JAMA Internal Medicine | Original Investigation

# Evaluation of Interventions Intended to Increase Colorectal Cancer Screening Rates in the United States
## A Systematic Review and Meta-analysis

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**IMPORTANCE** Colorectal cancer screening (CRC) is recommended by all major US medical organizations but remains underused.

**OBJECTIVE** To identify interventions associated with increasing CRC screening rates and their effect sizes.

**DATA SOURCES** PubMed, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Library, and ClinicalTrials.gov were searched from January 1, 1996, to August 31, 2017. Key search terms included *colorectal cancer* and *screening*.

**STUDY SELECTION** Randomized clinical trials of US-based interventions in clinical settings designed to improve CRC screening test completion in average-risk adults.

**DATA EXTRACTION AND SYNTHESIS** At least 2 investigators independently extracted data and appraised each study's risk of bias. Where sufficient data were available, random-effects meta-analysis was used to obtain either a pooled risk ratio (RR) or risk difference (RD) for screening completion for each type of intervention.

**MAIN OUTCOMES AND MEASURES** The main outcome was completion of CRC screening. Examination included interventions to increase completion of (1) initial CRC screening by any recommended modality, (2) colonoscopy after an abnormal initial screening test result, and (3) continued rounds of annual fecal blood tests (FBTs).

**RESULTS** The main review included 73 randomized clinical trials comprising 366 766 patients at low or medium risk of bias. Interventions that were associated with increased CRC screening completion rates compared with usual care included FBT outreach (RR, 2.26; 95% CI, 1.81-2.81; RD, 22%; 95% CI, 17%-27%), patient navigation (RR, 2.01; 95% CI, 1.64-2.46; RD, 18%; 95% CI, 13%-23%), patient education (RR, 1.20; 95% CI, 1.06-1.36; RD, 4%; 95% CI, 1%-6%), patient reminders (RR, 1.20; 95% CI, 1.02-1.41; RD, 3%; 95% CI, 0%-5%), clinician interventions of academic detailing (RD, 10%; 95% CI, 3%-17%), and clinician reminders (RD, 13%; 95% CI, 8%-19%). Combinations of interventions (clinician interventions or navigation added to FBT outreach) were associated with greater increases than single components (RR, 1.18; 95% CI, 1.09-1.29; RD, 7%; 95% CI, 3%-11%). Repeated mailed FBTs with navigation were associated with increased annual FBT completion (RR, 2.09; 95% CI, 1.91-2.29; RD, 39%; 95% CI, 29%-49%). Patient navigation was not associated with colonoscopy completion after an initial abnormal screening test result (RR, 1.21; 95% CI, 0.92-1.60; RD, 14%; 95% CI, 0%-29%).

**CONCLUSIONS AND RELEVANCE** Fecal blood test outreach and patient navigation, particularly in the context of multicomponent interventions, were associated with increased CRC screening rates in US trials. Fecal blood test outreach should be incorporated into population-based screening programs. More research is needed on interventions to increase adherence to continued FBTs, follow-up of abnormal initial screening test results, and cost-effectiveness and other implementation barriers for more intensive interventions, such as navigation.

*JAMA Intern Med*. 2018;178(12):1645-1658. doi:10.1001/jamainternmed.2018.4637
Published online October 15, 2018.

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Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.[1] Screening for CRC reduces the incidence and mortality[2,3] and is cost-effective.[4] Multiple US medical guidelines endorse population-based screening for adults[2,5] through multiple modalities, including colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, and fecal blood tests (FBTs) using a guaiac fecal occult blood test (gFOBT) or fecal immunochemical (FIT) test, with or without multitargeted stool DNA.[2] However, testing is up to date in only 63% of eligible adults, and rates are lower among minority race/ethnicity groups and the underinsured.[6]

Such underuse has brought CRC screening to the forefront of national public health campaigns,[7] yet implementation of approaches with a positive association for increasing CRC uptake[8-11] has been comparatively slow. An up-to-date synthesis of the literature on interventions to increase CRC screening could help enhance clinicians' and policymakers' ability to select approaches most likely to benefit their populations and help researchers to identify and address remaining knowledge gaps.

The purpose of this review and meta-analysis is to systematically evaluate interventions designed to increase CRC screening rates in US settings. The review was structured according to 3 key questions (KQs). These KQs examined the interventions that have been tested and their effect sizes for increasing completion of KQ1, any initial CRC screening test; KQ2, colonoscopy following an abnormal initial screening test result (FBT, flexible sigmoidoscopy, or radiologic test); and KQ3, continued annual FBTs.

### Key Points

**Question** Which interventions increase completion of colorectal cancer screening tests in the United States?

**Findings** In this sytematic review and meta-analysis of 73 randomized clinical trials, Patient navigation and fecal test outreach had the strongest evidence supporting a significant increase in completion of initial screening; combining interventions (eg, navigation with test outreach) was associated with further increases in screening.

**Meaning** Multicomponent programs, including screening test outreach with as-needed patient navigation, should be implemented to reach national goals for colorectal cancer screening rates.

## Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[12]

### Data Sources and Searches

A medical librarian searched PubMed, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library for English-language articles published from January 1, 1996, to August 31, 2017 (eTable 1 in the Supplement). We also searched the ClinicalTrials.gov database for completed but unpublished studies and manually searched reference lists of pertinent prior review articles (eTable 5 in the Supplement). Key search terms included *colorectal cancer* and *screening*.

### Study Selection and Eligibility Criteria

Each phase of study selection, data extraction, and risk-of-bias assessment was performed by at least 2 individuals. We limited the review to randomized clinical trials (RCTs) of interventions intended to improve completion of any CRC screening test recommended during the study period in average-risk populations in the United States (eAppendix 1 in the Supplement, full eligibility criteria). The primary outcome was objective documentation of screening completion. We assessed risk of bias within studies according to PRISMA recommendations using a tool based on Agency for Healthcare Research and Quality guidance (eMethods, eTable 2 in the Supplement). We rated each study as having low, medium, or high risk of bias.

### Data Synthesis and Analysis

We organized the interventions into logical categories according to group consensus. The primary comparator was usual care. For trials with multiple arms, we assessed the outcomes of all active interventions vs usual care and vs other active comparators. If 2 or more studies of a sufficiently similar intervention made the same comparison, we used random-effects meta-analysis to obtain pooled risk ratios (RRs) and risk differences (RDs) for completion of any screening test. For interventions with multiple-cluster RCTs with different, nonzero baseline screening rates, we estimated only RD. Our primary analyses for each intervention included studies at low or medium risk of bias, with a sensitivity analysis including studies at all risks of bias. Following the Community Preventive Services Task Force,[13] we also compared the effects of multicomponent vs single-component interventions. Between-study heterogeneity was determined using the $I^2$ statistic.[12] If more than 8 RCTs reported a study characteristic (eg, type of screening test, outcome time point, or a demographic feature), we explored heterogeneity with meta-regression. For interventions with more than 8 studies (including those with high risk of bias), we used funnel plots and the Harbord test or Egger test to detect small-study effects (eg, publication bias). Unpublished studies identified in ClinicalTrials.gov helped to inform assessment of publication bias. For the principal comparisons, we graded the strength of evidence as high, moderate, or low using an established approach (eMethods in the Supplement).

