74]	70-75 ngHb/ml	5,005	93.0% (89.0% to 95.0%)*
Prospective / Cohort	4 [39, 46, 49, 74]	100 ngHb/ml	11,162	95.4% (90.1% to 95.8%)*
LR +ve				
Prospective / Cohort	2 [39, 74]	50 ngHb/ml	2,026	8.4 (7.2 to 9.6)£
Prospective / Cohort	2 [39, 74]	70-75 ngHb/ml	2,026	9.9 (8.4 to 11.4)£
Prospective / Cohort	2 [39, 74]	100 ngHb/ml	2,026	11.85 (9.3 to 14.4) £
LR -ve				
Prospective / Cohort	2 [39, 74]	50 ngHb/ml	2,026	0.12 (0.10 to 0.14) £
Prospective / Cohort	2 [39, 74]	70-75 ngHb/ml	2,026	0.19 (0.10 to 0.27) £
Prospective / Cohort	2 [39: 19011]	100 ngHb/ml	2,026	0.18 (0.10 to 0.26) £
NNS				
Prospective / Cohort	2 [39, 46]	50 ngHb/ml	2,026	183 (179 to 186) £
Prospective / Cohort	2 [39, 46]	70-75 ngHb/ml	2,026	211 (209 to 213) £
Prospective / Cohort	4 [38, 46, 49, 59]	100 ngHb/ml	30,189	211 (72 to 430)*

Findings Summary Table 5.4 Test Properties iFOBT – OC LIGHT:

Study Design	# of studies	Cut-point (ngHb/ml)	Sample Size	Results
PPV				
Prospective / Cohort	1 [44]	50 ngHb/ml	1,756	10.8% (6.3% to 17.8%) ¥
Case-Control	1 [50]	50 ngHb/ml	164	95.8% (89.7% to 98.4%) ¥
NPV				
Prospective / Cohort	1 [44]	50 ngHb/ml	1,756	100% (98.0% to 100%) ¥
Case-Control	1 [50]	50 ngHb/ml	164	87.0% (77.0% to 93.0%) ¥
Sensitivity				
Prospective / Cohort	1 [44]	50 ngHb/ml	1,756	100% (73.2% to 100%) ¥
Case-Control	2 [50, 66]	50 ngHb/ml	345	92.5% (91.0% to 94.0%) £
Prospective / Cohort	1 [69]	100 ngHb/ml	24,913	73.8% (57.4% to 85.0%) ¥
Specificity				
Prospective / Cohort	1 [44]	50 ngHb/ml	1,756	92.7% (89.3% to 95.0%) ¥
Case-Control	2 [50, 66]	50 ngHb/ml	345	95.4% (93.8% to 94.0%) £

Findings Summary Table 5.5 Test Properties iFOBT – Magstream:

Study Design	# of studies	Cut-point (ngHb/ml)	Sample Size	Results
PPV				
Prospective / Cohort	3 [59-61]	20 ngHb/ml	5,9363	7.6% (4.0% to 7.9%)*
Specificity				
Prospective / Cohort	1 [60]	20 ngHb/ml	19,244	96.5% (96.3% to 96.7%) ¥
NNS				
Prospective / Cohort	2 [59, 60]	20 ngHb/ml	39,041	196 (95 to 296) £

Findings Summary Table 5.6 Test Properties iFOBT – FOB GOLD (SENT):

Study Design	# of studies	Cut-point (ngHb/ml)	Sample Size	Results
PPV				
Prospective / Cohort	2 [52, 58]	100 ngHb/ml	27,364	5.4% (4.0% to 6.8%) £
Sensitivity				
Prospective / Cohort	1 [52]	100 ngHb/ml	4,133	67.9%
Specificity				
Prospective / Cohort	1 [58]	100 ngHb/ml	23,231	95.7%
NNS				
Prospective / Cohort	1 [58]	100 ngHb/ml	23,231	369

*Median with range.
¥ Mean with 95% CI.
£ Mean with range.

Findings Summary Table 5.7 Test Properties iFOBT – other tests (single study):

Test type (iFOBT)	Study Design	# of studies	Cut-point	Sample Size	Predictive values	Sensitivity	Specificity	Likelihood ratios
FlexSure OBT	Prospective / Cohort	1 [63]	0.3 mgHb/g	5,932	**PPV**: 5.2%	81.8%	96.9%	**LR+ve**: 26.7
RIDASCREEN -Haemoglobin	Prospective / Cohort	1 [76]	24.5 µgHb/g	2235	**PPV**: 8.1% **NPV**: 99.7%	60%	95.4%	**LR+ve**: 13.06 **LR-ve**: 0.42
RIDASCREEN Hb–Haptoglobin	Prospective / Cohort	1 [76]	7.95 µgHb/g	2235	**PPV**: 7.3% **NPV**: 99.7%	53.3%	95.4%	**LR+ve**: 11.61 **LR-ve**: 0.49
Instant-View	Prospective / Cohort	1 [62]	50 µgHb/g	17,215	**PPV**: 5.9%	-	-	-
Immudia-HemSp	Prospective / Cohort	1 [53]	0.3 mgHb/g	2,336	**PPV**: 7.4%	-	-	-
InSure	Prospective / Cohort	1 [51]	50 µgHb/g	2,351	-	82.4%	-	-
ImmoCARE	Case - Control	1 [66]	30 µgHb/g	181	-	92%	97%	-

Findings Summary Table 5.8 Test Properties gFOBT – Hemoccult/Hemoccult II:

Study Design	# of studies	Sample Size	Results
PPV			
Prospective / Cohort	14 [28, 41, 42, 45, 46, 49, 56, 58-62, 65, 76]	413,023	7.4% (4.5% to 15%)*
NPV			
Prospective / Cohort	1 [76]	2,235	99.5%
Sensitivity			
Prospective / Cohort	8 [45, 48, 54, 55, 57, 73, 74, 76]	95,570	38.1% (12.9% to 61.0%)*
Specificity			
Prospective / Cohort	8 [46, 49, 55, 57, 58, 60, 74, 76]	121,337	96.4% (92.4% to 98.1%)*
LR +ve			
Prospective / Cohort	2 [74, 76]	3,005	5.49 (4.0 to 6.98) £
LR -ve			
Prospective / Cohort	2 [74, 76]	3,005	0.75 (0.7 to 0.8) £
NNS			
Prospective / Cohort	4 [46, 49, 58, 59]	50,239	597 (239 to 936)*

Findings Summary Table 5.9 Test Properties gFOBT – Hemoccult Sensa:

Study Design	# of studies	Sample Size	Results
PPV			
Prospective / Cohort	2 [43, 63]	8,065	5.3% (1.5% to 9.1%) £
Sensitivity			
Prospective / Cohort	3 [48, 51, 63]	10,647	64.3% (47.1% to 75.0%)*
Specificity			
Prospective / Cohort	1 [63]	5,799	90.1% (89.3% to 90.8%) ¥
LR +ve			
Prospective / Cohort	1 [63]	5,799	6.5 (4.3 to 9.6) ¥

Findings Summary Table 5.10 Test Properties gFOBT – Hema Screen:

Study Design	# of studies	Sample Size	Results
PPV			
Prospective / Cohort	4 [47, 67, 68, 71]	524,007	9.1% (5.29% to 12.0%)*

Findings Summary Table 5.11 Test Properties gFOBT – Hemo FEC:

Study Design	# of studies	Sample Size	Results
PPV			
Prospective / Cohort	1 [44]	1,756	13.6% (6.4% to 25.5%) ¥
NPV			
Prospective / Cohort	1 [44]	1,756	99.6% (97.4% to 100%) ¥
Sensitivity			
Prospective / Cohort	1 [44]	1,756	54.2% (27.3% to 79.1%) ¥

Specificity			
Prospective / Cohort	1 [44]	1,756	96.9% (93.9% to 98.5%) ¥

Findings Summary Table 5.12 Test Properties gFOBT – CFOBB:

Study Design	# of studies	Sample Size	Results
Sensitivity			
Prospective / Cohort	1 [72]	7,411	37.5%

*Median with range.

¥ Mean with 95% CI.

£ Mean with range.

Evidence Set 3 KQ3: Harms of Screening

- Findings Summary Table 6.1: Harms of Screening Colonoscopy
- Findings Summary Table 6.2 Harms of Follow-up Colonoscopy
- Findings Summary Table 6.3: Harms of Screening Flexible Sigmoidoscopy
- Findings Summary Table 6.4: Harms of Screening CT Colonoscopy
- Findings Summary Table 6.5: Harms of Follow-up CT Colonoscopy
- Findings Summary Table 6.6: Harms of iFOBT (FIT)
- Findings Summary Table 6.7: Harms of gFOBT (Guaiac)
- Forest Plots 2.1 to 2.15
    - 2.1: Harms of Screening Colonoscopy – Perforation
    - 2.2: Harms of Screening Colonoscopy – Minor bleeding with no hospitalization
    - 2.3: Harms of Screening Colonoscopy – Major bleeding requiring hospitalization
    - 2.4: Harms of Screening Colonoscopy – Death
    - 2.5: Harms of follow-up Colonoscopy – Perforation
    - 2.6: Harms of follow-up Colonoscopy – Minor bleeding with no hospitalization
    - 2.7: Harms of follow-up Colonoscopy - Major bleeding requiring hospitalization
    - 2.8: Harms of follow-up Colonoscopy – Death
    - 2.9: Harms of Screening Sigmoidoscopy – Perforation
    - 2.10: Harms of Screening Sigmoidoscopy - Minor bleeding with no hospitalization
    - 2.11: Harms of Screening Sigmoidoscopy - Major bleeding requiring hospitalization
    - 2.12: Harms of iFOBT (FIT) – False positives (%)
    - 2.13: Harms of iFOBT (FIT) – False negatives (%)
    - 2.14: Harms of gFOBT (Guaiac) – False positives (%)
    - 2.15: Harms of gFOBT (Guaiac) – False negatives (%)

Findings Summary Table 6.1 Harms of Screening Colonoscopy

Study Design	# of studies	Base Population	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
Death					
uncontrolled	1	No. of Colonoscopies	12 / 38,472	0.31 per 1,000 (0.18 to 0.55)	VERY LOW*
uncontrolled	2	No. of Patients	2 / 70,828	0.02 per 1,000 (0.0 to 0.06)	VERY LOW*
Perforation					
uncontrolled	3	No. of Colonoscopies	16 / 39,235	0.41 per 1,000 (0.19 to 0.62)	VERY LOW*
uncontrolled	5	No. of Patients	45 / 84,850	0.53 per 1,000 (0.37 to 0.69)	VERY LOW*
Major Bleeding (requiring hospitalization)					
uncontrolled	1	No. of Colonoscopies	0 / 324	0.0 per 1,000 (0.0 to 11.72)	VERY LOW*
uncontrolled	3	No. of Patients	94 / 79,486	1.08 per 1,000 (0.85 to 1.32)	VERY LOW*
Minor Bleeding (not requiring hospitalization)					
uncontrolled	1	No. of Colonoscopies	103 / 38,472	2.68 per 1,000 (2.21 to 3.25)	VERY LOW*
uncontrolled	4	No. of Patients	9 / 8,974	0.84 per 1,000 (0.0 to 1.98)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.2: Harms of Follow-up Colonoscopy

Study Design	# of studies	Base Population	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
Death					
uncontrolled	3	No. of Colonoscopies	3 / 22,674	0.03 per 1,000 (0.0 to 0.19)	VERY LOW*
uncontrolled	2	No. of Patients	7 / 19,569	0.35 per 1,000 (0.06 to 0.64)	VERY LOW*
Perforation					
uncontrolled	5	No. of Colonoscopies	41 / 37,035	1.04 per 1,000 (0.69 to 1.39)	VERY LOW*
uncontrolled	10	No. of Patients	31 / 51,741	0.61 per 1,000 (0.10 to 1.11)	VERY LOW*
Major Bleeding (requiring hospitalization)					
uncontrolled	3	No. of Colonoscopies	68 / 14,379	4.73 per 1,000 (3.59 to 5.87)	VERY LOW*
uncontrolled	7	No. of Patients	28 / 25,178	1.11 per 1,000 (0.65 to 1.57)	VERY LOW*
Minor Bleeding (not requiring hospitalization)					
uncontrolled	2	No. of Colonoscopies	47 / 15,261	3.02 per 1,000 (2.07 to 3.98)	VERY LOW*
uncontrolled	8	No. of Patients	67 / 25,188	2.75 per 1,000 (1.01 to 4.50)	VERY LOW*
False Positive (proportion)					
uncontrolled	1	No. of Colonoscopies	288 / 10,277	28.0 per 1,000 (25.0 to 31.4)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.3: Harms of Screening Flexible Sigmoidoscopy

