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Interventions to Improve Follow-up of Positive Results on Fecal Blood Tests

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Abstract

Background: Fecal immunochemical testing is the most commonly used method for colorectal cancer screening worldwide. However, its effectiveness is frequently undermined by failure to obtain follow-up colonoscopy after positive test results.

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Purpose: To evaluate interventions to improve rates of follow-up colonoscopy for adults after a positive result on a fecal test (guaiac or immunochemical).

Data Sources: English-language studies from the Cochrane Central Register of Controlled Trials, PubMed, and Embase from database inception through June 2017.

Study Selection: Randomized and nonrandomized studies reporting an intervention for colonoscopy follow-up of asymptomatic adults with positive fecal test results.

Data Extraction: Two reviewers independently extracted data and ranked study quality; 3 rated overall strength of evidence for each category of study type.

Data Synthesis: Twenty-three studies were eligible for analysis, including 7 randomized and 16 nonrandomized studies. Three were at low risk of bias. Eleven studies described patient-level interventions (changes to invitation, provision of results or follow-up appointments, and patient navigators), 5 provider-level interventions (reminders or performance data), and 7 system-level interventions (automated referral, precolonoscopy telephone calls, patient registries, and quality improvement efforts). Moderate evidence supported patient navigators and provider reminders or performance data. Evidence for system-level interventions was low. Seventeen studies reported the proportion of test-positive patients who completed colonoscopy compared with a control population, with absolute differences of -7.4 percentage points (95% CI, -19 to 4.3 percentage points) to 25 percentage points (CI, 14 to 35 percentage points).

Limitation: More than half of studies were at high or very high risk of bias; heterogeneous study designs and characteristics precluded meta-analysis.

Conclusion: Patient navigators and the provision to providers of reminders or performance data may help improve colonoscopy rates of asymptomatic adults with positive fecal blood test results. Current evidence about useful system-level interventions is scant and insufficient.

TOC summary

Follow-up of asymptomatic adults with positive screening test results is sometimes poor. This systematic review of 23 studies details evidence about the effectiveness of patient-, provider-, and system-level interventions aimed at improving rates of follow-up colonoscopy after a positive result on a fecal test (guaiac or immunochemical).

Colorectal cancer (CRC), the second leading cause of cancer death in the United States (1), is largely preventable with screening (2). Annual or biennial testing for fecal occult blood with high-sensitivity guaiac or fecal immunochemical tests (fecal tests) has proven effectiveness based on randomized controlled trials (RCTs) (3) and is recommended for CRC screening in adults aged 50 to 75 years (4, 5). Fecal immunochemical testing has become the most commonly used method for CRC screening worldwide (5). It is also increasingly used in the United States to maximize population-level screening rates (6). However, the effectiveness of fecal screening tests depends on timely follow-up diagnostic colonoscopy of patients with positive test results; guidelines generally recommend colonoscopy within 1 to 3 months (5, 7, 8). A long interval between a positive test result and colonoscopy can have important implications for CRC prognosis (9–11).

The proportion of test-positive patients having a timely colonoscopy (for example, within 6 months) varies widely and can be lower than 50% (12, 13), compared with 80% to 90% in landmark RCTs (14, 15). Colonoscopy follow-up is complex because it involves the interaction of several levels of care and evaluating the appropriateness of an invasive diagnostic test (16, 17). Several patient-, provider-, and system-level factors have been evaluated to improve follow-up of test-positive patients (13, 18–21), but lack of comparative data impedes implementation of potentially effective interventions.

Previous reviews of interventions to improve follow-up of fecal tests either have not used a systematic search strategy, have not determined levels of evidence for intervention types, or are outdated (22, 23). Our aims were therefore to identify interventions that have been evaluated for improving rates of follow-up colonoscopy after positive fecal test results and to assess whether evidence supports these interventions.

Methods

Our protocol is registered in PROSPERO (CRD42016048286). In contrast to the analysis plan stated there, meta-analyses were not done because of study heterogeneity. Reporting conformed to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (24).

Data Sources and Searches

We searched the Cochrane Central Register of Controlled Trials, PubMed, and Embase without language restrictions from inception through 30 June 2017 (Appendix Table 1, available at [Annals.org](https://annals.org)). Conference proceedings were included, and pertinent reference lists were manually searched. Both [ClinicalTrials.gov](https://clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry were searched for unpublished studies, returning 2 relevant trials. We contacted the study investigators: 1 trial was never completed (25), and the other's investigator did not respond (26).