## Results

### Search Results

The search yielded 2123 unique abstracts, with dual review including 104 full-text articles describing 232 intervention comparisons in 457 534 patients (**Figure 1**). Ninety-two studies addressed initial screening uptake (KQ1), 6 addressed follow-up

of positive initial screening test results (KQ2), and 13 addressed continued completion of FBTs (KQ3; 9 studies also addressed initial screening). Seventy-three studies at medium or low risk of bias, describing 181 intervention comparisons in 366 766 patients, were included in primary analyses (eTable3 in the Supplement indicates risk-of-bias ratings; the **Box** provides intervention categorization; eAppendix 2 in the Supplement reports sensitivity, subgroup, and funnel plot analyses).

## KQ1: Completion of Any Initial CRC Screening

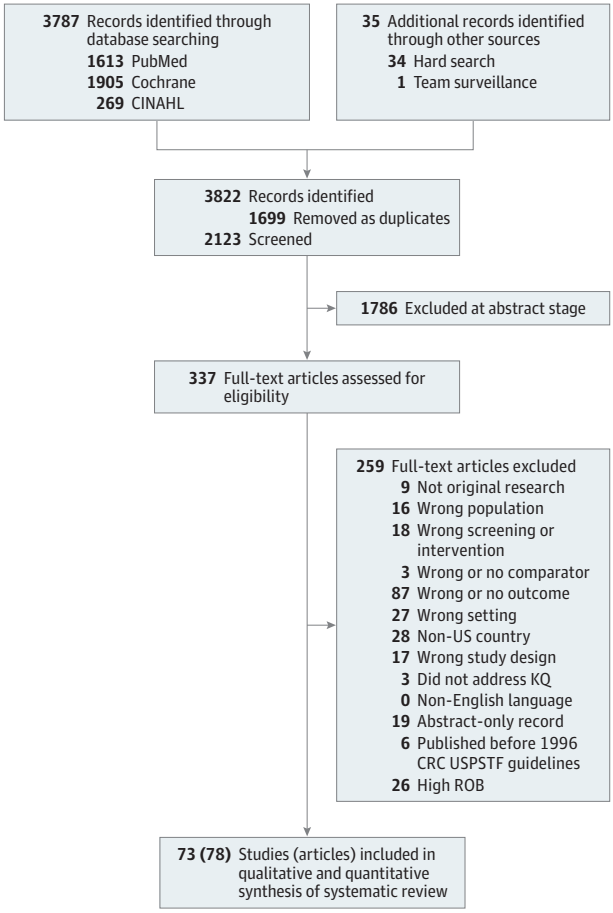
### Patient-Directed Interventions

**FBT Outreach** | A frequently tested intervention was active distribution of FBTs, aimed at circumventing structural barriers to accessing screening. Twenty studies compared FBT outreach with usual care, with 17 at medium or low risk of bias (eTable 4 in the Supplement). Fifteen studies used mailed FBTs and 5 tied FBT distribution to a patient encounter (3 involved influenza vaccination).[14-18]

All medium or low risk-of-bias studies reported superiority of FBT outreach over usual care for increasing completion of any CRC screening test (RR, 2.26; 95% CI, 1.81-2.81; RD, 22%; 95% CI, 17%-27%) (**Figure 2**A[14-16,18-31]; eFigure 1A and eFigure 2 in the Supplement). There was a significantly large variance of study results ($I^2$ = 98%), although the heterogeneity reflects differences in the magnitude but not direction of the association (Figure 2A).[14-16,18-31] Bivariate meta-regression did not reveal statistically significant effect modification by mean age; proportions of minority race/ethnicity (eFigure 9 in the Supplement), female sex, uninsured (eFigures 10 and 11 in the Supplement), and ever-screened participants (eFigures 7 and 8 in the Supplement); use of FIT or gFOBT (eFigures 5 and 6 in the Supplement); length of follow-up (eFigures 3 and 4 in the Supplement); non-FBT cointerventions (eg, patient navigation); risk of bias; or FBT distribution method (mailed or in-person; eFigures 1A and eFigure 2 in the Supplement). The $I^2$ level was reduced to 63% to 69% when the analysis was restricted to outcomes with the same follow-up time (either 26 or 52 weeks) (eFigure 4 in the Supplement); further restricting study characteristics did not reduce heterogeneity (eFigure 12 in the Supplement).

**Patient Navigation** | Patient navigation is a barriers-focused intervention[44] whereby a trained individual guides a patient through a complex health care system, addressing sociocultural, educational, and logistical barriers with the main goal of minimizing loss to follow-up. We considered interventions to be navigation if they appeared to fulfill these characteristics, even if differently named (eg, patient management,[32,35] health promotion,[27] or targeted telephone education[38,39]). Navigators were mostly health care professionals,[20,21,23,24,32-40,45-47] although 4 studies used lay or peer navigators.[30,41,43,48] Navigation had a consistent association with increased CRC screening completion over usual care in the 16 studies at medium or low risk of bias (RR, 2.01; 95% CI, 1.64-2.46) (Figure 2B)[20,21,23,24,27,30,32-41] (RD, 18%; 95% CI, 13%-23%) (eFigure 14 in the Supplement).

Figure 1. Summary of Evidence Search and Study Selection




Seventy-three randomized clinical trials were described in a total of 78 articles. The extra articles were either reports or extended follow-up or additional analyses. CINAHL indicates Cumulative Index to Nursing and Allied Health Literature; CRC, colorectal cancer; KQ, key question; ROB, risk of bias; USPSTF, United States Preventive Services Task Force.

If navigation interventions involved an additional component that was more than a nontailored educational mailing or reminder (eg, clinician-directed intervention,[30,32] video decision aid,[41] or intensive automated reminder program[23]), the combined interventions were associated with larger screening increases than pure navigation interventions (RR, 2.33; 95% CI, 1.79-3.04 vs RR, 1.69; 95% CI, 1.35-2.11; and RD, 25%; 95% CI, 20%-31% vs RD 11%; 95% CI, 7%-15%). Regarding FBT distribution, interventions incorporating standing orders for the navigator to distribute FBTs were more associated with increased screening than those that did not (Figure 2B; eFigure 1B and eFigure 14 in the Supplement). Five studies directly comparing navigation plus mailed FBT with mailed FBT alone[23,24,26,27,29] demonstrated a small but significant benefit of adding navigation (RR, 1.14; 95% CI, 1.07-1.23; RD, 6%; 95% CI, 1%-11%) (eFigure 15 in the Supplement).