Study Design	# of studies	Base Population	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
Death					
uncontrolled	1	No. of Patients	6 / 40,332	0.15 per 1,000 (0.07 to 0.32)	VERY LOW*
Perforation					
uncontrolled	3	No. of Sigmoidoscopies	3 / 116,680	0.03 per 1,000 (0.0 to 0.07)	VERY LOW*
uncontrolled	4	No. of Patients	4 / 277,421	0.01 per 1,000 (0.0 to 0.03)	VERY LOW*
Major Bleeding (requiring hospitalization)					
uncontrolled	2	No. of Patients	14 / 149,866	0.09 per 1,000 (0.04 to 0.15)	VERY LOW*
Minor Bleeding (not requiring hospitalization)					
uncontrolled	2	No. of Sigmoidoscopies	0 / 9,444	0.0 per 1,000 (0.0 to 0.29)	VERY LOW*
uncontrolled	5	No. of Patients	101 / 281,887	0.5 per 1,000 (0.25 to 0.74)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.4: Harms of Screening CT Colonoscopy

Study Design	# of studies	Base Population	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
Perforation					
uncontrolled	1	No. of Patients	0 / 11,707	0.0 per 1,000 (0.0 to 0.33)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.5 Harms of Follow-up CT Colonoscopy

Study Design	# of studies	Base Population	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
Perforation					
uncontrolled	1	No. of Patients	2 / 10,216	0.20 per 1,000 (0.05 to 0.71)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.6: Harms of iFOBT (FIT)

Study Design	# of studies	Cut-Point (ng/ml)	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
False Positives (%)					
uncontrolled	2	50 ng/ml	3,022 / 23,442	128.9 per 1,000 (124.6 to 133.2)	VERY LOW*
uncontrolled	2	70-75 ng/ml	2,010 / 23,442	93.7 per 1,000 (72.0 to 115.4)	VERY LOW*
uncontrolled	3	100 ng/ml	1,707 / 43,239	55.52 per 1,000 (22.05 to 88.9)	VERY LOW*
False negatives (%)					
uncontrolled	1	50 ng/ml	1 / 770	1.30 per 1,000 (0.23 to 7.32)	VERY LOW*
uncontrolled	2	70-75 ng/ml	1 / 1,994	0.21 per 1,000 (0.12 to 0.16)	VERY LOW*
uncontrolled	2	100 ng/ml	5 / 5,793	0.83 per 1,000 (0.0 to 1.67)	VERY LOW*

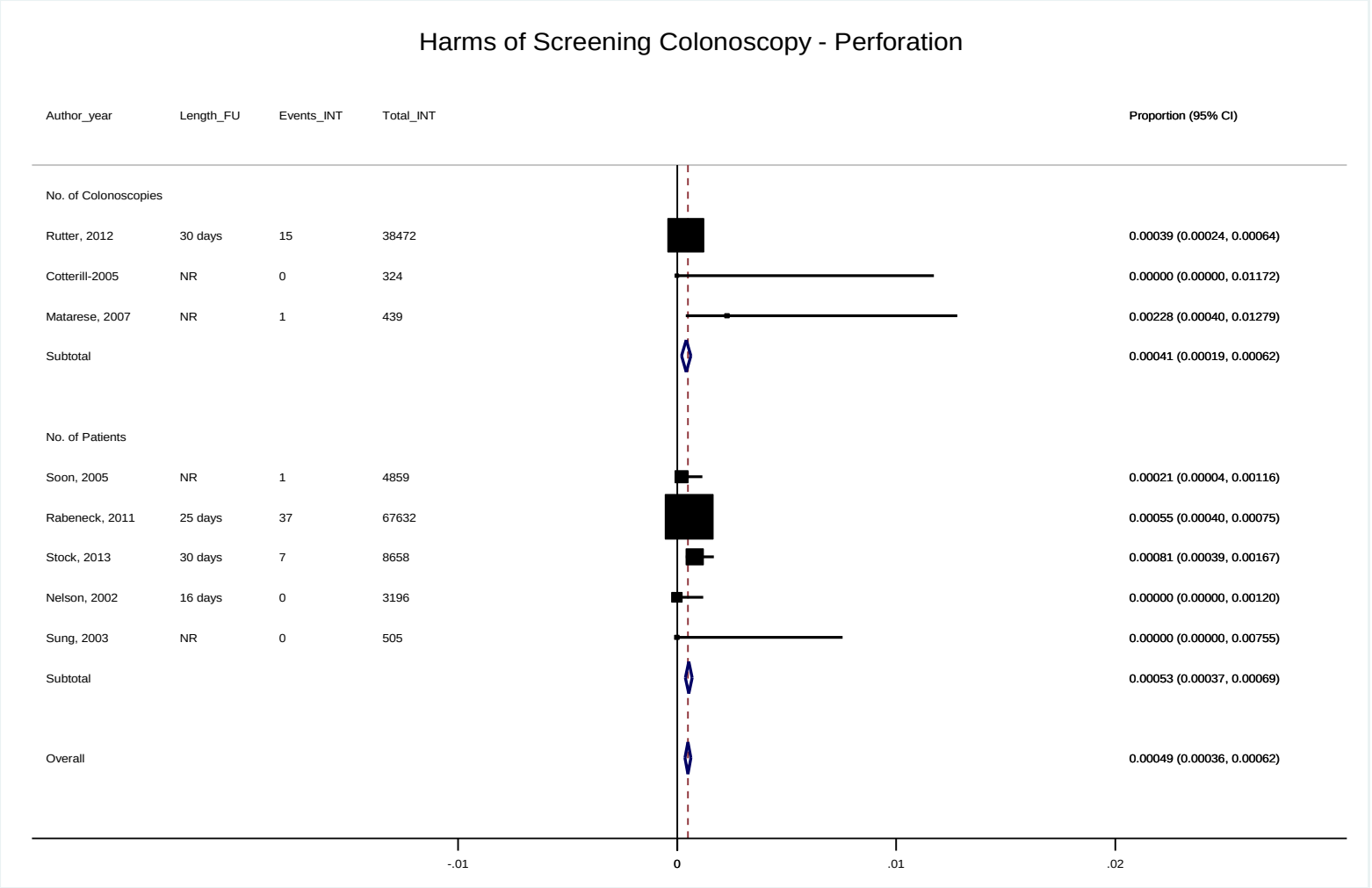
*uncontrolled studies start at very low quality in GRADE evidence rankings.

Findings Summary Table 6.7: Harms of gFOBT (Guaiac)

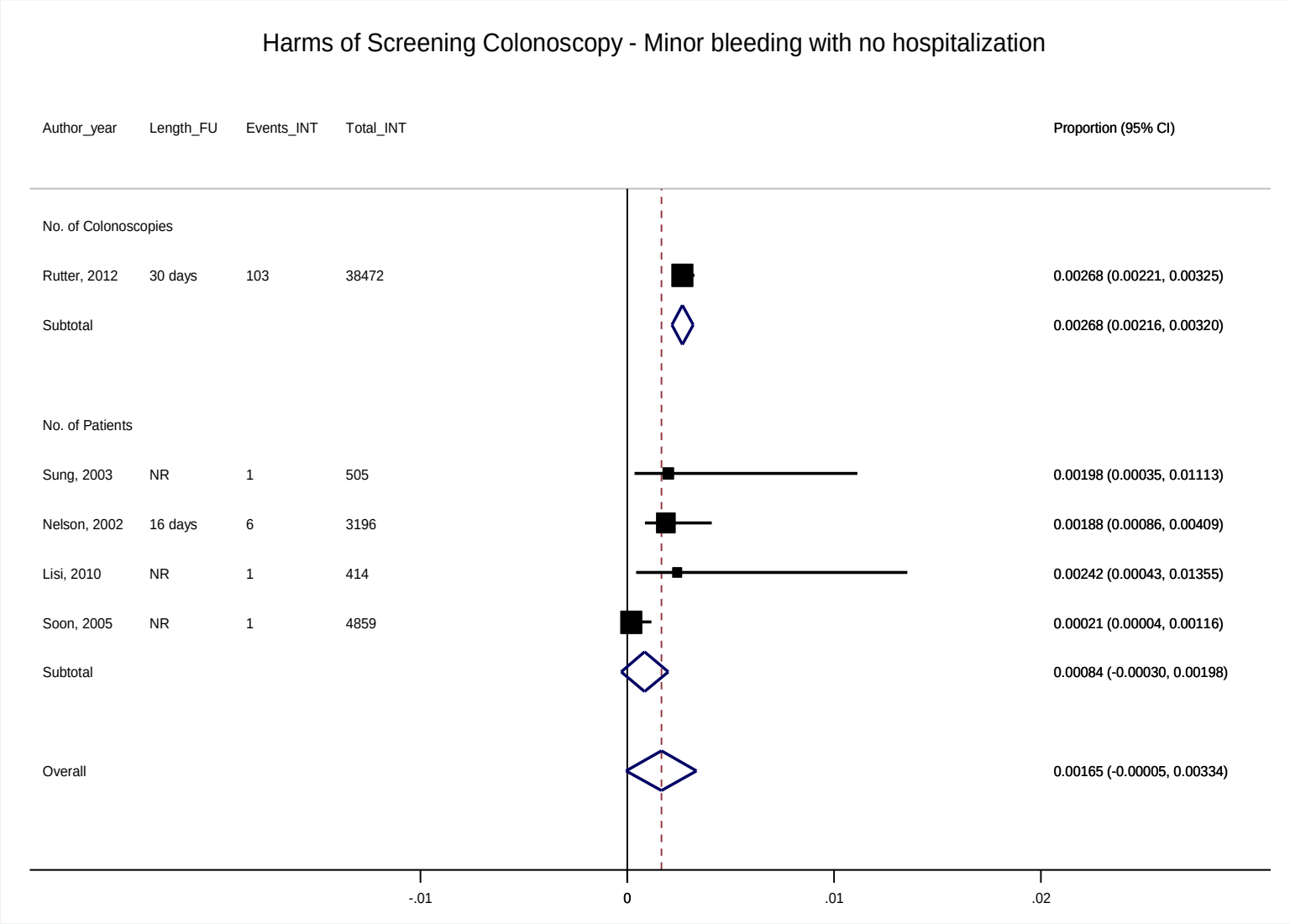
Study Design	# of studies	Sample Size (Events / Total)	Results (proportion per 1,000 with 95% CI)	GRADE Rating
False Positives (%)				
uncontrolled	2	251 / 20567	12.2 per 1,000 (10.71 to 13.70)	VERY LOW*
False negatives (%)				
uncontrolled	3	18 / 3,270	5.51 per 1,000 (2.80 to 8.22)	VERY LOW*

*uncontrolled studies start at very low quality in GRADE evidence rankings.

