Title: Interventions to Improve Follow-up of Abnormal Stool-Based Colorectal Cancer Screening Tests in Safety-Net Settings: A Systematic Review

Short title: Follow-up of abnormal screening tests

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Introduction

Colorectal cancer (CRC) is the 2nd leading cause of cancer deaths in the United States (U.S.).[1] Despite evidence that screening effectively reduces incidence and mortality, screening is suboptimal especially in safety-net healthcare systems and federally qualified health centers (FQHCs).[2] Safety-net healthcare systems represent 25% of U.S. hospitals and are defined as hospitals that organize and deliver a significant level of healthcare and other related services to individuals without insurance, receiving Medicaid, and other vulnerable patients.[3] FQHCs are systems of outpatient clinics that provide primary and preventive care to individuals in the U.S. regardless of their ability to pay. In 2022, more than 30 million people received care from FQHCs and 90% had household incomes at or below the federal poverty line.[4] In both of these settings, due to convenience and patient preference, stool-based CRC screening strategies, including the fecal immunochemical tests (FIT), guaiac fecal occult blood test (gFOBT), and multi-target stool DNA (mt-sDNA) are commonly used.[5,6]

The effectiveness of stool-based CRC screening tests depends on timely follow-up colonoscopy in patients with abnormal results. In landmark, randomized controlled trials (RCTs), the proportion of individuals with abnormal stool-based screening tests who completed a follow-up colonoscopy ranged from 80% to 90%.[7,8] However, our prior research in a safety-net healthcare system and systematic reviews of real-world data, suggests that approximately 18% to 56% of patients with an abnormal stool-based CRC screening test complete a follow-up colonoscopy within 1 year of their result.[9-11] Individuals who do not complete a follow-up colonoscopy within 6 to 10 months of their abnormal result have a higher incidence of CRC and advanced stage CRC compared to those who complete a colonoscopy within 1 month.[12-15] Among those who never complete a follow-up colonoscopy, there is a 2-fold increased risk of death from CRC compared to those who do complete a colonoscopy.[16]

Previous reviews of interventions to improve follow-up of stool-based tests either have not focused on safety-net healthcare systems or FQHCs[17] or are outdated.[18,19] Therefore, we aim to update prior reviews by identifying interventions that have been evaluated to improve the follow-up of abnormal stool-based CRC screening tests specifically in safety-net healthcare systems and FQHCs and when possible, to quantify the pooled effect of similar interventions and assess the evidence supporting those interventions.

Methods

Data Sources and Literature Searches

We developed our search strategy with medical librarians (DS, EJ) using keywords for stool-based CRC screening tests, safety-net healthcare systems and interventions from prior studies. The librarians independently searched PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature

(CINAHL), Web of Science and Cochrane databases from study inception until August 31, 2023. The search was repeated in January 2024 to capture studies published between September 1, 2023, and December 31, 2023. References of all eligible studies and registered clinical trials were also reviewed. Search results were uploaded to Rayyan, a cloud-based web application used to store, screen and organize publications for reviews, with duplicates removed.[20] This systematic review was conducted according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The search strategy and terms are summarized in Supplemental Table 1.

Study Eligibility and Selection

We included original studies that used any intervention to improve follow-up colonoscopy completion after an abnormal stool-based CRC screening test in a safety-net healthcare system or FQHC. Given limited evidence in the population of interest, conference abstracts were also included. To ensure concordance, two investigators (RBI, ABB) independently screened titles and abstracts using a shared protocol, prior to independently reviewing full-text articles. We included both RCTs and observational studies that examined adults with an abnormal stool-based test for CRC screening and reported any intervention aimed to improve follow-up colonoscopy completion. Studies that evaluated the effect of an intervention across multiple cancer types were included but only the effect on colonoscopy completion after an abnormal stool-based test was included. Studies that either described follow-up colonoscopy without an intervention, were not conducted in safety-net systems or FQHCs, case-studies, reviews, commentaries and protocols were excluded. Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

The reviewers (RBI, ABB) independently and sequentially extracted data from the included studies. Information was collected on the following variables: study design, geographic setting, data sources, study population, intervention details, intervention effect, follow-up time, and comparative interventions and effects if reported **(Table 1**). Two reviewers independently assigned studies reported in a full manuscript, a risk of bias (low, moderate, high), based on guidelines of the Agency for Healthcare Research and Quality (AHRQ)[21] and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group (Supplemental Table 2).[22] Briefly, RCTs were considered to be at low risk of bias but were upgraded to moderate or high if there were flaws in recruitment, randomization or follow-up. Observational or non-randomized studies were at high risk of bias and were downgraded to moderate if the study design and reported measures were strong. Risk of bias was not assessed in the conference abstracts.