Meta-regression revealed that shorter time frames for end point evaluation were associated with increased screening rates, although navigation was superior to usual care at

Box. Categories of Interventions for Increasing Colorectal Cancer Screening Completion[a]

**KQ1: Interventions to Increase Uptake of an Initial Screening Test**

Patient directed
- FBT outreach: 20 studies
  - Mailed FBT outreach: 15 studies
  - Visit-based FBT outreach (often with influenza vaccination): 5 studies
- Patient navigation: 27 studies
  - Explicitly named patient navigation: 18 studies
  - Navigation equivalents: 9 studies
- Patient education (not part of larger intervention in 1 or 2): 25 studies
  - Information only (brochures/videos/websites/calls/in-person): 13 studies
  - Decision aids: 6 studies
  - Provision of personalized risk information: 5 studies
  - Motivational interviewing: 2 studies
- Patient reminders (without included FBT): 14 studies
  - Postal mail only: 6 studies
  - Telephone: 8 studies
    - Automated: 5 studies (1 text message)
    - Personal: 3 studies
- Financial incentives for FBT completion: 2 studies
  - Fixed incentives ($5-$20): 2 studies
  - Lottery-based incentives (1-in-N chance to win larger sum): 1 study
- Strategic presentation of screening tests: 4 studies
  - Presenting choice of FBT or colonoscopy (vs presenting only 1 option): 1 study
  - Screening with 2-card FIT (vs 3-card gFOBT with dietary restrictions): 2 studies
  - Screening with 1-card FIT (vs 2-card FIT): 2 studies

Clinician directed
- Non–visit based: 11 studies
  - Academic detailing: 11 studies
    - With audit and feedback: 5 studies
- Visit based: 8 studies
  - Reminders: 8 studies

**KQ2: Interventions to Increase Uptake of Complete Diagnostic Evaluation or Colonoscopy after Abnormal Initial Screening Test Result**

Patient directed: 4 studies
- Patient navigation: 4 studies

Clinician directed: 2 studies
- Academic detailing and audit + feedback: 1 study
- Task-shifting (automatic GI referral): 1 study

**KQ3: Interventions to Increase Uptake of Annual FBT (After Negative Initial Test Result)**

Patient directed
- Repeated rounds of mailed FBT: 5 studies
- With as-needed patient navigation: 4 studies
- Without patient navigation: 1 study
- Patient reminders: 1 study
- Original presentation of choice of FBT or colonoscopy (vs only 1 option): 1 study

Clinician directed
- Academic detailing, audit + feedback, and quality improvement: 3 studies

Abbreviations: FBT, fecal blood test (FIT or gFOBT); FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; GI, gastrointestinal; KQ, key question.

[a] Numbers of studies are the comparisons with usual care unless another comparator is specified. Totals were generally mutually exclusive except in a few occasions in which studies had multiple arms from different categories.

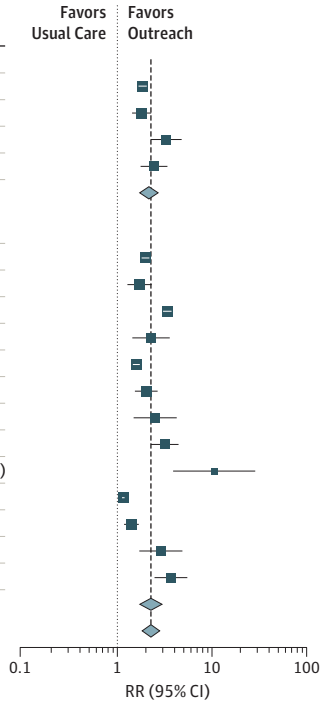
all time points (eFigure 16 and eFigure 17 in the Supplement). Culturally tailored navigation was not significantly more effective vs usual care than standard navigation, although all navigators were language concordant and often culturally concordant, even without specifically culturally tailored scripts or materials (eFigure 18 in the Supplement). Four studies directly comparing some form of culturally or otherwise enhanced navigation with standard navigation[32,47] (2 with a high risk of bias[46,48]) also failed to show increased effectiveness of the enhanced arms (RR, 1.04; 95% CI, 0.98-1.11; RD, 1%; 95% CI, 0%-1%) (eFigure 19 in the Supplement). Restricting analysis to studies with uniform lengths of follow-up (eFigure 16 and eFigure 17 in the Supplement), CRC screening test type (eFigure 21 and eFigure 22 in the Supplement), prior screening tests (eFigure 20 in the Supplement), insurance status (eFigure 23 in the Supplement), and cointerventions reduced $I^2$ but with exclusion of a substantial number of studies.

**Patient Education** | Fifty-two studies used some form of patient education, although 12 of those studies targeted the completion of screening tests already ordered or distributed[49-57] or completion of continued annual FBTs.[23,42,58,59] Nineteen studies,[31,60-77] including 6 with high risk of bias,[72-77] compared an intervention with patient education as the focal point (excluding extensive cointerventions, eg, navigation and FBT outreach) with usual care, and overall were associated with increased screening rates (RR, 1.20; 95% CI, 1.06-1.36; RD 4%; 95% CI, 1%-6%). Among these studies, those with some additional component beyond patient education (clinician prompt[67,69] or patient ability to request FBT directly[62,66]) led to a significant increase in screening completion over usual care (RR, 1.43; 95% CI, 1.16-1.75; RD, 8%; 95% CI, 2%-15%), while those without additional components did not (RR, 1.08; 95% CI, 0.97-1.20; RD, 2%; 95% CI, 0%-4%) (eFigure 25 and eFigure 26 in the Supplement). Subgroup analyses were notable for favorable results of interventions that included personal telephone calls[64,70] or mailings with telephone calls after a visit with screening test distribution,[54,56,78] but were nonsignificant for pooled effects of decision aids[49,53,61,65,67,68,71,78-80] or tailored interventions.[60-62,64,71,73] The $I^2$ value was significantly reduced in several subgroup analyses (eAppendix 2 and eFigures 27-37 in the Supplement).