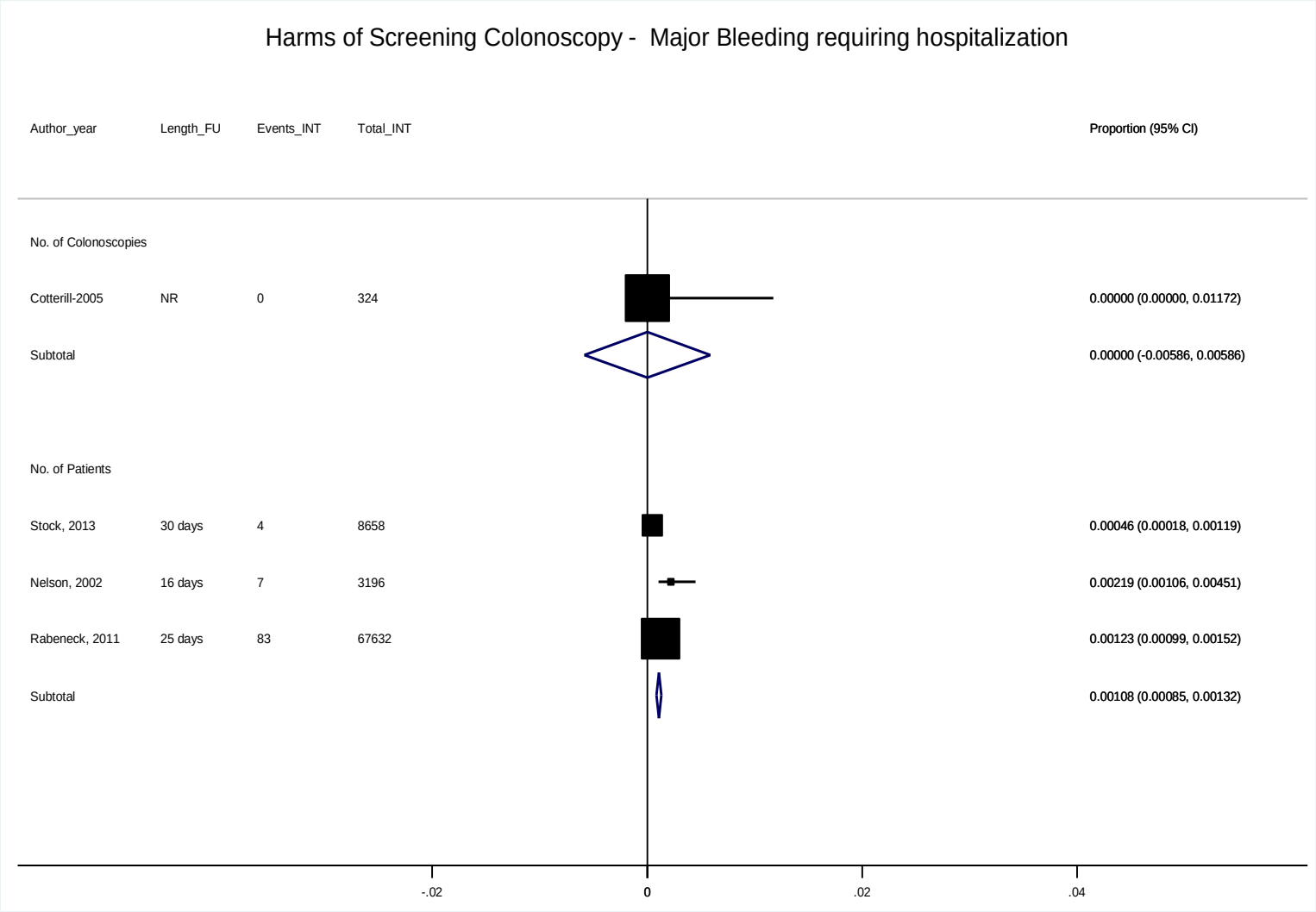
Forest Plot 2.1: Harms of Screening Colonoscopy – Perforation



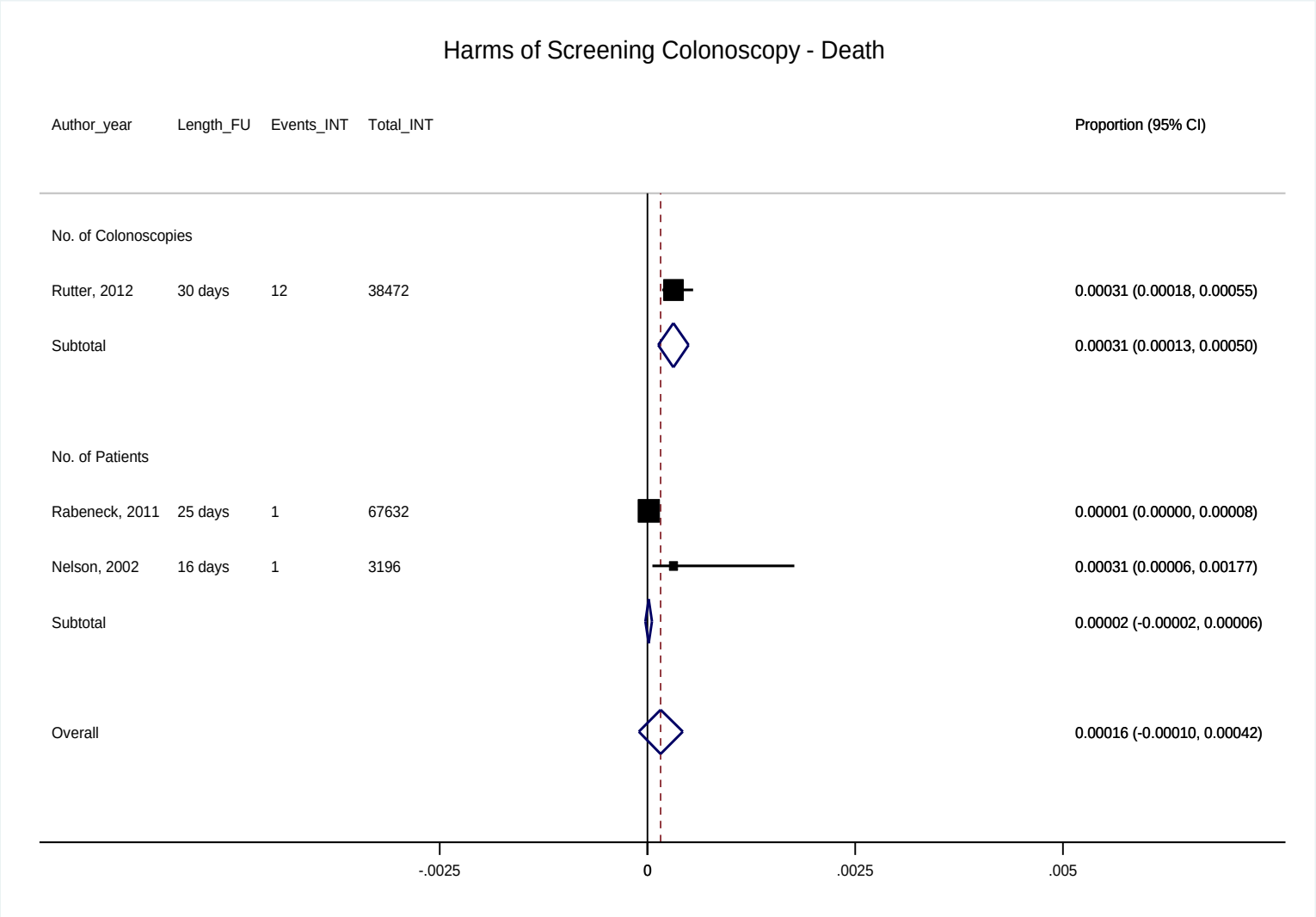
Forest Plot 2.2: Harms of Screening Colonoscopy – Minor bleeding with no hospitalization



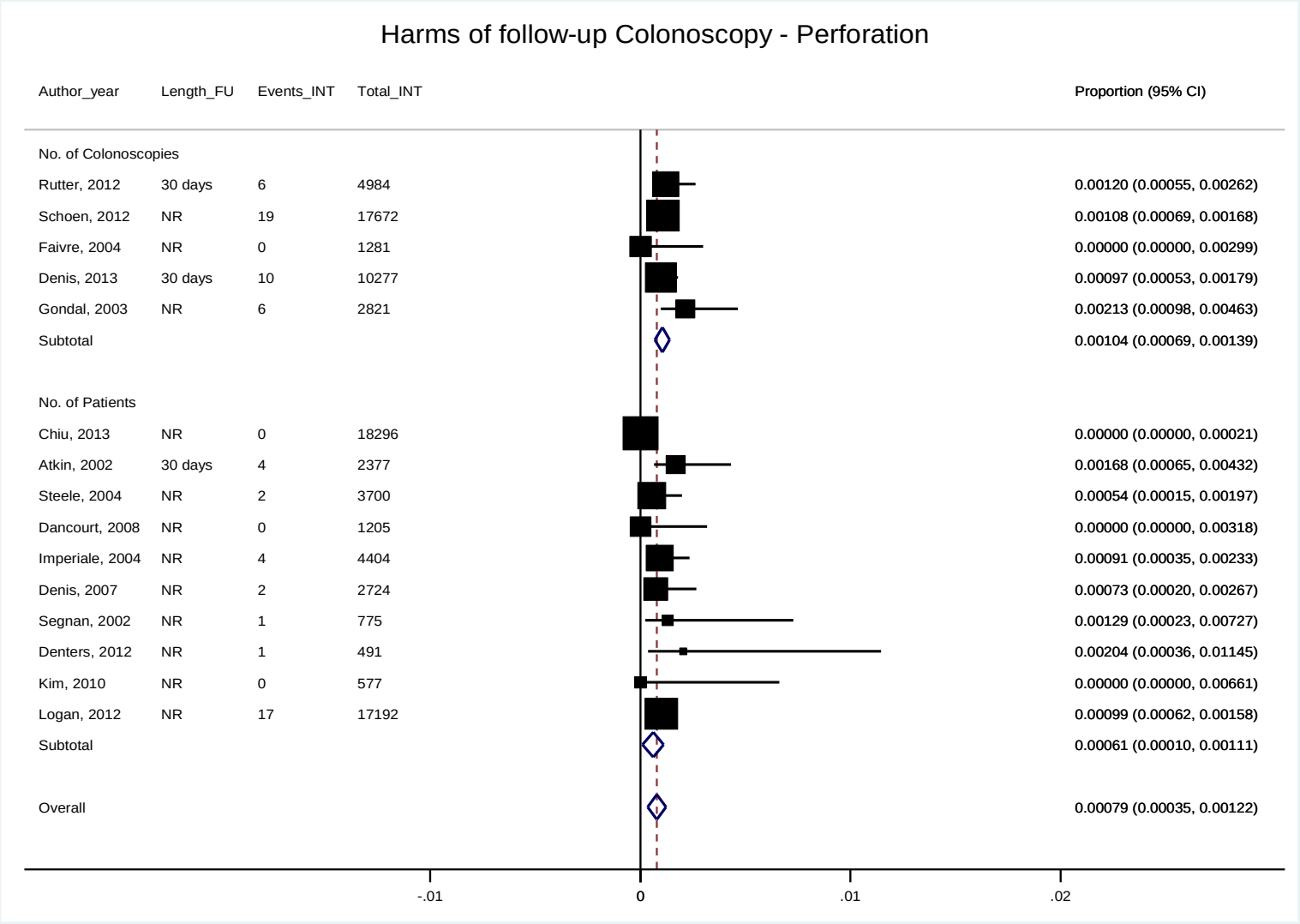
Forest Plot 2.3: Harms of Screening Colonoscopy – Major bleeding requiring hospitalization