Data Synthesis and Analysis

When available, we calculated the percent of follow-up colonoscopy completion in the intervention arm compared to the control arm and reported the mean difference. Due to the limited number of studies and heterogeneity in study methods, no meta-analysis was completed.

Results

Our two-stage search identified 547 studies. In total, 534 were excluded after removal of duplicates and screening titles and abstracts, including 156 studies that focused on CRC screening and 47 studies that described inadequate follow-up of abnormal stool-based results without testing an intervention. Thirteen studies (five full manuscripts and eight conference abstracts) were included in the final analysis (**Figure 1**).[23-35] The five manuscripts included one RCT, one prospective cohort study, two retrospective cohort studies and one pre-post quality improvement initiative.[30-32,34,35] The eight conference abstracts included four prospective cohort studies, two retrospective cohort studies, one cross-sectional study and one quality improvement initiative.[23-29,33] All 13 articles that met inclusion criteria described the use of patient navigation either as a stand-alone intervention or embedded within an organized CRC screening program. The proportion of test-positive individuals who had a follow-up colonoscopy with and without an intervention was available for three studies (two manuscripts and one conference abstract).[27,30,34] The remaining studies either only reported colonoscopy completion in the intervention group or the decrease in loss-to- follow-up colonoscopy between groups without providing exact values.

Full Manuscripts

Patient Navigation

All 5 manuscripts described the use of patient navigation either as a stand-alone intervention or embedded within an organized CRC screening program. Of these, one study had low risk of bias, the remainder had moderate or high risk of bias. Only two articles reported the proportion of individuals that completed a colonoscopy with and without the intervention. In the first study, a RCT of patient navigators for the follow-up of multiple abnormal cancer screening tests, the navigators attended an annual training conference, institutional trainings, and met with a psychologist to learn and deploy a strengths-based approach to navigation.[34] Using these tools, the navigators helped patients identify assets available to them throughout cancer care and maintained regular patient contact until the completion of follow-up. In this study, 78.9% (90/114) of patients in the intervention group completed a colonoscopy or another follow-up test (not otherwise defined), compared with 57.8% (70/121) in the control group, a difference of 21.1 percentage points. While the authors reported via Kaplan Meier curves that navigation significantly shortened the time for colorectal screening resolution, an exact time to colonoscopy

completion was not provided. Notably, this study included some patients with potential CRC symptoms and resolution of the abnormal result included other tests (e.g. sigmoidoscopy or otherwise not defined), which makes comparisons to other studies, challenging. There was no statistically significant difference in the adenocarcinomas diagnosed in the navigated group versus the non-navigated group (3% vs 4%, p=0.53).

In the second study, a pre-post quality improvement study, the navigators consisted of nurse practitioners or physicians.[30] These navigators worked within the colonoscopy services unit which was outside of the referring physician's office. They facilitated communications between patients and the healthcare systems, assisted with colonoscopy scheduling, educated patients, provided patient reminders and followed-up with patients who did not attend their colonoscopy. In the intervention group, 45.6% (600/1317) completed a follow-up colonoscopy within 6 months versus 40.6% colonoscopy completion (493/1214) in the control group, a difference of 5.0 percentage points. There was no statistically significant difference in the adenocarcinomas diagnosed in the navigated group versus the non-navigated group (2.2% vs 1.8%, p=0.70). In both studies, the control groups received usual care, which included no additional resources or information to complete a colonoscopy.