Figure 2. Risk Ratio for Completion of Colorectal Cancer (CRC) Screening Test

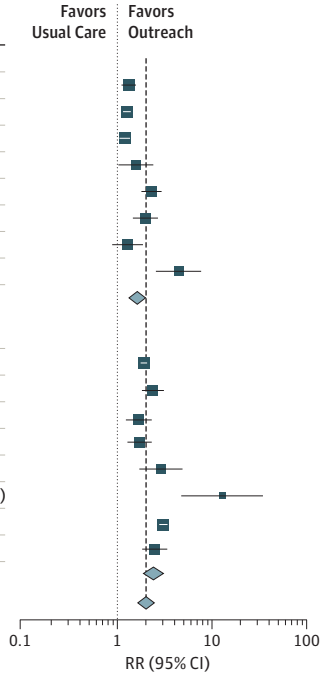
A Screening completion with fecal test outreach, lower risk-of-bias studies

| Source | Events No./Total No. Outreach | Events No./Total No. Usual Care | RR (95% CI) |
|---|---|---|---|
| Visit-based FBT distribution | | | |
| Potter et al,[14] 2013 | 996/3551 | 438/2884 | 1.85 (1.67-2.04) |
| Potter et al,[16] 2011 | 168/695 | 91/677 | 1.80 (1.43-2.27) |
| Potter et al,[15] 2009 | 83/122 | 24/116 | 3.29 (2.26-4.79) |
| Tu et al,[18] 2006 | 73/105 | 30/105 | 2.43 (1.75-3.38) |
| Subtotal: $I^2$ = 72.0%, ($P$ = .013) | 1320/4473 | 583/3782 | 2.16 (1.72-2.70) |
| Mailed FBT distribution | | | |
| Singal et al,[19] 2016 | 1410/2400 | 355/1199 | 1.98 (1.81-2.18) |
| Goldman et al,[20] 2015 | 84/210 | 49/210 | 1.71 (1.28-2.30) |
| Gupta et al,[21] 2013 | 648/1593 | 471/3898 | 3.37 (3.04-3.73) |
| Hendren et al,[22] 2014 | 43/114 | 21/126 | 2.26 (1.43-3.57) |
| Green et al,[23] 2013 | 728/1169 | 459/1166 | 1.58 (1.45-1.72) |
| Myers et al,[24] 2013 | 115/316 | 57/317 | 2.02 (1.53-2.67) |
| Jean-Jacques et al,[25] 2012 | 40/104 | 15/98 | 2.51 (1.49-4.25) |
| Levy et al,[26] 2013 | 105/186 | 33/185 | 3.16 (2.27-4.42) |
| Coronado et al,[27] 2011 | 43/168 | 4/165 | 10.56 (3.88-28.75) |
| Sequist et al,[28] 2009 | 4809/10930 | 4164/10930 | 1.15 (1.12-1.19) |
| Myers et al,[29] 2007 | 177/387 | 126/387 | 1.40 (1.17-1.68) |
| Fiscella et al,[30] 2011 | 47/163 | 16/160 | 2.88 (1.71-4.87) |
| Charlton et al,[31] 2014 | 103/500 | 28/500 | 3.68 (2.47-5.48) |
| Subtotal: $I^2$ = 97.9%, ($P$ < .001) | 8352/18240 | 5798/19341 | 2.28 (1.74-2.97) |
| Overall: $I^2$ = 97.5%, ($P$ < .001) | 9672/22713 | 6381/23123 | 2.26 (1.81-2.81) |




B Screening completion with patient navigation, lower risk-of-bias studies

| Source | Events No./Total No. Outreach | Events No./Total No. Usual Care | RR (95% CI) |
|---|---|---|---|
| No FBT outreach/distribution | | | |
| Ling et al,[32] 2009 | 184/342 | 105/257 | 1.32 (1.10-1.57) |
| Dietrich et al,[33] 2006 | 438/696 | 347/694 | 1.26 (1.15-1.38) |
| Dietrich et al,[34] 2013 | 206/562 | 514/1678 | 1.20 (1.05-1.36) |
| Dietrich et al,[35] 2007 | 47/261 | 30/261 | 1.57 (1.02-2.40) |
| Percac-Lima et al,[36] 2009 | 112/409 | 97/814 | 2.30 (1.80-2.93) |
| Percac-Lima et al,[37] 2016 | 109/792 | 57/820 | 1.98 (1.46-2.69) |
| Basch et al,[38] 2015 | 51/199 | 37/185 | 1.28 (0.88-1.86) |
| Basch et al,[39] 2006 | 61/226 | 14/230 | 4.43 (2.56-7.69) |
| Subtotal: $I^2$ = 86.1%, ($P$ < .001) | 1208/3487 | 1201/4939 | 1.62 (1.32-1.98) |
| FBT outreach/distribution possible | | | |
| Green et al,[23] 2013 | 875/1170 | 459/1166 | 1.90 (1.76-2.06) |
| Myers et al,[24] 2013 | 133/312 | 57/317 | 2.37 (1.81-3.10) |
| Lasser et al,[40] 2011 | 79/235 | 46/230 | 1.68 (1.23-2.30) |
| Goldman et al,[20] 2015 | 84/210 | 49/210 | 1.71 (1.28-2.30) |
| Fiscella et al,[30] 2011 | 47/163 | 16/160 | 2.88 (1.71-4.87) |
| Coronado et al,[27] 2011 | 52/168 | 4/165 | 12.77 (4.73-34.50) |
| Gupta et al,[21] 2013 | 766/2072 | 471/3898 | 3.06 (2.76-3.39) |
| Reuland et al,[41] 2017 | 90/133 | 36/132 | 2.48 (1.83-3.36) |
| Subtotal: $I^2$ = 90.7%, ($P$ < .001) | 2126/4463 | 1138/6278 | 2.41 (1.89-3.07) |
| Overall: $I^2$ = 94.3%, ($P$ < .001) | 3334/7950 | 2339/11217 | 2.01 (1.64-2.46) |




The fecal test outreach plots are stratified by mailed or visit-based fecal blood test (FBT) distribution (A) and the navigation plots by FBT or colonoscopy outreach components (B). Principal meta-analyses excluded studies at high risk of bias. Principal analyses also excluded 1 study of patients with recently completed fecal tests[42] and another of patients already referred by their health care professionals for colonoscopy[43] despite lower risks of bias. Including these studies did not change the result (risk ratio [RR], 2.25; 95% CI, 1.82-2.77; $I^2$ = 97%; RR, 1.94; 95% CI, 1.61-2.34; $I^2$ = 95% for FBT outreach and patient navigation, respectively), and they were included in the sensitivity analysis along with the studies at high risk of bias. The difference between CRC completion in navigation interventions with and without either predistribution of FBT or colonoscopy referral or else universal ability of the navigator to distribute or refer for these tests (B) was nonsignificant ($P$ = .09). The difference between mailed and visit-based FBT distribution (A) was nonsignificant ($P$ = .84).

**Patient Reminders** | Patient reminders were compared with usual care in 14 studies (4 with a high risk of bias), excluding interventions in which reminders were built into more extensive interventions (ie, navigation). Reminders were slightly associated with increased screening overall (RR, 1.20; 95% CI, 1.02-1.41; RD, 3%; 95% CI, 0%-5%), with larger associations among interventions using a telephone component[63,64,66,70] (eFigure 38 and eFigure 39 in the Supplement). The benefit of a telephone component was also present in 3 trials directly measuring the benefit of adding a telephone reminder to a mail-

ing (RR, 1.12; 95% CI, 1.00-1.26; RD, 6%; 95% CI, 2%-9%) (eFigure 40 in the Supplement).[23,81,82] A text message reminder to reach Alaska Natives was also positively effective,[83] while mail-based[31,60] or email/internet-based[60,62,84] reminders were less effective. Heterogeneity was reduced in several subgroup analyses (eFigures 41-45 in the Supplement).