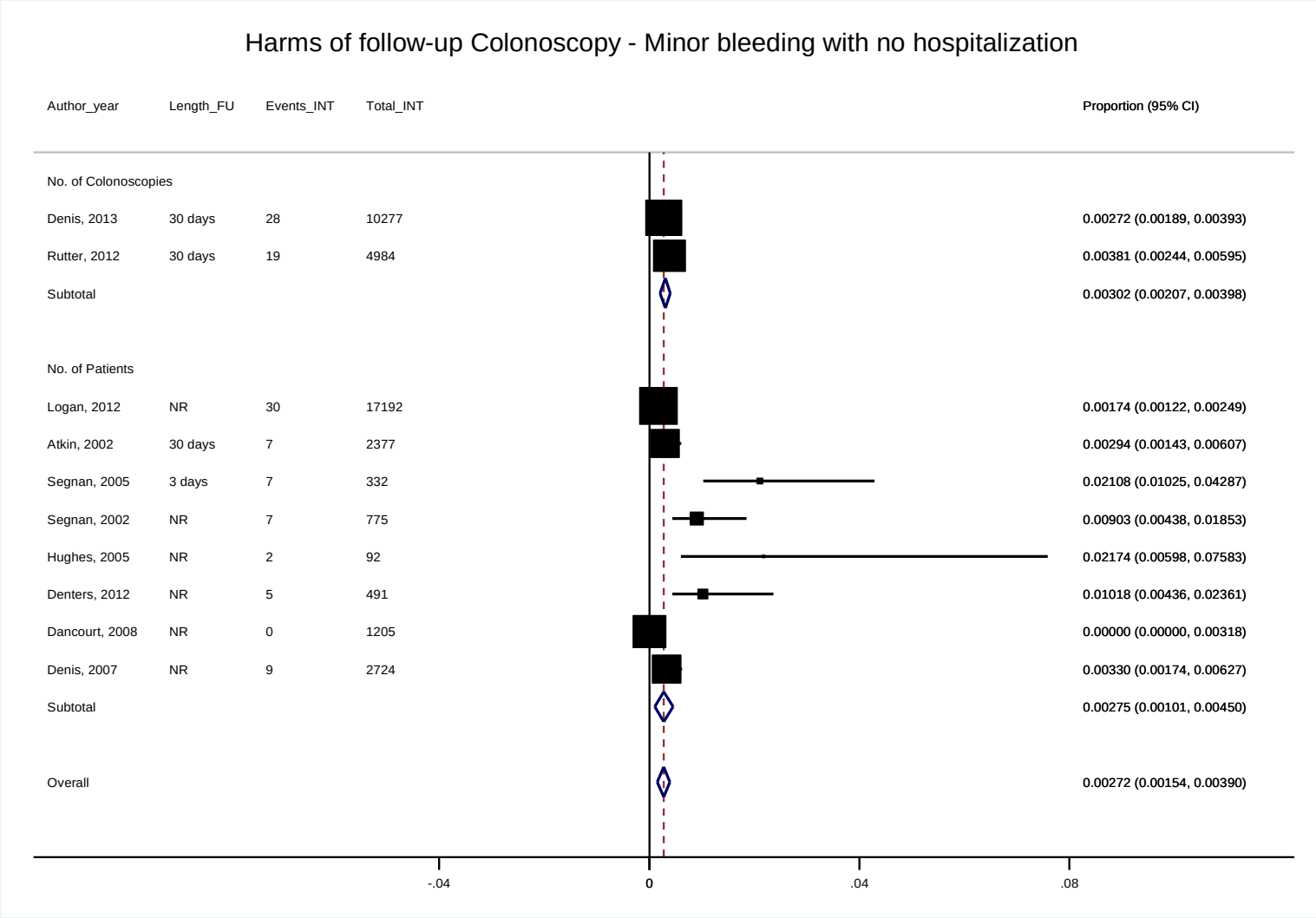
Forest Plot 2.4: Harms of Screening Colonoscopy – Death



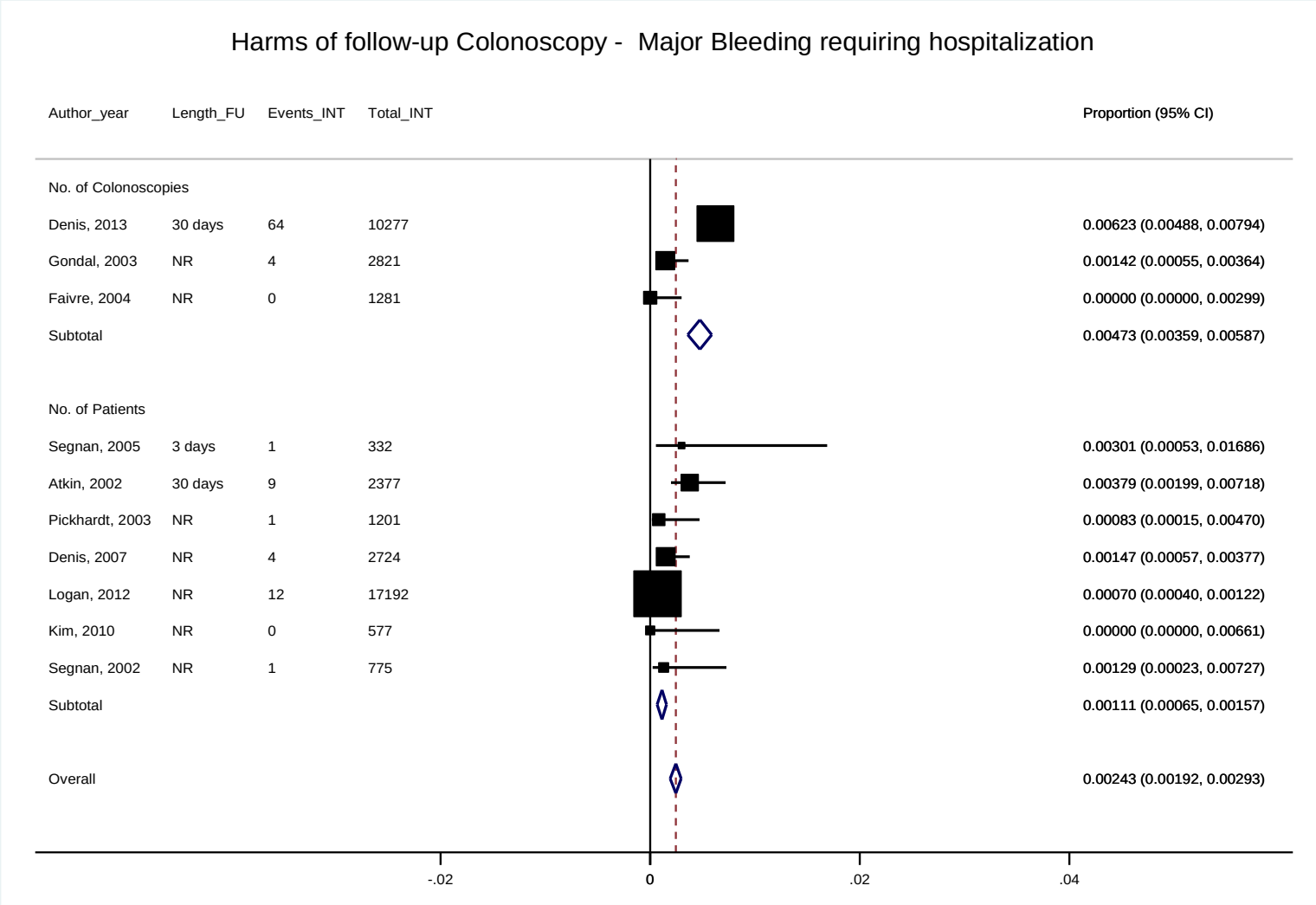
Forest Plot 2.5: Harms of follow-up Colonoscopy – Perforation



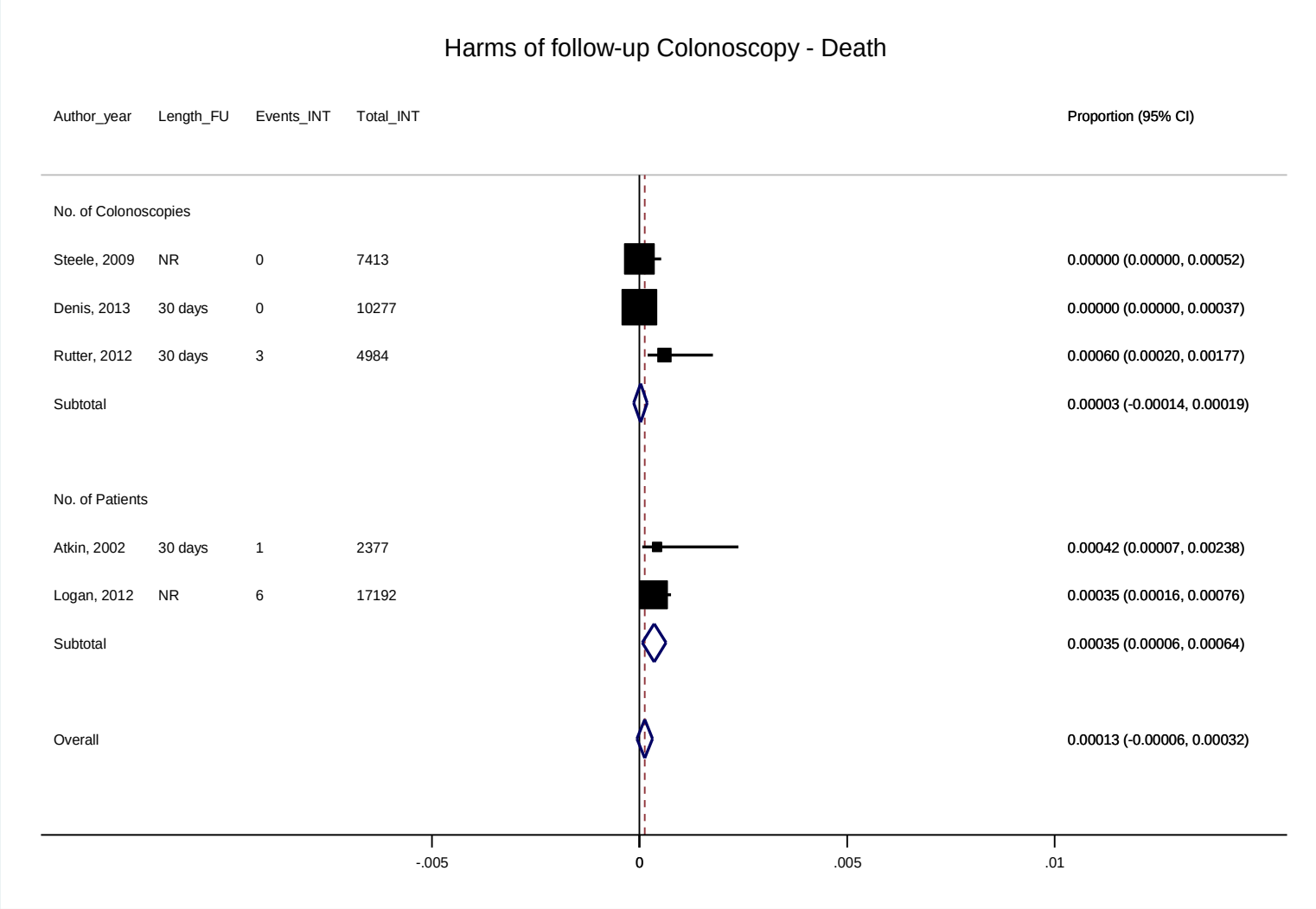
Forest Plot 2.6: Harms of follow-up Colonoscopy – Minor bleeding with no hospitalization



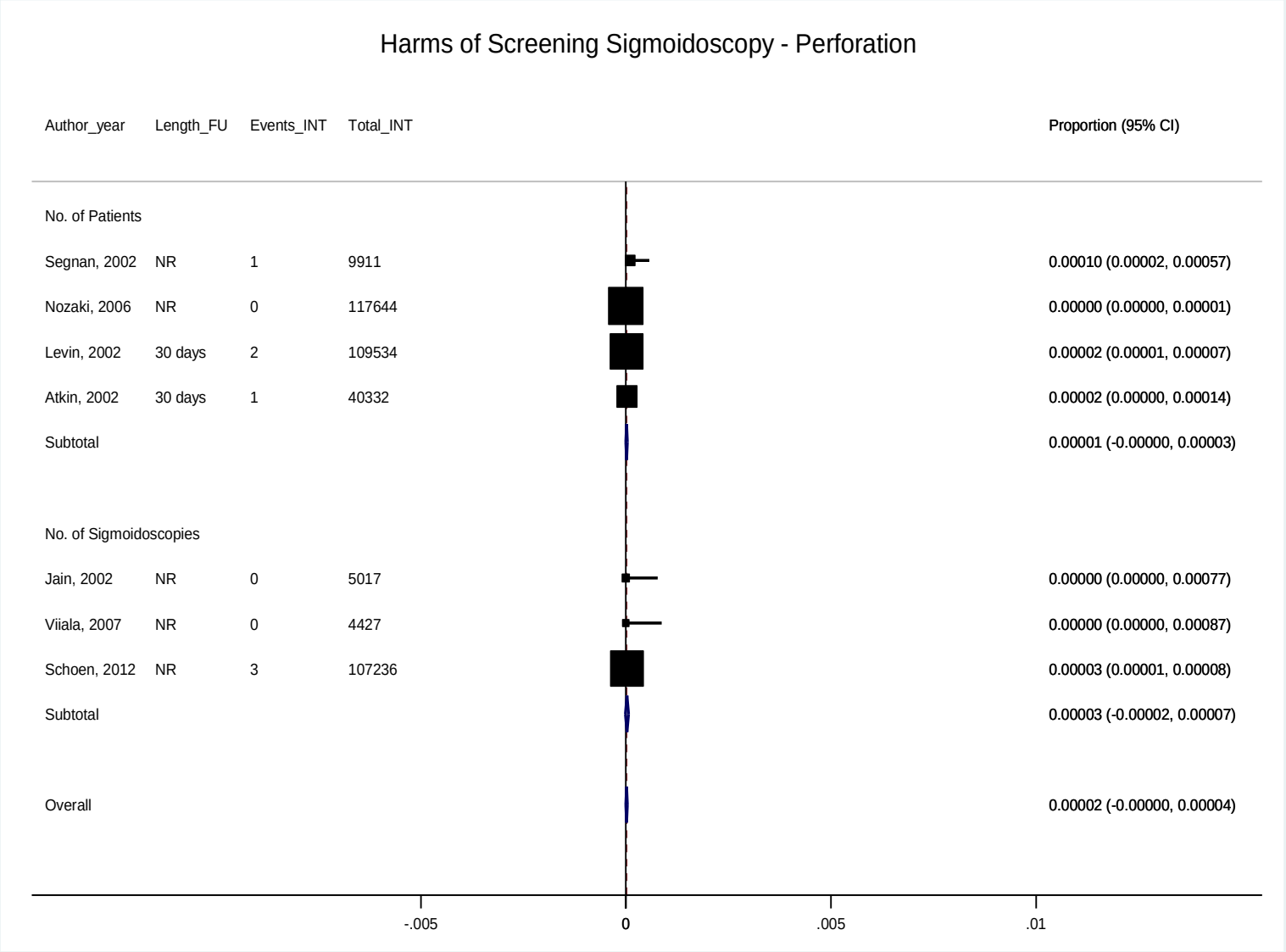
Forest Plot 2.7: Harms of follow-up Colonoscopy – Major bleeding requiring hospitalization