Study Selection

Two investigators (K.S. and C.B.) independently screened titles and abstracts. We included both randomized and nonrandomized studies that examined asymptomatic adults aged 41 years or older with a positive result on a fecal immunochemical test or fecal occult blood test (FOBT), that primarily used colonoscopy to evaluate those patients, and that reported an intervention focused on improving follow-up.

Two investigators then independently evaluated the full-text articles. Interventions covering more than 1 cancer type were included, but only the effect on fecal blood test follow-up was considered. Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

Two investigators extracted data, using as the primary outcome measure the absolute difference between the intervention and control groups in the proportion of patients with positive fecal test results who had completed a colonoscopy by 180 days after the test. We

chose 180 days because more than 90% of follow-up colonoscopies occur within that interval and longer delays have clinical implications (11, 13). Other time periods were used if 180-day results were not available or the follow-up interval was not specified. Given that most patients had colonoscopy and colonoscopy is the examination of choice after a positive finding from a fecal test (27), all results were presented as the proportion of test-positive patients receiving a follow-up colonoscopy. When necessary, we contacted study authors to specify screening versus symptomatic patients and the absolute numbers of participants who had colonoscopy. One study was excluded because it included symptomatic patients (28), and another because the intervention was unclear without additional information (29). One author provided additional results not available in the report (30); 4 authors of included studies either did not respond or no longer had access to the study data set (31–35).

Two reviewers independently assigned each study a level for risk of bias (low, medium, high, or very high) for the absolute increase in colonoscopy completion (Appendix Table 2, available at [Annals.org](https://www.annals.org)) (36, 37). Randomized controlled trials were considered to be at low risk of bias but were upgraded to moderate or high risk if they had flaws in recruitment, randomization, or follow-up. Observational or nonrandomized interventional studies were considered to be at high risk of bias and were downgraded to moderate risk if their design and measurement were particularly strong. Conversely, they were upgraded to very high risk if important flaws existed in their eligibility criteria, measurement, and loss to follow-up.

Data Synthesis and Analysis

Primary investigations were organized by type of intervention (patient-, provider-, or system-level). We first used a descriptive approach to summarize study characteristics and outcomes for each category. A 10% absolute increase in colonoscopy completion was considered to be clinically important (9). Stata, version 14 (StataCorp), was used to calculate the absolute change in colonoscopy completion with CIs and *P* values when not available in included articles.

Two investigators (K.S. and J.L.) independently assigned overall strength-of-evidence ratings to each category using criteria from the Agency for Healthcare Research and Quality based on risk of bias, consistency, directness, and precision (36). Differences were resolved by consensus and input from a third reviewer (D.C.). Overall strength of evidence for each type of intervention was rated as high, moderate, or low on the basis of the level of confidence that the evidence reflected the true effect and the likelihood that future research will change the estimate.

Role of the Funding Source

The National Cancer Institute funded this study through the PROSPR (Population-based Research Optimizing Screening through Personalized Regimens) consortium (U54 CA163262 [Dr. Corley]). The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Results

After removal of duplicate records, the search identified 7232 studies, of which we evaluated 77 full-text articles (Figure 1). A total of 23 reports containing 26 comparisons were retained, including 7 randomized and 16 nonrandomized studies. Figure 2 provides an overview of the 26 comparisons, organized by intervention level and category, and Table 1 gives details of study populations and interventions. Three studies had low risk of bias (Van Roosbroeck and colleagues [38], Green and colleagues [39], and Raich and colleagues [40]). The number of fecal test–positive patients ranged from 14 to 39 105; the number of patients included was not reported in 2 studies. Fourteen studies reported government funding, 2 corporate funding (38, 41), 1 funding from local volunteer organizations (42), and 9 did not specify any funding sources (7, 31, 32, 34, 43–46). Five studies investigated follow-up of fecal immunochemical tests (38, 43, 46–48) and 18 of guaiac-based FOBTs.

The proportions of test-positive patients who had follow-up colonoscopy with and without the intervention were available for 17 studies; the 6 remaining studies either had no control group or reported only coefficients of change in colonoscopy completion rates (31, 33–35, 45, 48). The 17 studies with control and intervention proportions reported absolute differences of –7.4 percentage points (95% CI, –19 to 4.3 percentage points) to 25 percentage points (CI, 14 to 35 percentage points). Reported follow-up intervals varied between 30 days and 1 year, although 12 studies did not specify a time interval. Given the heterogeneity in study interventions, study design, and whether usual care was used as a control group, no meta-analysis was done.