**Financial Incentives** | Two publications at low risk of bias,[85,86] with 1 including 2 substudies,[86] examined financial incentives for FBT completion. Among the 8 interventions tested in the 3 studies, only 1 study offering a 1-in-10 chance of receiving $50 upon completion demonstrated a statistically significant increase of FBT returns.[86] Pooling data across trials demonstrated slightly increased screening completion with $5 (RR, 1.09; 95% CI, 1.01 to 1.18; RD, 3%; 95% CI, 0% to 6%) (eFigure 47 in the Supplement) but not $10 incentives (RR, 1.02; 95% CI, 0.85 to 1.23; RD, 1%; 95% CI, −7% to 8%) (eFigure 48 in the Supplement) or with pooling all financial incentive groups (RR, 1.16; 95% CI, 0.95 to 1.42; RD, 6%; 95% CI, −2% to 14%).

**Strategies for Presenting Screening** | Several studies examined the effect of different modes of presenting screening tests on uptake. In a diverse urban clinic network, completion of initial screening increased if patients were offered gFOBT (67.2%) or a choice between gFOBT and colonoscopy (68.8%) compared with those that offered only colonoscopy (58.1%),[87] although this difference was not sustained at 3 years post-intervention.[88] Several trials reported modestly increased uptake of FBT with lesser complexity and number of samples (eFigure 49 and eFigure 50 in the Supplement).[89-91] Mailings of 2-sample FITs were 1.13 (95% CI, 1.02-1.26) times as likely to be returned than a 3-sample gFOBT mailing with dietary restrictions,[89,90] for an RD of 8% (95% CI, 1%-14%).

### Clinician-Directed Interventions

Eighteen studies of 19 clinician-directed interventions were identified: 8 of visit-based interventions and 11 of non-visit-based interventions (1 combined both interventions).[92] Most were cluster RCTs (12 of 18 total and 10 of 11 non-visit based), with the units of randomization usually comprising the practice but occasionally comprising the clinician. All non-visit-based interventions had a component of academic detailing (face-to-face education of clinicians), with the 6 studies at medium or low risk of bias consistently demonstrating greater increases in screening vs usual care (RD, 10%; 95% CI, 3%-17%) (eFigure 51 in the Supplement). All visit-based interventions consisted of a reminder to the clinician via paper or electronic medical record. All of these interventions were beneficial, with a screening increase of 13 percentage points (95% CI, 8%-19%) over usual care (eFigure 52 in the Supplement). Subgroup analyses by insurance status, length of follow-up, type of screening test, and prior screening are shown in eFigures 53-56 in the Supplement.

**Multicomponent Interventions** | Interventions were multicomponent if they addressed either multiple structural barriers to screening access or multiple approaches directed at increasing patient demand, patient access (including structural barriers), or clinician delivery of screening services.[13] Eighteen studies were at high risk of bias.[17,48,55,72-77,93-100] In 52 studies with medium or low risk of bias, interventions with multiple components were associated with greater increases in screening rates compared with usual care than those with single components (RR, 1.92; 95% CI, 1.69-2.19 vs RR, 1.43; 95% CI, 1.19-1.71; RD, 19%; 95% CI, 16%-23% vs RD, 6%; 95% CI, 4%-8%) (eFigures 58-61 in the Supplement), albeit with high statistical and clinical heterogeneity. Compared with usual care, multicomponent interventions increased screening by a mean of 13 percentage points (95% CI, 7%-19%) more than single-component interventions for a number needed to intervene of 7.5 persons exposed to multicomponent interventions per additional person screened. Meta-regression suggested that a screening test outreach component was more essential to the multicomponent effect than navigation, patient reminder, or clinician reminder components (eAppendix 2 and eFigures 67-70 in the Supplement). Additional subgroup analyses are shown in eFigures 63-66 in the Supplement. Nine studies (none at high risk of bias) directly compared multicomponent interventions with less intensive, single-component active interventions, demonstrating a pooled RR of 1.18 (95% CI, 1.09-1.29) and RD of 7% (95% CI, 3%-11%) (eFigure 62 and eFigure 71 in the Supplement).

## KQ2: Colonoscopy After Abnormal Initial Screening

Of 6 studies identified in the search that evaluated completion of colonoscopy after an abnormal FBT, sigmoidoscopy, or radiologic test result, 3 were at high risk of bias, including 2 studies of navigation[101,102] and 1 of automated referral to colonoscopy vs usual clinician-dependent referral.[103] Of the remaining studies, 2 examined navigation[104,105] and 1 examined academic detailing plus audit-feedback intervention for clinicians[106] (eTable 4 in the Supplement). All demonstrated positive effects for completion of follow-up colonoscopy, which were statistically significant for RD (10%; 95% CI, 1%-18% for clinician intervention; 14%; 95% CI, 0.2%-29% for navigation) (eFigure 75 in the Supplement). The pooled RR for navigation was not statistically significant (1.21; 95% CI, 0.92-1.60) (eFigure 74 in the Supplement) because of a relatively large variance of the 2 small contributing studies.[104,105]

## KQ3: Completion of Annual FBT Screenings

Thirteen studies examined longitudinal adherence to FBT screening programs, including trials without usual care comparators. Of these, 2 trials (n = 2658) randomized individuals with previous negative test results to interventions to increase repeat screening.[42,59] Eleven trials (n = 29 341) extended an intervention over at least 2 rounds of screening,[23,29,45,58,88,94,107-111] although 3 reported only completion of any screening over 2 years (rather than repeat screening rates).[29,94,107] Most trials involved mailed FBT and educational materials,[23,29,45,58,59,107-109] usually with a navigation component.[23,29,45,58,108]

Of the 8 trials at medium or low risk of bias, 2 lacked usual care comparators.[88,109] Four of the remaining 6 RCTs compared annually mailed FBTs with varying levels of follow-up reminders and/or navigation to usual care.[23,42,59,108] This strategy was associated with increased screening completion in year

2 (RR, 2.09; 95% CI, 1.91-2.29; RD, 39%; 95% CI, 29%-49%) (eFigure 76 in the Supplement)[23,42] as well as an increased rate of complete adherence to screening guidelines through 3 years (RR, 5.98; 95% CI, 0.16-217; RD, 18%; 95% CI, 14%-21%) (eFigure 77 in the Supplement).[59,108]

### Strength of Evidence Grading

Fecal blood test outreach and navigation had high strength of evidence (**Table**) based on large effect sizes likely representing clinically significant results, despite heterogeneity. Patient reminders, minimizing number of stool samples, and multicomponent vs single-component interventions had moderate strength of evidence because effect sizes were small enough to lose clinical significance if the detected heterogeneity, study limitations, or reporting bias contributed to an inaccurate estimate. Additional funnel plots contributing to assessment of reporting bias are shown in eFigures 13, 24, 46, 57, 72, and 73 in the Supplement. Interventions at low strength of evidence lacked either statistically significant pooled effect sizes or consistent low risk-of-bias studies supporting the estimates.