The three remaining studies all evaluated navigation embedded within an organized CRC screening outreach program.[31,32,35] In these studies, patients in either a RCT for mailed FIT outreach or a programmatic CRC screening initiative who completed a FIT and had an abnormal result were offered navigation to colonoscopy. The investigators used a centralized approach which usually included a single, bilingual (English and Spanish speaking) navigator who provided patients assistance with scheduling, preparing for and completing colonoscopy. In O'Leary et al., 55.8% (24/43) of those who accepted navigation completed a colonoscopy; 7.0% (3/43) of those who the navigator contacted but declined navigation completed a colonoscopy, and 11.6% (5/43) of those who were not successfully contacted completed a colonoscopy within 9 months of the abnormal result.[32] Among navigated patients, the navigator spent a median of 48.5 minutes (range 24-277 mins) per patient including the time spent preparing and completing the calls. This time increased to 102.0 minutes (range 32-277 minutes) for self-pay patients. Most navigated patients (81.0%) identified informational barriers to colonoscopy completion (e.g., medication adjustments prior to colonoscopy). In Scott et al., 72.5% (271/374) of patients with an abnormal FIT result completed a follow-up colonoscopy at any time over a 3-year period, with a median time to completion of 55 days.[35] In Murphy et al., 50.5% (146/289) of patients with an abnormal FIT result completed a colonoscopy within 6 months, 61.2% (177/289) completed a colonoscopy within 12 months.[31] These studies did not report a control group.

Conference Abstracts

Patient Navigation

All 8 conference abstracts also described the use of patient navigation to improve colonoscopy completion. Four of these studies described navigation through a mailed FIT program and one described navigation as part of a bulk-ordering FIT campaign[27]. Of the remaining three, one used navigation for patients in a health system with abnormal FIT results to address health system barriers (e.g., failure to order a colonoscopy) and patient barriers (e.g., explaining the FIT results);[29] one used navigation in combination with patient education videos in a health system population with abnormal FIT results;[24] and the third used navigation to direct FQHC patients to free diagnostic colonoscopy services.[26] Colonoscopy completion varied from 33.6% to 93.1% and time to colonoscopy was not consistently reported. Dougherty et al, which reported 93.1% follow-up colonoscopy, was a gastroenterologist-driven initiative to provide no-cost colonoscopy to uninsured FIT-positive patients through North Carolina.[26] Between January 2016 and September 2018, 92 FIT-positive patients were referred to the initiative, 58 were eligible based on income and 54 completed a colonoscopy. In Elangovan et al, the only conference abstract to report colonoscopy completion rates for the intervention compared to a control, 67.8% of patients who received a FIT kit through bulk outreach completed a colonoscopy within 120 days of their abnormal FIT result compared to 53.2% of patients who received a FIT through regular orders.[27]

Discussion

This systematic review evaluated interventions aimed to improve follow-up of abnormal stool-based CRC screening test results in safety-net healthcare systems and FQHCs. Our search found 13 eligible studies, all of which examined the effect of patient navigation in various forms including as a stand-alone intervention, embedded within an organized CRC screening outreach program, coupled with patient educational videos, or navigation to no-cost colonoscopy programs. Two full manuscripts and one conference abstract reported the effect of the intervention on colonoscopy completion compared to a control group. In these studies, navigation was associated with an average 13.6% (range 5.0 to 21.1 percentage point) increase in follow-up colonoscopy completion.

We and others have described multiple barriers to follow-up of abnormal stool-based CRC screening tests in safety-net settings including at the patient, provider, and healthcare system-levels.[36-40] Yet, our systematic review only found studies that evaluated patient navigation to address this issue, albeit some studies deployed navigation at the patient-level while others deployed navigation at the healthcare system level. There is a critical need to develop and evaluate interventions that address multiple barriers to follow-up at multiple levels of care.

Patient navigation has been widely endorsed as one strategy to improve follow-up of abnormal screening results, including stool-based tests. However, navigation alone has not improved follow-up colonoscopy to the U.S. Multisociety Task Force on CRC (USMSTF) 80% goal, uptake has been slow and variable, and few safety-net health systems have successfully implemented and sustained navigation programs. The results from this systematic review are promising as they suggest an important role for navigation in improving follow-up colonoscopy in safety-net settings and highlight opportunities for future research. For example, studies that include implementation details would enable safety-net settings to identify the essential components of navigation programs in these settings, adaptations needed for success, and how to sustain navigation when resources are limited by identifying and prioritizing those who could benefit most.[41] Standardizing the time from abnormal stool-based tests to colonoscopy completion would also allow more comparison across studies. Finally, novel interventions that compare outcomes to control groups are needed.

To our knowledge this is the first systematic review on interventions to improve follow-up of abnormal stool-based tests in safety-net settings. Despite searching multiple databases, we may have missed studies in the gray literature or unpublished conference abstracts. The inclusion of conference abstracts provided a comprehensive overview of existing research but could also be misleading as they don't represent final research reports.