Patient-Level Interventions

The 11 patient-level intervention studies used the following 3 general strategies: changes to the screening invitation strategy (38, 42), provision to patients of test results or follow-up appointments (33, 43, 45, 47), and patient navigator programs (31, 32, 39, 40, 48).

We included 2 studies focusing on changes made by organized programs to their invitation strategies to increase overall participation because they subsequently reported the proportion of patients with positive test results who had colonoscopy (38, 42). One of the studies was at low risk of bias and tested the effect of an invitation letter with a fecal immunochemical test included that could be returned by mail. Among 435 test-positive participants, similar proportions completed follow-up colonoscopy in the control and intervention groups (absolute difference, –1.9% [CI, –11% to 7.4%]) despite higher overall adherence to screening in the intervention group receiving the fecal test kit by mail (38). The second study showed that having primary care physicians sign an invitation letter increased not only FOBT completion but also colonoscopy follow-up of positive results. These 2 studies suggest that changes to programs' invitation strategies to increase screening are not associated with important *decreases* in colonoscopy follow-up of patients with positive test results.

Four studies examined mailing or calling all patients to provide them with their test results or appointments to discuss follow-up colonoscopy, with a total of 6 between-group comparisons (33, 43, 45, 47). Mailing FOBT results to all participants in a systematic

screening program and, if test results were positive, informing them of the need for colonoscopy increased colonoscopy completion rates by 16.1% ($P = 0.04$) (33). Two studies added systematic follow-up telephone calls to patients with positive results, compared with control groups receiving results only by mail (43, 47). In 1 of these, an RCT with moderate risk of bias, addition of a telephone call to the initial invitation did not significantly change follow-up (change, 2.0% [CI, -2.2% to 6.2%]). Among initial nonresponders, a reminder call from a specialized nurse did increase follow-up by 12% (CI, 0.5% to 24%), whereas a reminder from a generalist physician had a trend toward a decrease in follow-up (change, -7.4% [CI, -19% to 4.3%]). A final study mailed a second appointment time to test-positive patients who did not present for an initial appointment (45).

The 5 studies of patient navigation interventions included 2 randomized trials with low risk of bias (39, 40). The first compared usual care (a patient registry and electronic health record [EHR] reminders) with the addition of registered nurse patient navigators (39). The navigators helped with logistic barriers and used motivational interviewing, resulting in a non-statistically significant, but potentially clinically relevant, adjusted increase from 80.8% to 91.0% of patients completing colonoscopies (difference, 10.1% [CI, -1.5% to 22%]). The study was powered to detect a 15% difference, and the authors attributed the lack of a significant increase to the fact that the usual care group already had high-quality tracking of patients. The second study was an RCT of patient navigators for the follow-up of abnormal results on breast, colorectal, and prostate screening tests who maintained regular contact with participants until the completion of follow-up. It showed substantial improvements using a “strengths-based” approach to focus on participants’ assets and encourage action: 79% of patients in the intervention group had either colonoscopy or another definitive follow-up test, compared with 58% in the control group (difference, 21 percentage points [CI, 9.5 to 33 percentage points]) (40). However, this study included some patients with CRC symptoms and counted several possibilities of test resolution other than colonoscopy, making the results less comparable to those of other studies. The other 3 studies used similar navigators, who provided personalized contact and problem solving to patients, but were observational studies with high or very high risk of bias (31, 32, 48).

Provider-Level Interventions

All 5 provider-level intervention studies used provider reminders or performance data (30, 35, 41, 49, 50). They used electronic algorithms to clearly identify ordering providers and remind those who had taken no initial action or inadequate action within 60 or 90 days of a positive fecal test result. Four of the studies came from integrated systems in the United States and showed statistically significant, positive results with absolute improvements in colonoscopy completion of 9 to 25 percentage points (30, 41, 49, 50). The fifth study used centrally generated reports from a provincial screening program and did not show any difference in colonoscopy rates (hazard ratio, 0.95 [CI, 0.79 to 1.13]) (35).

System-Level Interventions

The 7 studies of system-level interventions used automated referral of patients with positive fecal test results to a gastroenterologist for colonoscopy scheduling (46, 51), replacing the

precolonoscopy office visit with a telephone call (44), a registry to track patients with positive test results (52), or a multicomponent quality improvement effort (7, 34, 53).