## Discussion

This review of 73 RCTs found multiple interventions with demonstrated effectiveness for increasing CRC screening uptake in diverse populations within the United States. Navigation and FBT outreach were the most frequently studied and, consequently, have the strongest evidence base. These 2 interventions each increased screening rates by approximately 20 percentage points. This finding suggests that broad implementation of either of these interventions could bring the current national screening rate of 63% close to the national goal of 80%.[7] The net benefit could be even greater if these interventions were combined with clinician reminders or academic detailing or were implemented as part of multicomponent interventions in general. Clinicians, health administrators, and policymakers should consider how to incorporate patient navigation, FBT outreach, and/or clinician prompts into their health care settings and sociocultural contexts, using this review's findings to further support existing tools on implementation of research-tested interventions.[115]

This report is one of few systematic reviews of the topic over the last half-decade,[8-11,116,117] during which CRC prevention has gained increasing national attention and the number of large, high-quality trials has multiplied.[20,22,37,41,43,59,83,85,108] To our knowledge, we are the first to incorporate quantitative analysis in a comprehensive review of all interventions tested in a US setting for increasing CRC screening while examining outcomes at multiple steps across the screening continuum. Other recent publications have focused on specific strategies, populations, or elements of the screening process.[8-11,116,117] These reviews included observational[8,11,116,117] and international[8,116] data, with the accompanying difficulties accounting for confounding, heterogeneity, and generalizability. These limitations notwithstanding, the larger body of studies examined by Selby et al[116] led the authors to the same conclusion that, for follow-up of abnormal FBT results, patient navigation and clinician reminders had the strongest (moderate) evidence but that the issue overall requires further high-quality, standardized studies. Davis et al[117] confirmed the efficacy of mailed FBT outreach, navigation, and patient reminders in rural and low-income US settings while calling for more investigation and reporting of contextual factors and implementation strategies instead of only reporting efficacy. The present review supports these conclusions while quantitatively extending them at the national level.

### Limitations

Our study has limitations. First, we included only US RCTs, and our review is therefore most applicable to the US health care setting. Second, as in all systematic reviews and meta-analyses, publication and other reporting biases may have affected our findings. Third, we found substantial heterogeneity among study effects, which diminishes the precision of our estimates for intervention effect sizes. We suspect that this heterogeneity is largely clinical given the unique nuances of almost every intervention and context. Varied follow-up times and cointerventions were sources of heterogeneity, but $I^2$ was only partially reduced by adjusting for these 3 factors. Nevertheless, for intervention categories in which all point estimates and virtually all lower limits of 95% CIs include clinically important associations (FBT outreach and navigation), we are confident about the intervention's benefit. Fourth, our review did not address harms associated with these interventions nor did it address the complex issue of screening overuse in the elderly or populations with substantial comorbidity. Thus, our findings will be most useful in contexts in which there is evidence of screening underuse.

Finally, although this review establishes the clinical benefit of multiple interventions for increasing CRC screening rates, the economic outcome of their implementation remains to be determined. The value of more resource-intensive interventions, such as navigation, depends on the relative benefit to be gained and the ability to operationalize a streamlined intervention in practice. The intervention costs may ultimately be outweighed by the benefits in life-years gained and treatment costs saved from CRC cases averted, although maintaining the high rates of continued FBT adherence and follow-up necessary to realize the CRC mortality reduction remains a challenge.[88,108,111]

## Conclusions

Robust evidence supports the effectiveness of navigation and FBT outreach—and, to a lesser extent, clinician-directed interventions, patient education, and patient reminders—with increasing CRC screening rates. These interventions can be the foundational tools to meet the national goal of reducing CRC burden and disparities in the United States. Future research should move away from pure efficacy trials and toward studies aimed at understanding how best to implement and scale these strategies and the comparative cost-effectiveness of these interventions from various perspectives (those of society and sponsoring organizations). Future trials should also seek to identify the most effective strategies for retaining individuals in FBT screening programs and follow-up colonoscopy after

Table. Strength of Evidence for Uptake of Any Colorectal Cancer (CRC) Screening Test, by Intervention

| Intervention and Comparison | No. of Studies and Participants | Sources Reference No. | Study Limitations[a] | Supporting Judgment[b] | Results (95% CI)[c] | Strength of Evidence[d] | Rationale |
|---|---|---|---|---|---|---|---|
| Interventions to increase completion of initial screening test | | | | | | | |
| FBT outreach | | | | | | | |
| Stool test outreach vs usual care | 17 RCTs N = 45 836 | 14-16,18-31 | Overall, medium; low ROB, 5 studies; medium ROB, 12 studies; high ROB, 3 studies[17,93,107,d] | Consistent, precise, direct; RB: suspected based on funnel plot, no studies found in ClinicalTrials.gov | Association with screening: large; RR: 2.26 (1.81-2.81); RD: 22% (17%-27%); NNI, 4.5 | High | Clinical and statistical heterogeneity contribute to uncertainty in magnitude of association, but associations are universally positive, with lower limit of the 95% CIs still representing a clinical significant association |
| Patient navigation | | | | | | | |
| Standard navigation vs usual care | 18 RCTs N = 20 457 | 20, 21, 23, 24, 27, 30, 32-41 | Overall, low; low ROB, 9 studies; medium ROB, 9 studies; high ROB, 3 studies[48,95,96,e] | Consistent, precise, direct; RB: not detected | Association with screening: large; RR: 2.01 (1.64-2.46); RD: 18% (13%-23%); NNI 5.6 | High | Substantial clinical and statistical heterogeneity contribute to uncertainty in magnitude of association, but outcomes are universally positive, with lower limit of 95% CIs still representing a clinically significant association size |
| Enhanced navigation vs standard navigation[f] | 4 RCTs N = 16 930 | 32, 46-48 | Overall, high; low ROB, 1 study; medium ROB, 1 study; high ROB, 2 studies | Inconsistent, imprecise, direct; RB: insufficient numbers to assess | Association with screening: null; RR: 1.04 (0.98-1.11); RD: 1% (0%-1%) NNI, 100 | Low (for null association) | Incremental benefit of enhanced patient navigation not significant in any individual study or pooled association; limited evidence (4 studies with substantial ROB) suggests that benefit is negligible |
| Navigation with mailed FBT vs mailed FBT alone | 5 RCTs N = 4449 | 23, 26, 27, 29 | Overall, medium; low ROB, 1 study; medium ROB, 4 studies | Consistent, imprecise, direct; RB: insufficient numbers to assess | Association with screening: small; RR: 1.14 (1.07-1.23); RD: 6% (1%-11%); NNI, 16.7 | Moderate | Only 1 of 5 direct comparison studies individually significant, although all point estimates favorable, with a significant pooled estimate with low heterogeneity; the CIs include values that may not be clinically significant however |
| Patient education | | | | | | | |
| Education (as main component of intervention) vs usual care | 13 RCTs N = 34 357 | 31, 60-71 | Overall, medium; low ROB, 3 studies; medium ROB, 10 studies; high ROB, 6 studies[72-77,e] | Inconsistent, imprecise, direct; RB: suspected | Association with screening: small; RR: education alone, 1.08 (0.97-1.20); combined with other component (eg, ability to request screening, provider reminder), 1.43 (1.16-1.75): RD: education alone, 2% (0%-4%); NNI, 53; combined with other intervention, 8% (2%-15%); NNI, 12 | Low | Pooled association positive but small and nonsignificant (for education interventions alone), with several negative studies; publication bias may be present (Harbord $P = .07$), which may contribute to inflation of association size |
| Patient reminder | | | | | | | |
| Reminder vs usual care | 8 RCTs N = 33 339 | 31, 60, 62-64, 66, 70, 83 | Overall, medium; low ROB, 2 studies; medium ROB, 6 studies; high ROB, 4 studies[75-77,97,e] | Consistent, imprecise, direct; RB: suspected | Association with screening: small; RR: 1.20 (1.02-1.41); RD: 3% (0%-5%); NNI, 33 | Moderate | Majority of studies and pooled effect are positive; however, study limitations and some evidence of publication bias (Harbord $P = .08$) contribute to uncertainty of the already small association |