Conclusions

In conclusion, this study summarizes the limited data available on interventions to improve follow-up of abnormal stool-based CRC screening tests in safety-net settings. Our findings support patient navigation in this population, but more research is needed to inform effective implementation of navigation and other interventions that address this critical issue in CRC control and prevention.

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Study concept and design: Issaka
Acquisition, analysis and interpretation of data: Issaka, Bell-Brown,
Drafting of the manuscript: Issaka, Bell-Brown
Critical revision of the manuscript for important intellectual content: All authors.
Approval of the final manuscript: All authors**.**
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Figures & Tables

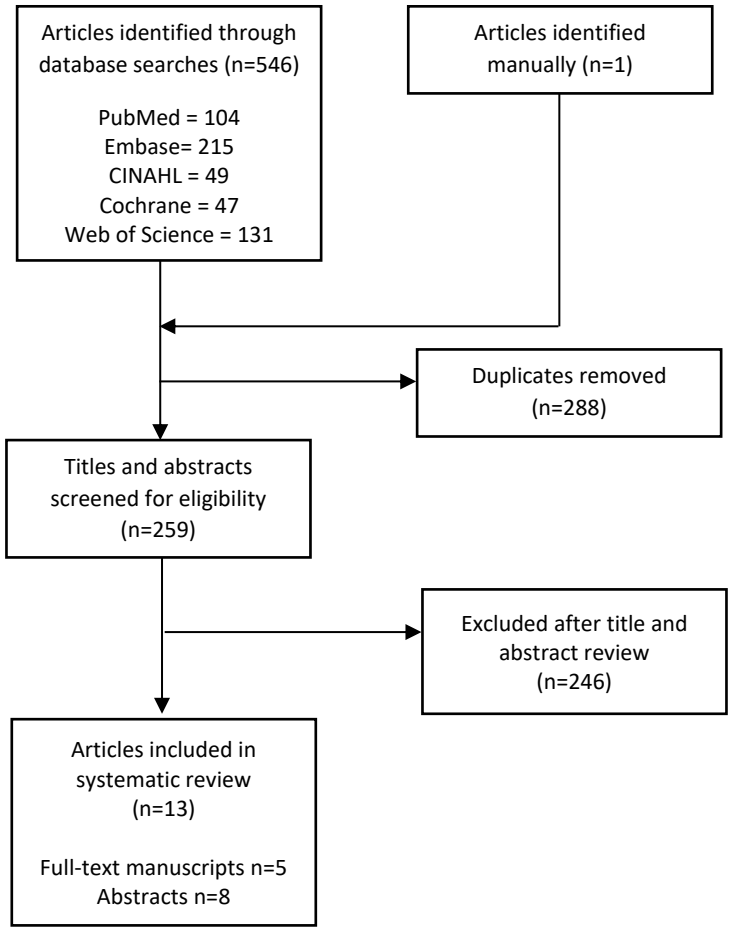
Figure 1: Study selection flow diagram

Table 1: Overview and characteristics of included studies of interventions to improve follow-up of abnormal stool-based CRC screening tests in safety-net populations

Supplemental Table 1: Search Strategies

Supplemental Table 2: Criteria Used for Determining Risk of Bias of Individual Studies