The 2 studies of automated referral involved directly sending all positive fecal test results to gastroenterologists rather than awaiting manual referral from a primary care provider (46, 51). One of the automated referral studies was designed as a cluster randomized trial, but because few sites completed the trial, analyses were done using before-and-after comparisons at intervention sites (51). It showed improvements in the number of referrals and decreases in time to colonoscopy but only a 6.5% change (CI, -6.0% to 19%) in colonoscopy completion (51).

Only 1 study examined the replacement of in-person precolonoscopy visits with telephone calls (44), and another examined the implementation of a patient registry to track positive fecal test results (52); both were at high risk of bias. Three studies described the effect of quality improvement efforts in the Department of Veterans Affairs (VA) health care system using nonrandomized study designs (7, 34, 53). A multicomponent intervention showed large improvements in rates of referral to a gastroenterologist and decreases in time to colonoscopy but a 6.0% improvement (CI, 2.7% to 9.2%) in the principal outcome of meeting the VA target of colonoscopy completion within 60 days of a positive test result.

Overall Strength of Evidence

The overall strength of evidence supporting the use of interventions from each category was evaluated using Agency for Healthcare Research and Quality criteria, with details provided in Table 2 (36). Two categories had moderate strength of evidence: patient navigators and the provision to providers of reminders or performance data. Patient navigator studies had moderate evidence because of 2 high-quality RCTs at low risk of bias with consistent positive trends in their results (39, 40). Although 1 did not achieve statistical significance (39), it was underpowered and its point estimate of a 10% improvement in follow-up reached our threshold for clinical importance. Moderate evidence for the provision to providers of reminders or performance data was based on consistent, direct evidence for increases in colonoscopy completion across 4 studies, although 1 recent study failed to show an effect (35). All other categories, including all categories of system-level interventions, had low strength of evidence due to various problems with risk of bias, inconsistent effects on colonoscopy rates, and imprecise estimates of the effect on colonoscopy rates.

Discussion

This systematic review evaluated many interventions for increasing follow-up colonoscopy completion rates after positive fecal test results, including patient-, provider-, and system-level interventions. Most studies had at least moderate risk of bias, and moderate evidence supported only patient navigators and the provision to providers of reminders or performance data.

Our systematic review, which used a broad search strategy and included detailed critical appraisal, differs from other reviews we identified (22, 23). A narrative review without a specified search strategy of interventions to improve follow-up of abnormal findings in

cancer screening from 2004 identified only 1 trial for FOBT (41) and 1 for sigmoidoscopies (22). A systematic review of Embase, MEDLINE, Cochrane Central Register of Controlled Trials, and Google Scholar from 2017 identified 13 studies, which we included in our review, but it did not include conference proceedings, had only 1 reviewer, and did not systematically evaluate risk of bias and levels of evidence (23). Similar to our findings, that review highlighted that “screening specialists to aid the patient journey,” or patient navigators, and “tracking and reminder systems” can “increase diagnostic testing” (23).

Timely diagnostic colonoscopy after a positive fecal test result is a critical step on the CRC screening continuum (16). Although research has primarily focused on screening completion (54, 55), fecal testing will not be effective if positive results are not followed up. The included studies reported changes in the proportion of test-positive patients receiving a follow-up colonoscopy between –7 and 23 percentage points (Figure 2). Modeling studies suggest that every 10% increase in follow-up colonoscopy after a positive fecal test result represents a clinically important increase of approximately 7 additional cancer cases detected per 1000 tests with positive results (9).

The finding of moderate evidence supporting patient navigators adds to strong evidence supporting their use for screening colonoscopy (55, 56) and for symptomatic patients with anemia or rectal bleeding (57, 58). Patient navigators can provide one-on-one education and individualized reduction of structural barriers. Cost may be a limiting factor, however: An economic evaluation concluded that patient navigation for the follow-up of abnormal results on cancer screening tests costs an additional \$275 per patient (CI, \$260 to \$290) (59).

Two promising, low-cost interventions for integrated systems are implementing provider reminder systems in the EHR and directly notifying endoscopists of all positive fecal test results. Nearly all test-positive patients will require colonoscopy, and comprehensive EHRs can allow the automatic transfer of patient information. A recent study found an association between VA clinics using direct gastroenterology notification and higher rates of colonoscopy completion at 6 months (odds ratio, 1.25 [CI, 1.06 to 1.47]) (60). However, direct notification requires accountability and patient-tracking capabilities by gastroenterology offices (61).