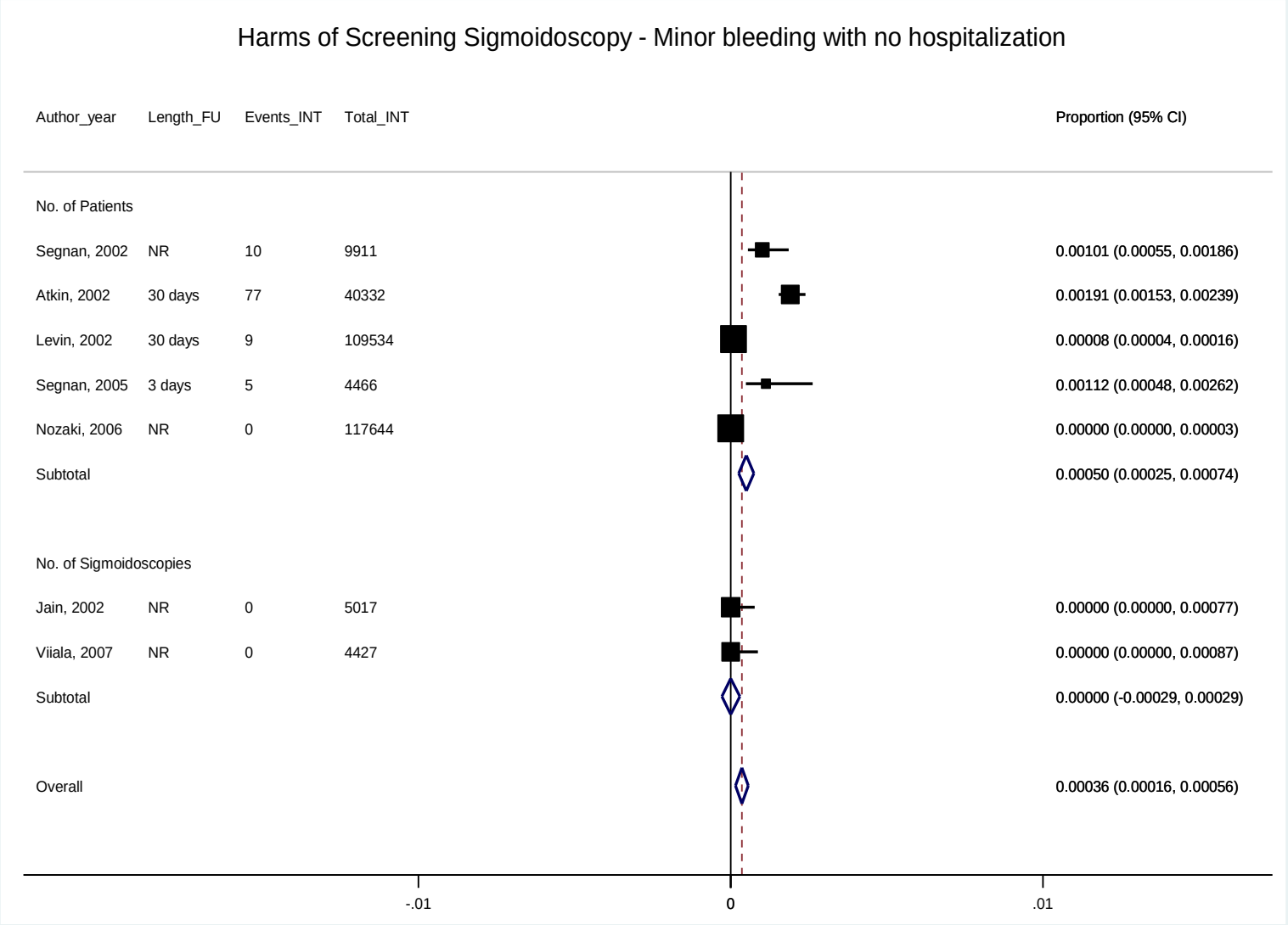
Forest Plot 2.8: Harms of follow-up Colonoscopy – Death



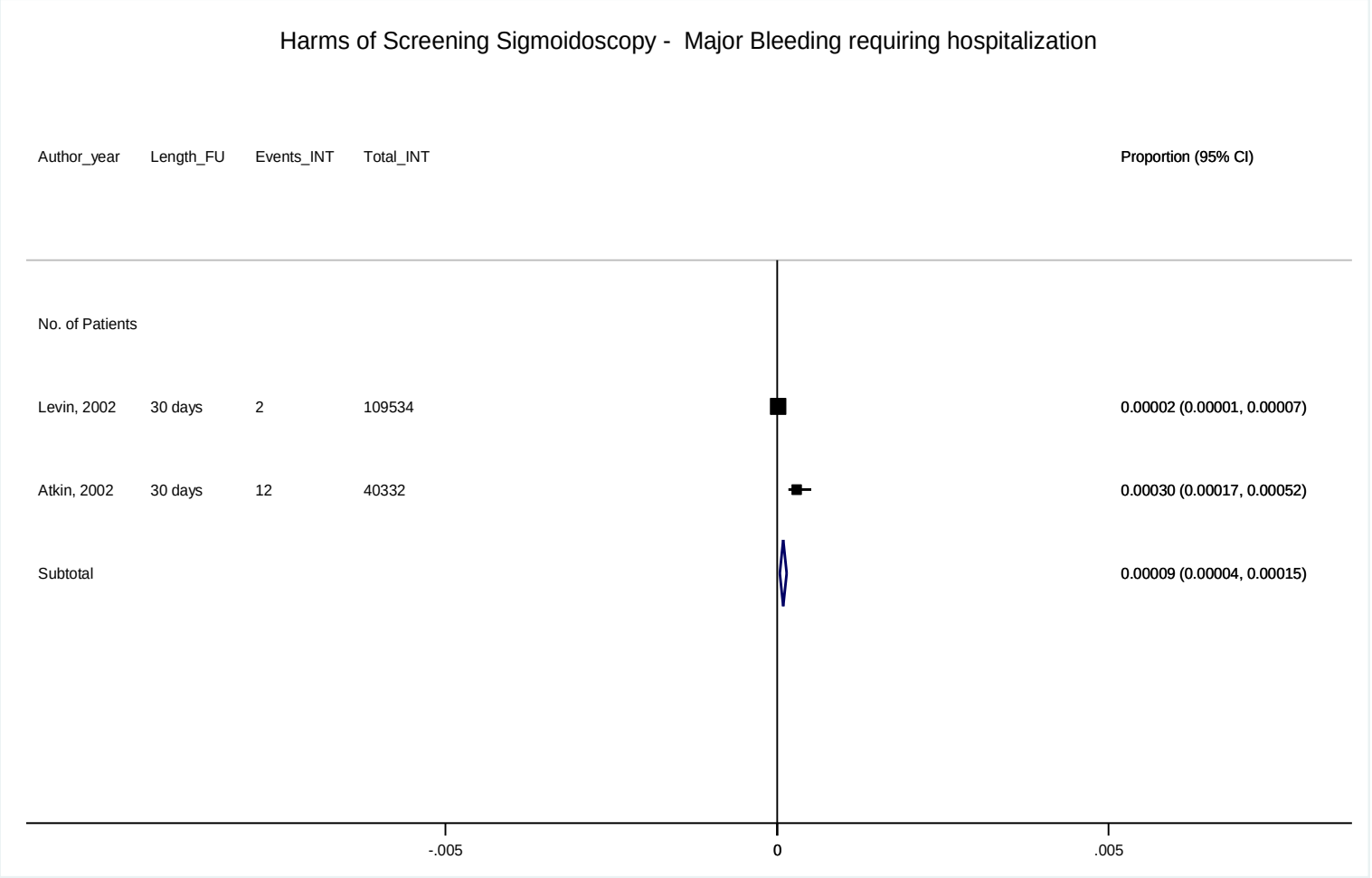
Forest Plot 2.9: Harms of Screening Sigmoidoscopy – Perforation



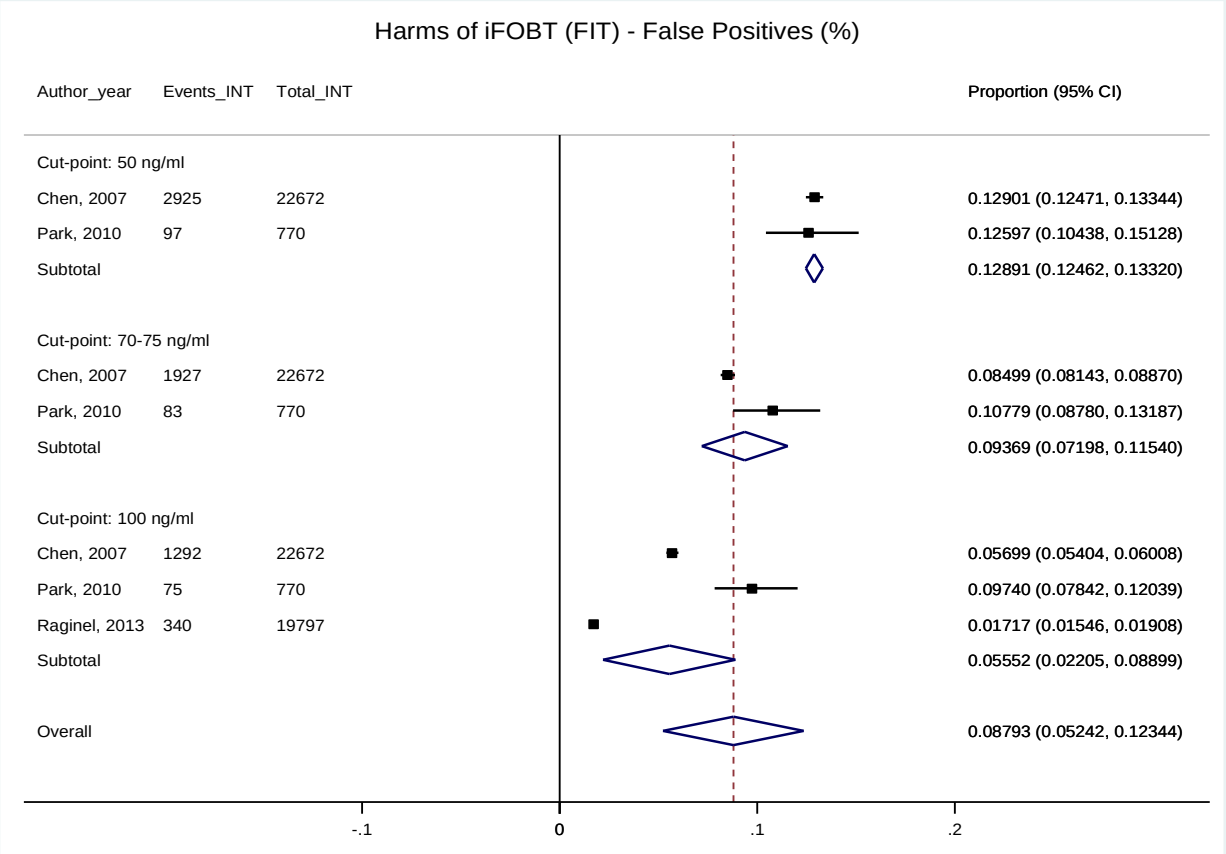
Forest Plot 2.10: Harms of Screening Sigmoidoscopy – Minor bleeding with no hospitalization