Figure 1: Study selection flow diagram



CINAHL - Cumulative Index to Nursing and Allied Health Literature

Supplemental Table 1: Search Strategies

Search Strategy for MEDLINE PubMed **(**("Safety-net Providers"[Mesh] OR "safety net" OR ("federally qualified" AND (health OR healthcare) AND (center OR centers OR centre OR centres OR clinic OR clinics)) OR FQHC OR FQHCs**)** AND **(**("Occult Blood"[Mesh] OR "Early Diagnosis"[Mesh] OR "Early Detection of Cancer"[Mesh] OR "Mass Screening"[Mesh:NoExp] diagnosis[sh] OR fecal immunochemical test OR faecal immunochemical test OR immunochemical fecal occult blood test OR immunochemical faecal occult blood test OR stool guaiac test OR stool DNA OR fecal occult blood test OR faecal occult blood test OR occult blood OR stool-based screening tests OR cancer screening OR early detection of cancer OR mass screening OR early detection OR screening**)** AND **(**"Patient Navigation"[Mesh] OR "Lost to Follow-up"[Mesh] OR "Reminder Systems"[Mesh] OR "Telephone"[Mesh] OR "Postal Service"[Mesh] OR "Electronic Mail"[Mesh] OR "Text Messaging"[Mesh] OR intervention OR patient navigation OR patient navigator* OR follow up OR followup OR follow-up OR lost to follow-up OR reminder systems OR reminders OR telephone OR phone OR smartphone* OR mail OR email* OR "e-mail*" OR text message OR texting OR automated referral OR phone-based OR letter OR intercede**)** AND **(**"Colonoscopy"[Mesh] OR "Sigmoidoscopy"[Mesh] OR "Colonoscopes"[Mesh] OR "Sigmoidoscopes"[Mesh] OR colonoscop* OR sigmoidoscop***)** AND **(**"Colorectal Neoplasms"[Mesh] OR "Sigmoid Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR colorectal neoplasms OR colorectal cancer* OR colon cancer OR colonic cancer OR sigmoid cancer OR rectal cancer***)** 104 results as of 12/31/23
Search Strategy for Ovid Embase **(**'safety net health care'/exp OR 'federally qualified health center'/exp OR 'safety net' OR ('federally qualified' NEXT/1 (health OR 'health care' OR healthcare) NEXT/1 (center OR centers OR centre OR centres OR clinic OR clinics)) OR FQHC OR FQHCs**)** **AND (**'occult blood test'/exp OR 'occult blood test kit'/exp OR 'early cancer diagnosis'/exp OR 'cancer screening'/exp OR 'screening'/de OR 'mass screening'/de OR 'diagnosis'/lnk OR 'fecal immunochemical test' OR 'faecal immunochemical test' OR 'immunochemical fecal occult blood test' OR 'immunochemical faecal occult blood test' OR 'stool guaiac test' OR 'stool DNA' OR 'fecal occult blood test' OR 'faecal occult blood test' OR 'occult blood' OR 'stool-based screening tests' OR 'cancer screening' OR 'early detection of cancer' OR 'mass screening' OR 'early detection' OR screening**)** **AND (**'follow up'/exp OR 'reminder system'/exp OR 'telephone'/exp OR 'mobile phone'/exp OR 'postal mail'/exp OR 'e-mail'/exp OR 'text messaging'/exp OR intervention OR interventions OR 'patient navigation' OR 'patient navigator*' OR 'follow up' OR followup OR follow-up OR 'lost to follow-up' OR 'reminder system*' OR reminders OR telephone OR phone OR smartphone* OR mail OR email* OR e-mail* OR 'text messag*' OR texting OR 'automated referral*' OR phone-based OR letter OR intercede**)** **AND (**'colonoscopy'/exp OR 'colonoscope'/exp OR 'sigmoidoscopy'/exp OR 'sigmoidoscope'/exp OR colonoscop* OR sigmoidoscop***)** **AND (**'colorectal cancer'/exp OR 'colon cancer'/exp OR 'sigmoid cancer'/exp OR 'rectosigmoid cancer'/exp OR 'rectum cancer'/exp OR (colorectal neoplasms) OR (colon cancer) OR (colonic cancer) OR (sigmoid cancer) OR (colorectal cancer*) OR (rectal cancer***))** 215 results as of 12/31/23
Search Strategy for CINAHL **(**MH "Safety-Net Providers" OR "safety net" OR ("federally qualified" W0 (health OR "health care" OR healthcare) W0 (center OR centers OR centre OR centres OR clinic OR clinics)) OR FQHC OR FQHCs**)** **AND (**MH "Occult Blood" OR MH "Cancer Screening" OR MH "Health Screening" OR MH "Early Detection of Cancer" OR MH "Early Diagnosis+" OR MW "DI" OR fecal immunochemical test OR faecal immunochemical test OR immunochemical fecal occult blood test OR immunochemical faecal occult blood test OR stool guaiac test OR stool DNA OR fecal occult blood test OR faecal occult blood test OR occult blood OR stool-based screening tests OR cancer screening OR early detection of cancer OR mass screening OR early detection OR screening**)** **AND (**MH "Patient Navigation" OR MH "Reminder Systems" OR MH "Telephone+" OR MH "Text Messaging+" OR MH "Cellular Phone+" OR MH "Mail+" OR MH "Email" OR intervention OR interventions OR patient navigation OR patient navigator* OR follow up OR followup OR follow-up OR lost to follow-up OR reminder system* OR reminders OR telephone OR phone OR smartphone* OR mail OR email* OR e-mail* OR text messag* OR texting OR automated referral* OR phone-based OR letter OR intercede**)** **AND (**MH "Colonoscopy+" OR MH "Sigmoidoscopy" OR colonoscop* OR sigmoidoscop***)** **AND (**(MH "Colorectal Neoplasms+") OR (MH "Sigmoid Neoplasms") OR (MH "Colonic Neoplasms+") OR (MH "Rectal Neoplasms+") OR colorectal neoplasm* OR colon cancer* OR colonic cancer *OR sigmoid cancer* OR colorectal cancer* OR rectal cancer***)** 49 results as of 12/31/23
Search Strategy for Cochrane (safety net health system OR safety net health systems OR safety net healthcare system OR safety net healthcare systems OR safety-net health system OR safety-net health systems OR safety-net healthcare system OR safety-net healthcare systems OR federally qualified health center OR federally qualified healthcare center OR federally qualified health centers OR federally qualified healthcare centers OR FQHC OR FQHCs) AND (fecal immunochemical test OR “fecal immunochemical test” OR faecal immunochemical test OR immunochemical fecal occult blood test OR immunochemical faecal occult blood test OR stool guaiac test OR stool DNA OR fecal occult blood test OR faecal occult blood test OR occult blood OR stool-based screening tests OR cancer screening OR early detection of