(continued)

Table. Strength of Evidence for Uptake of Any Colorectal Cancer (CRC) Screening Test, by Intervention (continued)

| Intervention and Comparison | No. of Studies and Participants | Sources Reference No. | Study Limitations[a] | Supporting Judgment[b] | Results (95% CI)[c] | Strength of Evidence[d] | Rationale |
|---|---|---|---|---|---|---|---|
| Financial incentives | | | | | | | |
| Incentives for completing FBT vs usual care | 3 RCTs (2 publications) N = 10 114 | 85, 86 | Overall, low; low ROB, 2 publications | Consistent, imprecise, direct; RB: insufficient numbers to assess | Association with screening: small; RR: $5, 1.09 (1.01 to 1.18); lottery-based incentive, 1.65 (1.30 to 2.10); any financial incentive, 1.16 (0.95 to 1.42); RD: $5, 3% (0% to 6%); NNI, 33; lottery-based: 20% (11% to 29%); NNI, 5.1; any incentive, 6% (−2% to 14%); NNI, 16.7 | Low | 2 High-quality publications demonstrated small and null associations; limited evidence suggests that any association of a financial incentive strategy may be too small to be cost-effective over no incentive |
| Strategies for presenting screening tests | | | | | | | |
| Strategies for stool blood test: 1-card FIT vs 2-card FIT or 3-card gFOBT | 3 RCTs N = 5719 | 89-91 | Overall, low; low ROB, 3 studies | Consistent, precise, direct; RB: insufficient numbers to assess | Association with screening: small; RR: 1- vs 2-card FIT: 1.09 (1.03-1.15); 2-card FIT vs 3-card gFOBT, 1.13 (1.02-1.26); RD: 1- vs 2-card FIT, 4% (1%-7%); NNI, 25; 2-card FIT vs 3-card gFOBT, 8% (1%-14%); NNI, 13 | Moderate | Consistent, clinically and statistically significant positive outcomes from well-conducted studies; however, there were only 2 studies per comparison |
| Clinician-directed interventions | | | | | | | |
| Clinician academic detailing vs usual care | 6 Trials (5 CRTs, 1 RCT) N = 61 250[g] | 11, 32, 38, 92, 112 | Overall: high; low ROB, 1 study; medium ROB, 5 studies; high ROB, 5 studies[94,98-100,107,e] | Consistent, imprecise, direct; RB: not detected | Association with screening: intermediate; RR: NA; RD: any academic detailing, 10% (3%-17%); NNI, 10; academic detailing with audit/feedback, 16% (15%-16%); NNI, 6.7 | Low | Consistent, intermediate-sized association in studies of multiple clinician-directed interventions at low ROB, but these were relatively few (n = 3) among an overall heterogeneous and higher ROB group of studies |
| Clinician reminder vs usual care | 7 Trials (2 CRTs, 5 RCTs) N = 24 368[g] | 22, 26, 28, 30, 69, 82, 92 | Overall, medium; low ROB, 2 studies; medium ROB, 5 studies; high ROB, 1 study[110,e] | Consistent, imprecise, direct; RB: suspected | Association with screening: intermediate; RR: NA; RD: 13% (8%-19%); NNI, 8 | Low | There is a consistent positive association, but few low ROB studies are able to isolate the association of the clinician reminder from the patient-directed components of each trial, with significant heterogeneity as well as the possibility of publication bias |
| Multicomponent interventions | | | | | | | |
| Multicomponent interventions vs single-component interventions | Indirect comparison[h] 48 RCTs 4 CRTs N = 162 570 Direct comparison, 9 RCTs N = 22 343[h] | 48 RCTs: 14-16, 18-43, 51, 52, 54, 56, 57, 60-71, 82, 83 4 CRTs: 92, 112-114 9 RCTs: 23, 24, 26-29, 32, 38, 82 | Indirect comparison[h]: overall, medium; low ROB, 21 studies; medium ROB, 31 studies; high ROB, 18 studies[17,48,55,72-77,93-100,107,e] Direct comparison[h]: overall, low; low ROB, 3 studies; medium ROB, 6 studies | Indirect comparison; consistent, imprecise, direct; RB: suspected; direct comparison:, consistent; imprecise; RB: not detected | Association with screening: intermediate; RR: direct comparison, 1.18 (1.09-1.29); indirect comparison, 1.37 (1.04-1.75); RD: direct comparison, 7% (3%-11%); NNI, 13.5; indirect comparison, 13% (7%-19%); NNI, 7.5 | Moderate | Consistent, clinically and statistically significant increased association of multicomponent over single-component interventions; direct comparison is most reliable but with 95% CIs that include values that may not be clinically significant; indirect comparison limited by (unavoidable) extreme statistical and clinical heterogeneity of interventions and study designs as well as possible publication bias |

(continued)