We identified several areas for future research. Greater standardization in results reporting between studies (that is, colonoscopy completion at 6 months) is needed to facilitate the comparison of strategies. The promising results of several nonrandomized studies should be replicated in high-quality randomized trials, especially in categories without any RCTs to date. Novel strategies to be evaluated could include increasing colonoscopy capacity in health systems by gastroenterologists, surgeons, or nonphysician staff; incentives for gastroenterology practices to encourage patient tracking and high completion rates; better engaging patients with access to their own medical records and low-cost reminder systems; and stratifying patient populations to target more intensive interventions to appropriate patients. Although the relatively small number of positive test results at any 1 clinic may limit research, making trials difficult outside of large integrated health systems like the VA, the widespread use of EHRs should allow better measurement of the effect of future interventions.

Several potential limitations merit mention. First, the included studies used heterogeneous outcome measurements, reporting follow-up colonoscopy rates at various time intervals or sometimes not at all. Second, the performance of colonoscopy is a surrogate outcome; however, several trials using FOBT screening and high rates of colonoscopy follow-up of patients with positive test results have shown that this approach can decrease CRC mortality (3). Third, most U.S. studies (10 of 14) were done in the VA system, which has an integrated organization structure and more than 90% male patients, possibly limiting the generalizability of our findings. Fourth, we cannot rule out publication bias and may not have found all trials reporting on changes in colonoscopy follow-up with different invitation strategies (for example, mailed fecal tests) because our search strategies were not specifically tailored to capture these studies. Finally, most studies were at moderate, high, or very high risk of bias, meaning that the effects reported on follow-up colonoscopy rates may be substantially different in future studies. The inclusion of nonrandomized studies provides a fuller picture of research results but may be misleading and overstate confidence in our results.

In conclusion, our systematic review found 23 studies focused on improving rates of follow-up colonoscopy after positive fecal blood test results. Moderate evidence supports the implementation of patient navigators and the provision to providers of reminders or performance data; low-level evidence exists in other areas. More research is needed given the critical role of the diagnostic resolution of positive test results in fecal blood-based screening.

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Appendix

Appendix Table 1.

Search Strategies

Search strategy for MEDLINE PubMed

(((((“Colonoscopy”[Mesh] OR colonoscope OR colonoscopy OR sigmoidoscope OR sigmoidoscopy)))

AND (((“early detection of cancer”[MeSH Terms] OR “mass screening”[MeSH Terms] OR “early detection” OR screening) AND (“colorectal neoplasms”[MeSH Terms] OR colon cancer OR colonic cancer OR sigmoid cancer OR colorectal cancer* OR rectal cancer*)) OR (“stool test” OR “fecal immunochemical test” OR “faecal immunochemical test” OR “fecal occult blood test” OR “faecal occult blood test” OR FIT OR FOBT OR “Stool DNA”))) OR (“Guaiaac” [Mesh] OR “Occult Blood”[Mesh] OR immunochemistry[mh]) AND (“Feces”[Mesh] OR stool))))

AND (((“Lost to Follow-Up”[Mesh] OR “lost to follow up” OR timely OR “time factors” OR prompt OR “time factors”[mh] OR reminder OR “reminder systems”[mh] OR “reminder system” OR “reminder systems” OR “reminder” OR “reminders” OR “tickler” OR “followup” OR “follow up” OR “telephone call” OR “telephone calls”))))))

Search strategy for Ovid Embase

1. 'colonoscope'/exp OR 'colonoscope' OR 'colonoscopy'/exp OR 'colonoscopy' OR 'sigmoidoscope'/exp OR 'sigmoidoscope' OR 'sigmoidoscopy'/exp OR 'sigmoidoscopy'

2. 'early detection of cancer' OR 'mass screening' OR 'early detection' OR screening

3. 'colorectal neoplasms'/exp OR 'colorectal neoplasms' OR 'colon cancer' OR 'colonic cancer' OR 'sigmoid cancer' OR 'colorectal cancer*' OR 'rectal cancer*' OR 'stool test' OR 'fecal immunochemical test' OR 'faecal immunochemical test' OR 'fecal occult blood test' OR fit OR fobt OR 'stool dna'

4. 'guaiaac'/exp OR 'guaiaac' OR 'occult blood'/exp OR 'occult blood' OR 'immunochemistry'/exp OR 'immunochemical'