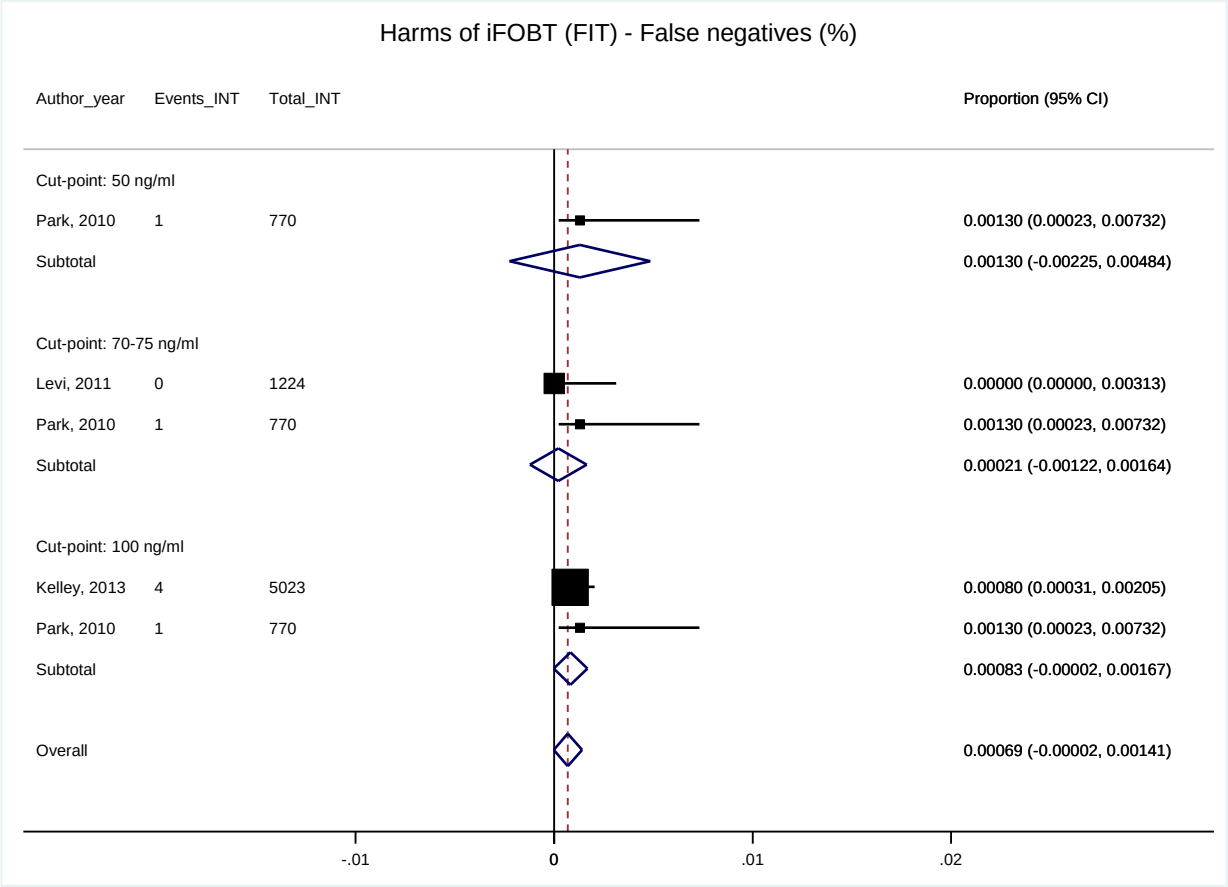
Forest Plot 2.11: Harms of Screening Sigmoidoscopy – Major bleeding requiring hospitalization



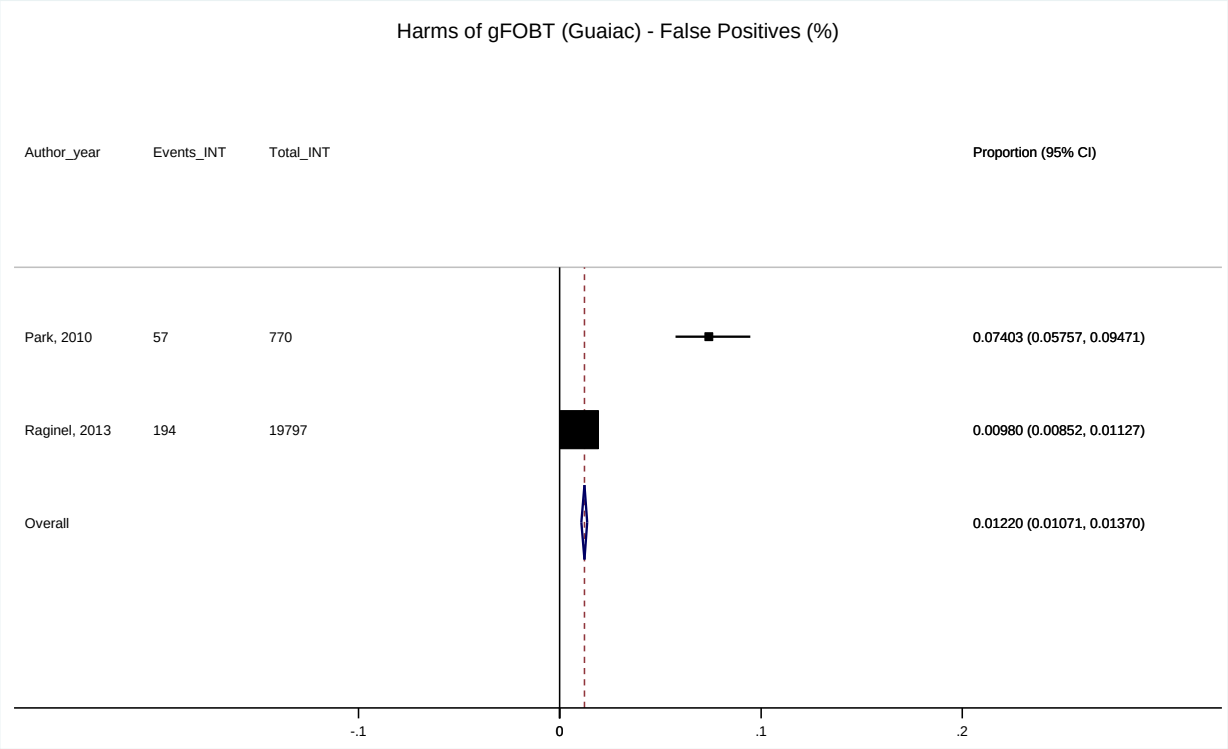
Forest Plot 2.12: Harms of iFOBT (FIT) – False positives (%)



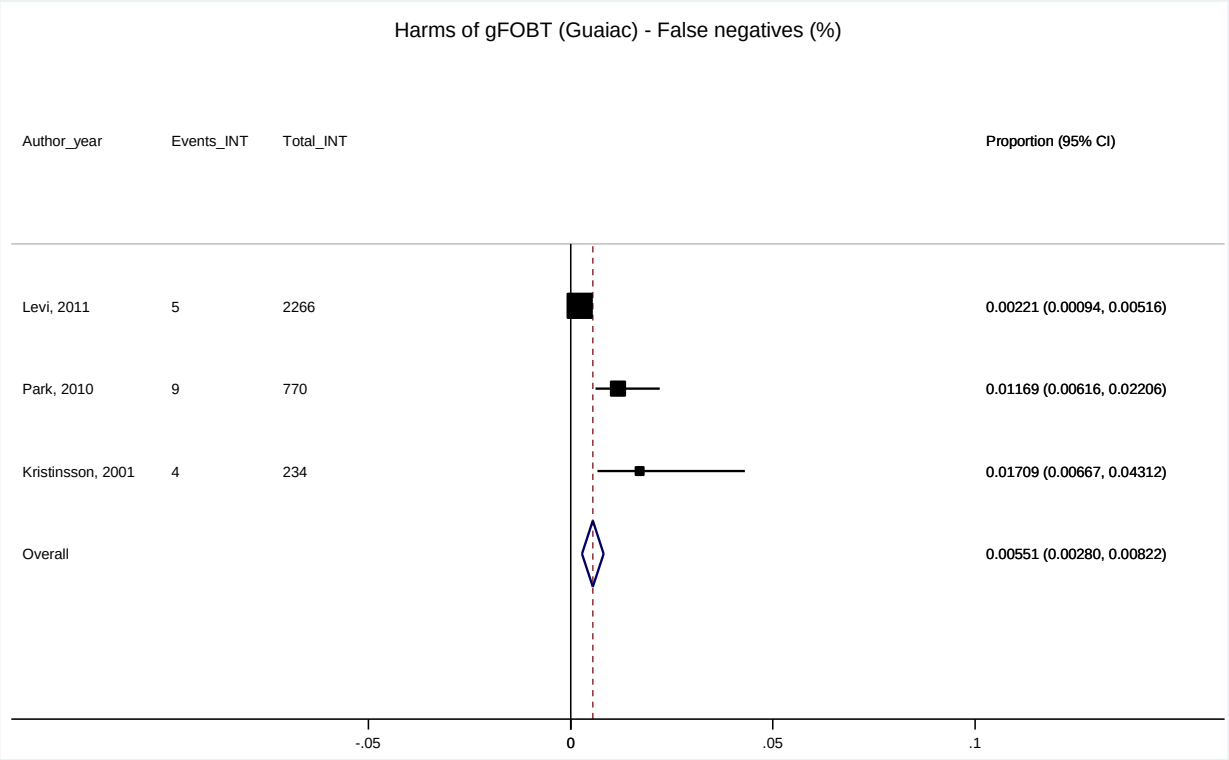
Forest Plot 2.13: Harms of iFOBT (FIT) – False negatives (%)



Forest Plot 2.14: Harms of gFOBT (Guaiac) – False positives (%)



Forest Plot 2.15: Harms of gFOBT (Guaiac) – False negatives (%)



Appendices

Appendix 1: Search Strategies for Key Questions (KQ)

Medline-OVID
Last Searched: Nov 21 2013
1. Colonoscopy/
2. Colonoscop*.ti,ab.
3. Sigmoidoscopy/ or Digital Rectal Examination/
4. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
5. Colonoscopy, Computed Tomographic/
6. Colonograph*.ti,ab.
7. Occult blood/
8. ifobt*.ti,ab.
9. fobt*.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. FlexSure OBT.ti,ab.
16. immoCARE.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.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. Guaiac/du
28. exp cohort studies/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. Epidemiologic studies/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional.tw.
35. Cross-sectional studies/
36. or/28-35
37. or/1-27
38. Stool screening.ti,ab.
39. Stool test*.ti,ab.
40. Stool based test*.ti,ab.
41. Feces/
42. or/38-41
43. Colorectal Neoplasms/

44. Colonic Neoplasms/
45. Sigmoid Neoplasms/
46. Rectal Neoplasms/
47. Anus Neoplasms/
48. Anal Gland Neoplasms/
49. Intestinal Polyps/
50. Colonic Polyps/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/43-51
53. 42 and 52
54. Mass Screening/
55. screen*.ti,ab.
56. or/54-55
57. 52 and 56
58. (clinical trial, all or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews).pt.
59. random*.ti,ab.
60. clinical trial*.ti,ab.
61. or/58-60
62. 37 or 53 or 57
63. 61 and 62
64. "Sensitivity and Specificity"/
65. "Predictive Value of Tests"/
66. "Reproducibility of Results"/
67. Reference Values/
68. Reference Standards/
69. False Negative Reactions/
70. False Positive Reactions/
71. ROC Curve/
72. Sensitiv*.mp.
73. Predictive value*.mp.
74. Accuracy.tw.
75. or/64-74
76. 37 and 75
77. 53 and 75
78. 57 and 75
79. Colonoscopy/st
80. Sigmoidoscopy/st or Digital Rectal Examination/st
81. 76 or 77 or 78 or 79 or 80
82. adverse.tw.
83. harm*.tw.
84. complication*.tw.
85. side effect*.tw.
86. mortality/
87. mortality.tw.
88. perforat*.tw.