cancer OR “early detection of cancer” OR mass screening OR early detection OR screening) AND (intervention* OR patient navigation OR "patient navigation" OR follow up OR followup OR follow-up OR lost to follow-up OR “lost to follow up” OR reminder systems OR reminders OR telephone OR phone OR mail OR email OR text message OR automated referral OR phone-based OR letter OR intercede) AND (colonoscopy OR [mh colonoscopy] OR colonoscope OR [mh colonoscopes] OR sigmoidoscope OR [mh sigmoidoscopes] OR sigmoidoscopy) AND (colorectal neoplasm* OR colon cancer* OR colonic neoplasms OR colonic cancer* OR sigmoid cancer* OR colorectal cancer* OR rectal cancer*)
47 results as of 12/31/23

Search Strategy for Web of Science

TS=((safety net health system OR safety net health systems OR safety net healthcare system OR safety net healthcare systems OR safety-net health system OR safety-net health systems OR safety-net healthcare system OR safety-net healthcare systems OR federally qualified health center OR federally qualified healthcare center OR federally qualified health centers OR federally qualified healthcare centers OR FQHC OR FQHCs) AND (fecal immunochemical test OR faecal immunochemical test OR immunochemical fecal occult blood test OR immunochemical faecal occult blood test OR stool guaiac test OR stool DNA OR fecal occult blood test OR faecal occult blood test OR occult blood OR stool-based screening tests OR cancer screening OR early detection of cancer OR mass screening OR early detection OR screening OR early diagnosis) AND (intervention OR patient navigation OR follow up OR followup OR follow-up OR lost to follow-up OR reminder system* OR reminder* OR telephone OR phone OR mail OR email OR text message OR automated referral OR phone-based OR letter OR intercede) AND (colonoscopy OR colonoscope OR sigmoidoscope OR sigmoidoscopy) AND (colorectal neoplasms OR colon cancer OR colonic cancer OR sigmoid cancer OR colorectal cancer* OR rectal cancer*))
131 results as of 12/31/23

Supplemental Table 2: Criteria Used for Determining Risk of Bias of Individual Studies*

Study Type	Criteria Used
Randomized controlled trial	Considered to be at low risk of bias. Upgraded to moderate risk if there was concern for the following problems in the study design or reporting: - Lack of allocation concealment - Lack of blinding that influences outcomes - Incomplete accounting of patients and outcome events - Selective outcome reporting bias - Recruitment bias in cluster-randomized trials
Observational study or nonrandomized interventional study (e.g., a pre–post or nonrandomized parallel group)	Considered to be at high risk of bias. Downgraded to moderate risk if the study design adequately accounted for and reported all of the following elements. Upgraded to very high risk if there were severe or multiple problems with these elements. - Development and application of appropriate eligibility criteria - Adequate measurement of both exposure and outcome - Adequate control for confounding, with both accurate measurement of all known prognostic factors and adjustment for these factors - Adequate follow-up of all participants

* Based on guidelines of the Agency for Healthcare Research and Quality[21] and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group[22]