5. 'feces'/exp OR 'feces' OR stool

6. #4 AND #5

7. #2 OR #3 OR #6

8. 'follow up'/exp OR 'lost to follow up' OR timely OR 'time factors' OR prompt OR 'time factor' OR 'reminder system'/exp OR 'reminder system*' OR reminder* OR tickler OR followup OR 'follow up' OR 'telephone call*'

9. #1 AND #7 AND #8

Search strategy for Cochrane Central Register of Controlled Trials

Identification	Search	Hits
#1	MeSH descriptor: [Colonoscopy] explode all trees	1815
#2	colonoscope or colonoscopy or sigmoidoscope or sigmoidoscopy	3654
#3	#1 or #2	3654
#4	MeSH descriptor: [Early Detection of Cancer] explode all trees	866
#5	MeSH descriptor: [Mass Screening] explode all trees	5504
#6	#4 or #5 or "early detection" or screening	27 634
#7	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6124
#8	#7 or colon cancer or colonic cancer or sigmoid cancer or colorectal cancer* or rectal cancer*	12 956
#9	"stool test" or "fecal immunochemical test" or "faecal immunochemical test" or "fecal occult blood test" or "faecal occult blood test" or FIT or FOBT or "Stool DNA"	4989
#10	MeSH descriptor: [Guaiaac] explode all trees	30
#11	MeSH descriptor: [Occult Blood] explode all trees	495
#12	#10 or #11	498
#13	MeSH descriptor: [Feces] explode all trees	2434

#14	#13 or stool	5550
#15	#12 and #14	85
#16	#8 or #9 or #15	17 471
#17	MeSH descriptor: [Follow-Up Studies] explode all trees	50 662
#18	MeSH descriptor: [Time Factors] explode all trees	57 027
#19	MeSH descriptor: [Reminder Systems] explode all trees	749
#20	#17 or "lost to follow up" or timely or "time factors" or prompt or #18 or reminder or #19 or "reminder system" or "reminder systems" or reminder or reminders or tickler or followup or "follow up" or "telephone call" or "telephone calls"	199 277
#21	#3 and #16 and #20	584

Appendix 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 study design)	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 (36) and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group (37).

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Figure 1.

Flow chart of study selection for interventions to improve follow-up of positive fecal blood tests for colorectal cancer screening. CENTRAL = Cochrane Central Register of Controlled Trials.

Figure 2.

Overview of included studies of interventions to improve follow-up of positive fecal blood tests for colorectal cancer screening, by intervention level and category. HR = hazard ratio; NA = not applicable; NR = not reported.

n/a: not available; UK: United Kingdom; USA: United States of America

*Studies with separate reporting of more than one comparison are listed as A, B, C with further details in Table 1

†Risk of bias for individual study according to Agency for Healthcare Research and Quality and GRADE criteria (36,37), details in Appendix B

‡Follow-up interval given only when specifically provided by authors, otherwise marked unspecified

#Adjusted absolute change, as reported by study authors

Table 1.

Details of Study Population, Interventions, and Controls, by Intervention Level and Type

Study, Year (Reference)	Details
Patient-level interventions	
Changes to invitation strategy to screening	
Grazzini et al, 2000 (42)	Regional screening program; Italy Male: 46% Age: NR Intervention A: Participants were sent a letter signed by their PCP with instructions to pick up an FOBT at a volunteer center Intervention B: Participants were sent a letter signed by their PCP with instructions to pick up an FOBT at their outpatient clinic Control: Letter signed by program coordinator
Van Roosbroeck et al, 2012 (38)	Regional screening program; Belgium Male: NR Age of patients with positive results: NR Intervention: A fecal immunochemical test was included with the mailed invitation letter Control: Patients received an invitation letter without a test and instructions to visit their PCP to receive one
Provision to patients of test results or follow-up appointments	
Cha et al, 2011 (43)	National screening program; South Korea Male: 59% Mean age: 62 y Intervention: Telephone reminder call in addition to mailing for patients with a positive fecal immunochemical test result Historical control: Mailed notification only
Stock et al, 2015 (33)	Regional screening program; Canada Male: 55% Mean age: 62 y Intervention: First, a revision of the letter was mailed to PCPs to explicitly define a positive FOBT result as blood on 1 FOBT windows. Second (primary comparison), an additional letter was mailed to participants notifying them of positive results and urging them to contact their PCP. Control: Notification of PCP by usual letter; no letter to participant
Tran et al, 2010 (45)	Single medical center; United Kingdom Male: NR Age: NR Intervention: Patients with positive results who did not attend their first colonoscopy visit were mailed a second appointment Control: No follow-up of patients who missed a colonoscopy visit
Zorzi et al, 2014 (47)	9 regional screening programs; Italy Male: 54% Mean age: 62 y Intervention A: Patients with positive results were notified by telephone in addition to mail Control: Mail notification only Interventions B or C: Patients with positive results who did not respond after the first intervention were invited for general practitioner counseling by phone or an appointment with a specialist screening practitioner Control: Mailing to nonresponders
Patient navigator	
Fasoli et al, 2010 (32)	Regional screening program; Italy Male: NR Age: NR Intervention: Medical counseling for patients with positive results, aimed at giving explanations, clarifying doubts, scheduling appointments, and finally administering intestinal preparation Control: Standard strategy of mailed or telephone test results