89. false positive.tw.
90. false negative.tw.
91. (overdiagnosis or over diagnosis).tw.
92. (overtreatment or over treatment).tw.
93. or/82-92
94. 62 and 93
95. Colonoscopy/ae, mo
96. Sigmoidoscopy/ae, mo or Digital Rectal Examination/ae, mo
97. 94 or 95 or 96
98. 36 or 61
99. 81 or 97
100. 98 and 99
101. 63 or 100
102. limit 101 to (english or french)
103. animals/ not humans/
104. 102 not 103
105. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen?).ti,jn.
106. 104 not 105
107. exp *Polymorphism, Genetic/
108. polymorphism.ti.
109. 107 or 108
110. 106 not 109
111. limit 110 to yr="2000 -Current"
112. limit 111 to (clinical conference or comment or congresses or editorial or letter or newspaper article)
113. 111 not 112
114. limit 113 to ed=20130730-20131121

EMBASE-OVID
Last Searched: Nov. 21, 2013
1. colonoscopy/
2. Colonoscop*.ti,ab.
3. sigmoidoscopy/
4. digital rectal examination/
5. Sigmoidoscopy/ or Digital Rectal Examination/ or barium enema/
6. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
7. computed tomographic colonoscopy/
8. Colonograph*.ti,ab.
9. occult blood/
10. ifobt*.ti,ab.
11. fobt*.ti,ab.
12. Fecal occult blood.ti,ab.
13. ((fecal or faecal) and immunochemical).ti,ab.
14. ((fecal or faecal) and dna).ti,ab.
15. Instant-view.ti,ab.
16. FlexSure OBT.ti,ab.

17. immoCARE.ti,ab.
18. HemeSelect.ti,ab.
19. MonoHaem.ti,ab.
20. ColoScreen.ti,ab.
21. Seracult.ti,ab.
22. HM-Jack.ti,ab.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. guaiac/
28. cohort analysis/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. community sample/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional studies/
35. or/28-34
36. Stool screening.ti,ab.
37. Stool test*.ti,ab.
38. Stool based test*.ti,ab.
39. feces analysis/
40. or/36-39
41. Colorectal cancer/
42. Colorectal tumor/
43. Colon polyp/
44. Adenomatous polyp/
45. exp intestine tumor/
46. Colorectal cancer.ti,ab.
47. Colorectal neoplas*.ti,ab.
48. Colon cancer.ti,ab.
49. colon neoplas*.ti,ab.
50. exp anus tumor/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/41-51
53. diagnostic accuracy/
54. diagnosis/ or diagnostic accuracy/ or exp diagnostic error/ or exp diagnostic test/ or diagnostic test accuracy study/ or diagnostic value/ or exp tumor diagnosis/
55. reference value/
56. predictive value/
57. reproducibility/ or measurement precision/
58. Sensitiv*.mp.
59. Predictive value*.mp.
60. Accuracy.tw.
61. or/53-60

62. screening/ or screening test/
63. cancer screening/
64. mass screening/
65. screen*.ti,ab.
66. or/62-65
67. random*.ti,ab.
68. "controlled clinical trial (topic)"/ or "clinical trial (topic)"/ or controlled study/ or "randomized controlled trial (topic)"/
69. (meta anal* or metaanal* or systematic review).ti,ab.
70. "systematic review"/
71. meta analysis/
72. or/67-71
73. adverse outcome/
74. *complication/co, di, pc [Complication, Diagnosis, Prevention]
75. side effect/
76. mortality/ or cancer mortality/
77. perforat*.tw.
78. false positive result/ or diagnostic error/
79. false negative result/
80. (false adj (positive or negative)).tw.
81. (overtreatment or over treatment).tw.
82. (overdiagnosis or over diagnosis).tw.
83. adverse.tw.
84. or/73-83
85. or/1-27
86. 40 and 52
87. 52 and 66
88. 85 or 86 or 87
89. 72 and 88
90. 61 and 85
91. 61 and 86
92. 61 and 87
93. 90 or 91 or 92
94. 84 and 88
95. 35 or 72
96. 93 and 95
97. 84 and 85
98. 84 and 86
99. 84 and 87
100. 94 and 95
101. 88 or 93 or 94
102. 95 and 101
103. 89 or 96 or 102
104. limit 103 to (english or french)

105. limit 104 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine)
106. 104 not 105
107. limit 106 to yr="2000 -Current"
108. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen? or neonat*).ti,jn.
109. 107 not 108
110. limit 109 to (book or book series or conference abstract or conference paper or conference proceeding or editorial or letter or note)
111. 109 not 110
112. polymorphism.ti.
113. *genetic polymorphism/ or *genetic heterogeneity/ or *molecular genetics/ or *population genetics/multimedia
114. 112 or 113
115. 111 not 114
116. limit 115 to em=201327-201346

Cochrane Central-OVID
Last Searched Nov. 21 2013
1. Colonoscopy/
2. Colonoscop*.ti,ab.
3. Sigmoidoscopy/ or Digital Rectal Examination/
4. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
5. Colonoscopy, Computed Tomographic/
6. Colonograph*.ti,ab.
7. Occult blood/
8. ifobt*.ti,ab.
9. fobt*.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. FlexSure OBT.ti,ab.
16. immoCARE.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.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.

27. Guaiac/du
28. exp cohort studies/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. Epidemiologic studies/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional.tw.
35. Cross-sectional studies/
36. or/28-35
37. or/1-27
38. Stool screening.ti,ab.
39. Stool test*.ti,ab.
40. Stool based test*.ti,ab.
41. Feces/
42. or/38-41
43. Colorectal Neoplasms/
44. Colonic Neoplasms/
45. Sigmoid Neoplasms/
46. Rectal Neoplasms/
47. Anus Neoplasms/
48. Anal Gland Neoplasms/
49. Intestinal Polyps/
50. Colonic Polyps/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/43-51
53. 42 and 52
54. Mass Screening/
55. screen*.ti,ab.
56. or/54-55
57. 52 and 56
58. (clinical trial, all or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews).pt.
59. random*.ti,ab.
60. clinical trial*.ti,ab.
61. or/58-60
62. 37 or 53 or 57
63. 61 and 62
64. "Sensitivity and Specificity"/
65. "Predictive Value of Tests"/
66. "Reproducibility of Results"/
67. Reference Values/
68. Reference Standards/
69. False Negative Reactions/
70. False Positive Reactions/
71. ROC Curve/

72. Sensitiv*.mp.
73. Predictive value*.mp.
74. Accuracy.tw.
75. or/64-74
76. 37 and 75
77. 53 and 75
78. 57 and 75
79. Colonoscopy/st
80. Sigmoidoscopy/st or Digital Rectal Examination/st
81. 76 or 77 or 78 or 79 or 80
82. adverse.tw.
83. harm*.tw.
84. complication*.tw.
85. side effect*.tw.
86. mortality/
87. mortality.tw.
88. perforat*.tw.
89. false positive.tw.
90. false negative.tw.
91. (overdiagnosis or over diagnosis).tw.
92. (overtreatment or over treatment).tw.
93. or/82-92
94. 62 and 93
95. Colonoscopy/ae, mo
96. Sigmoidoscopy/ae, mo or Digital Rectal Examination/ae, mo
97. 94 or 95 or 96
98. 36 or 61
99. 81 or 97
100. 98 and 99
101. 63 or 100
102. limit 101 to (english or french)
103. animals/ not humans/
104. 102 not 103
105. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen?).ti,jn.
106. 104 not 105
107. exp *Polymorphism, Genetic/
108. polymorphism.ti.
109. 107 or 108
110. 106 not 109
111. limit 110 to yr="2000 -Current"
112. limit 111 to (clinical conference or comment or congresses or editorial or letter or newspaper article)
113. 111 not 112
114. limit 113 to yr="2013"

CONTEXT QUESTIONS

Medline-OVID
Last Searched: December 18 2013
Questions 1-3
1. Colonoscopy/
2. Colonoscop*.ti,ab.
3. Sigmoidoscopy/ or Digital Rectal Examination/
4. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
5. Colonoscopy, Computed Tomographic/
6. Colonograph*.ti,ab.
7. Occult blood/
8. ifobt*.ti,ab.
9. fobt*.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. FlexSure OBT.ti,ab.
16. immoCARE.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.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. Guaiac/du
28. exp cohort studies/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. Epidemiologic studies/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional.tw.
35. Cross-sectional studies/
36. or/28-35
37. or/1-27
38. Stool screening.ti,ab.
39. Stool test*.ti,ab.
40. Stool based test*.ti,ab.
41. Feces/
42. or/38-41
43. Colorectal Neoplasms/

44. Colonic Neoplasms/
45. Sigmoid Neoplasms/
46. Rectal Neoplasms/
47. Anus Neoplasms/
48. Anal Gland Neoplasms/
49. Intestinal Polyps/
50. Colonic Polyps/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/43-51
53. 42 and 52
54. Mass Screening/
55. screen*.ti,ab.
56. or/54-55
57. 52 and 56
58. (clinical trial, all or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews).pt.
59. random*.ti,ab.
60. clinical trial*.ti,ab.
61. or/58-60
62. 37 or 53 or 57
63. 61 and 62
64. "Sensitivity and Specificity"/
65. "Predictive Value of Tests"/
66. "Reproducibility of Results"/
67. Reference Values/
68. Reference Standards/
69. False Negative Reactions/
70. False Positive Reactions/
71. ROC Curve/
72. Sensitiv*.mp.
73. Predictive value*.mp.
74. Accuracy.tw.
75. or/64-74
76. 37 and 75
77. 53 and 75
78. 57 and 75
79. Colonoscopy/st
80. Sigmoidoscopy/st or Digital Rectal Examination/st
81. 76 or 77 or 78 or 79 or 80
82. adverse.tw.
83. harm*.tw.
84. complication*.tw.
85. side effect*.tw.
86. mortality/
87. mortality.tw.
88. perforat*.tw.

89. false positive.tw.
90. false negative.tw.
91. (overdiagnosis or over diagnosis).tw.
92. (overtreatment or over treatment).tw.
93. or/82-92
94. 62 and 93
95. Colonoscopy/ae, mo
96. Sigmoidoscopy/ae, mo or Digital Rectal Examination/ae, mo
97. 94 or 95 or 96
98. 36 or 61
99. 81 or 97
100. 98 and 99
101. 63 or 100
102. limit 101 to (english or french)
103. animals/ not humans/
104. 102 not 103
105. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen?).ti,jn.
106. 104 not 105
107. exp *Polymorphism, Genetic/
108. polymorphism.ti.
109. 107 or 108
110. 106 not 109
111. limit 110 to yr="2000 -Current"
112. limit 111 to (clinical conference or comment or congresses or editorial or letter or newspaper article)
113. 111 not 112
114. risk prediction tools.mp.
115. *risk assessment/
116. (risk assessment or risk stratification or risk prediction).tw.
117. (risk adj3 (predication or tool or score or scale)).tw.
118. risk assessment/
119. 114 or 116 or 117 or 118
120. 110 and 119
121. (meta anal* or metaanal*).ti,ab.
122. meta-analysis.pt,ti,ab,sh.
123. (meta anal$ or metaanal$).ti,ab,sh.
124. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
125. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
126. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
127. (medline or embase or cochrane or pubmed or pub med).ti,ab.
128. or/125-127
129. review.pt,sh.
130. 128 and 129
131. or/122-124
132. 130 or 131
133. (Meta-analysis or review).pt. or systematic review.ti.

134. 132 or 133
135. 120 and 134
136. limit 135 to (english or french)
137. limit 136 to yr="2009 -Current"

Question 4
Last Searched December 18 2013
1. Colonoscopy/
2. Colonoscop*.ti,ab.
3. Sigmoidoscopy/ or Digital Rectal Examination/
4. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
5. Colonoscopy, Computed Tomographic/
6. Colonograph*.ti,ab.
7. Occult blood/
8. ifobt*.ti,ab.
9. fobt*.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. FlexSure OBT.ti,ab.
16. immoCARE.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.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. Guaiac/du
28. exp cohort studies/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. Epidemiologic studies/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional.tw.
35. Cross-sectional studies/
36. or/28-35
37. or/1-27
38. Stool screening.ti,ab.
39. Stool test*.ti,ab.