Study, Year (Reference)	Details
Green et al, 2014 (39)	Integrated health network; United States Male: 54% Mean age: 60 y Intervention: Nurse navigators performed referrals, scheduled appointments, provided precolonoscopy preparation needs, resolved barriers, and used motivational interviewing techniques Control: Registry of patients with positive FOBT results and EHR reminder to providers
Phillips-Angeles et al, 2013 (48)	10 medical centers in 1 city; United States Male: 25% Age: NR Intervention: Navigators tracked patients to coach them, ensure they received a referral for colonoscopy and they kept their appointments. The cost to the patient of screening tests and follow-up was also reduced Control: No control reported
Raich et al, 2012 (40)	Safety-net health care system; United States Male: 55% Age: NR Intervention: Navigator called within 3 d of result, then regular contact until resolution. Strengths-based approach to find assets was available to the patient. Patients with positive results were tracked. Control: Usual care without patient navigators
Ratner et al, 2016 (31)	Single academic practice; United States Male: NR Age: NR Intervention: Dedicated prevention care manager trained in social work with multiple roles: completed monthly reports of abnormal results; checked documentation in EHR to ensure patient notification; reminded PCPs; ensured that the patient was referred and booked for colonoscopy; and contacted the patient to facilitate Control: No control reported
Provider-level interventions	
Provision of reminders and/or performance data to providers	
Larson et al, 2009 (49)	Single Veterans Affairs medical center; United States Male: 95% Mean age: 65 y Intervention: "Lab Check Note" was entered in the patient chart for each patient with positive results to remind the ordering provider. An electronic alert offered the following choices: referral for colonoscopy, defer colonoscopy because of recent colonoscopy, defer colonoscopy because of severe comorbidity, document patient refusal, or other. Control: Usual care without electronic reminder
Murphy et al, 2015 (30)	Single Veterans Affairs and single private medical center; United States Male: 86% Mean age: 60 y Intervention: Automated EHR trigger identified patients with no colonoscopy 60 d after positive test results. PCPs were contacted by e-mail. If no response, an assistant called either the PCP or the patient's nurse. Control: Laboratory notified the ordering provider, not necessarily the PCP; no reminders
Myers et al, 2004 (41)	Managed care organization; United States Male: NR Age: NR Intervention: Physician-oriented reminder-feedback and educational outreach program. Reminder was an internal chart audit form listing patients without timely referral or colonoscopy. PCPs received 2 academic detailing visits, a tailored letter, and telephone calls. Control: Usual care, although patients received reminders in order to measure follow-up rates
Singh et al, 2009 (50)	Single Veterans Affairs medical center; United States Male: 97% Mean age: 64 y Intervention: Addition of a code to link patients to their PCP; important for tests ordered by other providers Control: PCPs notified only if they ordered the test

Study, Year (Reference)	Details
Stock et al, 2017 (35)	Regional screening program; Canada Male: 47% Mean age: 62 y Intervention: 1-time, centrally generated reports sent to PCPs with summaries of screening participation and a list of patients with positive results in their practice who remained outstanding for colonoscopy after 3 mo of follow-up Control: PCPs without a patient roster were not mailed reports
System-level interventions	
Automated referral to GI clinic	
Humphrey et al, 2011 (51)	Several Veterans Affairs medical centers; United States Male: 97% Mean age: 64 y Intervention: Automatic notification sent to PCP and GI clinic simultaneously for each positive test result Control: Positive result sent only to ordering provider, and follow-up must be initiated by the PCP
Van Kleeck et al, 2010 (46)	Single Veterans Affairs medical center; United States Male: 94% Mean age: 65 y Intervention: Nurse manager maintained an electronic registry and created an electronic colonoscopy request for each patient with positive results. PCP also notified. Control: Only PCP notification
Replacement of precolonoscopy visit with telephone call	
Rodger and Steele, 2008 (44)	Regional screening program; United Kingdom Male: 58% Mean age: 61 y Intervention: Participants were sent a letter offering a choice of face-to-face consultation or telephone interview with a colorectal nurse specialist. If assessment by telephone was satisfactory, patients received an appointment for colonoscopy. Historical control: All patients had precolonoscopy assessment in person
Registry to track patients with positive results	
Miglioretti et al, 2008 (52)	Integrated health network; United States Male: 51% Mean age: 64 y Intervention: In November 1998, an electronic registry of patients with positive results who had not received a complete diagnostic evaluation within 4 mo was created. In autumn 2003, a centralized manual audit system was created to supplement the electronic system. A nurse auditor or physician reviewed cases and recommended action. Historical control: Usual care without registry
Multicomponent quality improvement efforts	
Powell et al, 2009 (34)	125 Veterans Affairs medical centers; United States Male: NR Age: NR Intervention: Logistic regression was used to assess the association between the implementation of improvement strategies and 60-d colonoscopy rates. Statistically significant associations were found for tracking colonoscopy supply and demand, creating a system to track follow-up of positive FOBT results, strategies to decrease cancellations/no-shows, creating/revising primary care/GI service agreement, and revising colonoscopy preparation education/protocols.
Powell et al, 2011 (7)	21 Veterans Affairs medical centers; United States Male: 98% Mean age: 66 y Intervention: Implemented key components of breakthrough collaborative model of the Institute for Healthcare Improvement to give care teams a quality improvement framework. Local teams were given an improvement guide and a proposed set of strategies (e.g., a tracking system and PCP education). Control: usual care
Singh et al, 2009 (53)	Single Veterans Affairs medical center; United States

Study, Year (Reference)	Details
	Male: NR Age: NR Intervention: Distributed guidelines; GI service reduced colonoscopy backlog; instituted electronic reporting system for patients with positive results; additional paper notification of positive results to providers; coordinator tracked patients with positive results Control: Usual care

EHR = electronic health record; FOBT = fecal occult blood test; GI = gastroenterology; NR = not reported; PCP = primary care provider

Table 2.Strength-of-Evidence Grade, by Intervention Category^{*}

Intervention Level and Type	Risk of Bias of Included Studies [†]	Consistency [‡]	Directness [§]	Precision	Overall Strength of Evidence [¶]
Patient-level interventions					
Changes to invitation strategy to screening (38, 42)	1 low, 1 high	Inconsistent	Direct	Imprecise	Low
Provision to patients of test results or follow-up appointments (33, 43, 45, 47)	2 moderate, 1 high, 1 very high	Inconsistent	Direct	Imprecise	Low
Patient navigator (31, 32, 39, 40, 48)	2 low, 1 high, 2 very high	Consistent	Direct	Imprecise	Moderate
Provider-level interventions					
Provision of reminders and/or performance data to providers (30, 35, 41, 49, 50)	3 moderate, 2 high	Consistent	Direct	Precise	Moderate
System-level interventions					
Automated referral to gastroenterologist (46, 51)	1 moderate, 1 high	Consistent	Direct	Imprecise	Low
Replacement of precolonoscopy visit with telephone call (44)	1 high	Unknown	Direct	Imprecise	Low
Registry to track patients with positive results (52)	1 high	Unknown	Direct	Imprecise	Low
Multicomponent quality improvement efforts (7, 34, 53)	2 high, 1 moderate	Consistent	Indirect	Imprecise	Low

^{*} Using Agency for Healthcare Research and Quality criteria, based on risk of bias, consistency, directness, and precision of evidence (36).

[†] Assessment in individual studies incorporating study design and study conduct.

[‡] Whether reported effect sizes have the same direction of effect. Unknown if only 1 study is available.

[§] Whether the evidence links interventions directly to increases in colonoscopy completion.

^{||} Degree of certainty surrounding the effect estimate and whether the estimate allows a clinically useful conclusion.

[¶] Confidence that the evidence reflects the true effect and that future research will not change the estimate.