40. Stool based test*.ti,ab.
41. Feces/
42. or/38-41
43. Colorectal Neoplasms/
44. Colonic Neoplasms/
45. Sigmoid Neoplasms/
46. Rectal Neoplasms/
47. Anus Neoplasms/
48. Anal Gland Neoplasms/
49. Intestinal Polyps/
50. Colonic Polyps/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/43-51
53. 42 and 52
54. Mass Screening/
55. screen*.ti,ab.
56. or/54-55
57. 52 and 56
58. (clinical trial, all or clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews).pt.
59. random*.ti,ab.
60. clinical trial*.ti,ab.
61. or/58-60
62. 37 or 53 or 57
63. 61 and 62
64. "Sensitivity and Specificity"/
65. "Predictive Value of Tests"/
66. "Reproducibility of Results"/
67. Reference Values/
68. Reference Standards/
69. False Negative Reactions/
70. False Positive Reactions/
71. ROC Curve/
72. Sensitiv*.mp.
73. Predictive value*.mp.
74. Accuracy.tw.
75. or/64-74
76. 37 and 75
77. 53 and 75
78. 57 and 75
79. Colonoscopy/st
80. Sigmoidoscopy/st or Digital Rectal Examination/st
81. 76 or 77 or 78 or 79 or 80
82. adverse.tw.
83. harm*.tw.
84. complication*.tw.

85. side effect*.tw.
86. mortality/
87. mortality.tw.
88. perforat*.tw.
89. false positive.tw.
90. false negative.tw.
91. (overdiagnosis or over diagnosis).tw.
92. (overtreatment or over treatment).tw.
93. or/82-92
94. 62 and 93
95. Colonoscopy/ae, mo
96. Sigmoidoscopy/ae, mo or Digital Rectal Examination/ae, mo
97. 94 or 95 or 96
98. 36 or 61
99. 81 or 97
100. 98 and 99
101. 63 or 100
102. limit 101 to (english or french)
103. animals/ not humans/
104. 102 not 103
105. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen?).ti,jn.
106. 104 not 105
107. exp *Polymorphism, Genetic/
108. polymorphism.ti.
109. 107 or 108
110. 106 not 109
111. limit 110 to yr="2000 -Current"
112. limit 111 to (clinical conference or comment or congresses or editorial or letter or newspaper article)
113. 111 not 112
114. risk prediction tools.mp.
115. *risk assessment/
116. (risk assessment or risk stratification or risk prediction).tw.
117. (risk adj3 (predication or tool or score or scale)).tw.
118. risk assessment/
119. 114 or 116 or 117 or 118
120. 110 and 119
121. (meta anal* or metaanal*).ti,ab.
122. meta-analysis.pt,ti,ab,sh.
123. (meta anal$ or metaanal$).ti,ab,sh.
124. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
125. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
126. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
127. (medline or embase or cochrane or pubmed or pub med).ti,ab.
128. or/125-127
129. review.pt,sh.

130. 128 and 129
131. or/122-124
132. 130 or 131
133. (Meta-analysis or review).pt. or systematic review.ti.
134. 132 or 133
135. 120 and 134
136. limit 135 to (english or french)
137. limit 136 to yr="2009 -Current"

EMBASE-OVID
Last Searched December 18 2013
MERSC_CRC_CQs_embase
Dec 18 2013

1. colonoscopy/
2. Colonoscop*.ti,ab.
3. sigmoidoscopy/
4. digital rectal examination/
5. Sigmoidoscopy/ or Digital Rectal Examination/ or barium enema/
6. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
7. computed tomographic colonoscopy/
8. Colonograph*.ti,ab.
9. occult blood/
10. ifobt*.ti,ab.
11. fobt*.ti,ab.
12. Fecal occult blood.ti,ab.
13. ((fecal or faecal) and immunochemical).ti,ab.
14. ((fecal or faecal) and dna).ti,ab.
15. Instant-view.ti,ab.
16. FlexSure OBT.ti,ab.
17. immoCARE.ti,ab.
18. HemeSelect.ti,ab.
19. MonoHaem.ti,ab.
20. ColoScreen.ti,ab.
21. Seracult.ti,ab.
22. HM-Jack.ti,ab.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. guaiac/
28. cohort analysis/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. community sample/
32. (observational adj (study or studies)).tw.

33. Longitudinal.tw.
34. Cross-sectional studies/
35. or/28-34
36. Stool screening.ti,ab.
37. Stool test*.ti,ab.
38. Stool based test*.ti,ab.
39. feces analysis/
40. or/36-39
41. Colorectal cancer/
42. Colorectal tumor/
43. Colon polyp/
44. Adenomatous polyp/
45. exp intestine tumor/
46. Colorectal cancer.ti,ab.
47. Colorectal neoplas*.ti,ab.
48. Colon cancer.ti,ab.
49. colon neoplas*.ti,ab.
50. exp anus tumor/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/41-51
53. diagnostic accuracy/
54. diagnosis/ or diagnostic accuracy/ or exp diagnostic error/ or exp diagnostic test/ or diagnostic test accuracy study/ or diagnostic value/ or exp tumor diagnosis/
55. reference value/
56. predictive value/
57. reproducibility/ or measurement precision/
58. Sensitiv*.mp.
59. Predictive value*.mp.
60. Accuracy.tw.
61. or/53-60
62. screening/ or screening test/
63. cancer screening/
64. mass screening/
65. screen*.ti,ab.
66. or/62-65
67. random*.ti,ab.
68. "controlled clinical trial (topic)"/ or "clinical trial (topic)"/ or controlled study/ or "randomized controlled trial (topic)"/
69. (meta anal* or metaanal* or systematic review).ti,ab.
70. "systematic review"/
71. meta analysis/
72. or/67-71
73. adverse outcome/
74. *complication/co, di, pc [Complication, Diagnosis, Prevention]
75. side effect/
76. mortality/ or cancer mortality/

77. perforat*.tw.
78. false positive result/ or diagnostic error/
79. false negative result/
80. (false adj (positive or negative)).tw.
81. (overtreatment or over treatment).tw.
82. (overdiagnosis or over diagnosis).tw.
83. adverse.tw.
84. or/73-83
85. or/1-27
86. 40 and 52
87. 52 and 66
88. 85 or 86 or 87
89. 72 and 88
90. 61 and 85
91. 61 and 86
92. 61 and 87
93. 90 or 91 or 92
94. 84 and 88
95. 35 or 72
96. 93 and 95
97. 84 and 85
98. 84 and 86
99. 84 and 87
100. 94 and 95
101. 88 or 93 or 94
102. 95 and 101
103. 89 or 96 or 102
104. limit 103 to (english or french)
105. limit 104 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine)
106. 104 not 105
107. limit 106 to yr="2000 -Current"
108. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen? or neonat*).ti,jn.
109. 107 not 108
110. limit 109 to (book or book series or conference abstract or conference paper or conference proceeding or editorial or letter or note)
111. 109 not 110
112. polymorphism.ti.
113. *genetic polymorphism/ or *genetic heterogeneity/ or *molecular genetics/ or *population genetics/multimedia
114. 112 or 113
115. 111 not 114
116. limit 115 to em=201327-201346
117. meta analysis/

118. systematic review/
119. (systematic* adj3 (review* or overview*)).tw.
120. exp "ethnic and racial groups"/
121. first nations.tw.
122. (aboriginal? and canada).tw.
123. native canadians.tw.
124. (immigran* or new canadians).tw.
125. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian).mp.
126. rural health care/
127. rural population/
128. (rural adj (population? or area? or region?)).tw.
129. exp economic evaluation/
130. cost.tw.
131. or/129-130
132. exp patient attitude/
133. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
134. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
135. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
136. willingness to pay.tw.
137. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
138. or/132-137
139. ((process or performance or outcome) adj2 (measure? or indicator?)).tw.
140. performance measurement system/
141. or/139-140
142. exp socioeconomics/
143. exp social status/
144. (poor or disadvantaged or poverty or social status).tw.
145. health care disparity/
146. miscellaneous named groups/ or lowest income group/ or medically underserved/ or vulnerable population/
147. or/120-128
148. or/142-146
149. 131 or 138 or 141 or 147 or 148
150. exp Canada/
151. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).tw.
152. or/150-151
153. 117 or 118 or 119
154. 88 or 149 or 152
155. 149 or 152
156. 88 and 155
157. 153 and 156
158. 88 and 152
159. 157 or 158
160. limit 159 to human

161. limit 160 to (english or french)
162. limit 161 to yr="2009 -Current"

CQ 4
EMBASE-OVID
Last Searched December 18 2013

1. colonoscopy/
2. Colonoscop*.ti,ab.
3. sigmoidoscopy/
4. digital rectal examination/
5. Sigmoidoscopy/ or Digital Rectal Examination/ or barium enema/
6. (Sigmoidoscop* or digital rectal exam or barium enema).ti,ab.
7. computed tomographic colonoscopy/
8. Colonograph*.ti,ab.
9. occult blood/
10. ifobt*.ti,ab.
11. fobt*.ti,ab.
12. Fecal occult blood.ti,ab.
13. ((fecal or faecal) and immunochemical).ti,ab.
14. ((fecal or faecal) and dna).ti,ab.
15. Instant-view.ti,ab.
16. FlexSure OBT.ti,ab.
17. immoCARE.ti,ab.
18. HemeSelect.ti,ab.
19. MonoHaem.ti,ab.
20. ColoScreen.ti,ab.
21. Seracult.ti,ab.
22. HM-Jack.ti,ab.
23. OcculTech.ti,ab.
24. PreGen-Plus.ti,ab.
25. QuickVue.ti,ab.
26. HemoQuant.ti,ab.
27. guaiac/
28. cohort analysis/
29. (cohort adj (study or studies)).tw.
30. Cohort analy*.tw.
31. community sample/
32. (observational adj (study or studies)).tw.
33. Longitudinal.tw.
34. Cross-sectional studies/
35. or/28-34
36. Stool screening.ti,ab.
37. Stool test*.ti,ab.
38. Stool based test*.ti,ab.
39. feces analysis/

40. or/36-39
41. Colorectal cancer/
42. Colorectal tumor/
43. Colon polyp/
44. Adenomatous polyp/
45. exp intestine tumor/
46. Colorectal cancer.ti,ab.
47. Colorectal neoplas*.ti,ab.
48. Colon cancer.ti,ab.
49. colon neoplas*.ti,ab.
50. exp anus tumor/
51. ((colon or colorectal) adj (cancer* or neoplasm*)).ti.
52. or/41-51
53. diagnostic accuracy/
54. diagnosis/ or diagnostic accuracy/ or exp diagnostic error/ or exp diagnostic test/ or diagnostic test accuracy study/ or diagnostic value/ or exp tumor diagnosis/
55. reference value/
56. predictive value/
57. reproducibility/ or measurement precision/
58. Sensitiv*.mp.
59. Predictive value*.mp.
60. Accuracy.tw.
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62. screening/ or screening test/
63. cancer screening/
64. mass screening/
65. screen*.ti,ab.
66. or/62-65
67. random*.ti,ab.
68. "controlled clinical trial (topic)"/ or "clinical trial (topic)"/ or controlled study/ or "randomized controlled trial (topic)"/
69. (meta anal* or metaanal* or systematic review).ti,ab.
70. "systematic review"/
71. meta analysis/
72. or/67-71
73. adverse outcome/
74. *complication/co, di, pc [Complication, Diagnosis, Prevention]
75. side effect/
76. mortality/ or cancer mortality/
77. perforat*.tw.
78. false positive result/ or diagnostic error/
79. false negative result/
80. (false adj (positive or negative)).tw.
81. (overtreatment or over treatment).tw.
82. (overdiagnosis or over diagnosis).tw.
83. adverse.tw.

84. or/73-83
85. or/1-27
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87. 52 and 66
88. 85 or 86 or 87
89. meta analysis/
90. systematic review/
91. (systematic* adj3 (review* or overview*)).tw.
92. exp "ethnic and racial groups"/
93. first nations.tw.
94. 89 or 90 or 91
95. risk prediction tools.mp.
96. *risk assessment/
97. (risk assessment or risk stratification or risk prediction).tw.
98. (risk adj3 (predication or tool or score or scale)).tw.
99. or/95-98
100. 88 and 99
101. limit 100 to (english or french)
102. limit 101 to yr="2009 -Current"
103. 94 and 102

Appendix 2: Acknowledgements

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