Table. Strength of Evidence for Uptake of Any Colorectal Cancer (CRC) Screening Test, by Intervention (continued)

| Intervention and Comparison | No. of Studies and Participants | Sources Reference No. | Study Limitations[a] | Supporting Judgment[b] | Results (95% CI)[c] | Strength of Evidence[d] | Rationale |
|---|---|---|---|---|---|---|---|
| Interventions to increase completion of CRC screening after initial test completion | | | | | | | |
| Follow-up of abnormal initial test results | | | | | | | |
| Patient navigation vs usual care | 2 RCTs N = 375 | 104, 105 | Overall, medium; medium ROB: 2 studies (other issues: first included unspecified No. of non-screening [ie, symptomatic] tests[105] second was underpowered[104]); high ROB: 2 studies[101,102,e] | Consistent, imprecise, direct; RB: insufficient numbers to assess | Association with screening: intermediate; RR: follow-up colonoscopy, 1.21 (0.92-1.60); RD: follow-up colonoscopy, 14% (0%-29%); NNI, 7.1 | Low | Pooled effect is only borderline statistically significant based on only 2 studies, with significant limitations related to the heterogeneity of inclusion criteria |
| Clinician-directed interventions vs usual care | 1 CRT N = 554 (patients analyzed) | 106 | Overall, medium; medium ROB: 1 study; high ROB: 1 study[103,e] | Consistency unknown, imprecise, direct; RB: insufficient numbers to assess | Association with screening: small; RR: complete diagnostic evaluation after academic detailing with audit feedback, 1.18 (1.02-1.36); RD: complete diagnostic evaluation after academic detailing and audit with feedback, 10% (1%-18%); NNI, 11 | Low | Single study at medium risk of bias, with small but statistically significant association |
| Longitudinal adherence to annual FBT | | | | | | | |
| Continued mailed FBT ± step-up to navigation vs usual care | 3 Cohorts (5 publications with 4 episodes of random-ization) N = 5285 | 19, 23, 42, 59, 108 | Overall, low; low ROB: 3 studies | Consistent, imprecise, direct; RB: insufficient numbers to assess | Association with screening: large; RR: 2 consecutive years: 2.09 (1.91-2.29); 3 of 3 y: 6.0 (0.16-2.17); RD: 2 consecutive years: 39% (29%-49%); NNI, 2.6; 3 of 3 y: 18% (14%-21%); NNI, 5.6 | Moderate | Consistent, clinically and statistically significant positive association from a few high-quality studies; heterogeneous baseline characteristics prohibit precise pooled estimates of associations |

Abbreviations: CRT, cluster-randomized trial; FBT, fecal blood test; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; NA, not applicable; NNI, number needed to intervene (for 1 additional person to complete screening): RB, reporting bias; RCT, patient-level randomized clinical trial; RD, risk difference; ROB, risk of bias; RR, risk ratio; SOE, strength of evidence.

[a] Also referred to as ROB, rated as low, medium, or high.

[b] Considers the 4 domains of consistency, precision, directness, and RB; further detailed in the eMethods in the Supplement.

[c] Association rated as large, intermediate, small, or null.

[d] High indicates confidence such that an additional study would be unlikely to affect the conclusion, moderate indicates that the conclusions are mostly stable but the body of evidence could be stronger, and low indicates limited confidence in the association and the need for more or better evidence.

[e] High ROB studies were not considered in assessments of strength of evidence unless they formed the majority of included studies, in which case the strength of evidence was low. Inclusion of the high ROB studies did not appreciably change the association in all comparisons except for the clinician-directed interventions, in which the differences in percentage screened diminished from 10% to 7% and 13% to 10% in non–visit-based and visit-based clinician-directed interventions, respectively. Each of these outcomes remained statistically significant. The 2 high ROB studies involving follow-up of abnormal initial test results did not provide CRC-specific estimates to evaluate whether or how the 2 studies would affect the pooled estimate.

[f] These interventions were enhanced by culturally[46,48] or individually tailoring the interventions, for instance, with patient-specific materials[32] or input from the patient's physician.[47]

[g] Total No. is sum only of participants analyzed, which are subsets of all the individuals experiencing an intervention in some CRTs.

[h] The indirect comparison compares the association vs usual care of multicomponent and single-component interventions derived from separate studies. The direct comparison compares the association of multicomponent vs single-component interventions from the same study. Risk ratios and differences from indirect comparisons are estimated with metaregression.

abnormal FBT results. Committing appropriate resources to these research priorities as well as the evidence-based practices highlighted in this review will enable us to realize one of the major public health goals of the past decade.

## ARTICLE INFORMATION

**Accepted for Publication:** July 19, 2018.

**Published Online:** October 15, 2018. doi:10.1001/jamainternmed.2018.4637

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**Conflict of Interest Disclosures:** Dr Wheeler received unrelated grant funding to her institution from Pfizer as PI of a Pfizer/National Comprehensive Cancer Network Independent Grant for Learning and Change. No other disclosures were reported.

**Funding/Support:** Major funding for the study was provided by the University of North Carolina Lineberger Comprehensive Cancer Center through its University Cancer Research Fund (Drs Brenner, Wheeler, Malo, and Reuland, Mr Coker-Schwimmer, and Ms Cubillos). Dr Reuland was also supported by American Cancer Society grant RSG-13-165-01-CPPB. In addition, the investigators received support from National Institutes of Health grants T32 DK007634 (Dr Dougherty) and KL2TR001109 (Dr Crockett), and from the Centers for Disease Control and Prevention– and National Cancer Institute (NCI)–supported Cancer Prevention and Control Research Network grant 3 U48 DP005017-01S8 (Drs Brenner, Wheeler, and Reuland). This work was supported in part by the University of North Carolina at Chapel Hill's Connected Health Applications & Interventions Core through NCI grant P30-CA16086 to the Lineberger Comprehensive Cancer Center.

**Role of the Funder/Sponsor:** The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** The review's literature searches were conducted by Christiane Voisin, MSLS (librarian, Sheps Center for Health Services Research, University of North Carolina at Chapel Hill). Charli Randolph, MCS, LC (research assistant, Sheps Center for Health Services Research, University of North Carolina at Chapel Hill), Shynah James, MPH (research assistant, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill), Oluoma Chukwu, MHA, and Samuel Lee (graduate students Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill), Adrian Compean Garcia (research assistant, Department of Medicine, University of North Carolina at Chapel Hill), and Jewels Rhode, MPH (research associate, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill), provided assistance extracting data and retrieving publications. Ms James, Mss Rhodes and Chukwu also assisted with review of publications for inclusion. Dan Jonas, MD, MPH (associate professor, Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill), provided multiple consultations throughout the course of the review and reviewed an earlier draft of the manuscript. Mss Voisin and Chukwu, Mr Lee, and Dr Jonas did not receive compensation for their contributions to this work; the other contributors did.

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Invited Commentary

# Colorectal Cancer Control
## Where Have We Been and Where Should We Go Next?

Beverly B. Green, MD, MPH

**Colorectal cancer (CRC)** is the second leading cause of cancer death in the United States, but it does not have to be. Screening prevents CRC by finding precancerous lesions so they can be removed before they become cancerous. Screening can also detect CRC early and, when CRC is localized, 5-year survival is over 90%, with many patients cured. Five-year survival for late-stage CRC, however, is less than 20%.[1]

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Colorectal cancer screening rates have been steadily increasing in the United States, yet only 62% of age-eligible adults are up-to-date for CRC screening.[2] Rates are lower among low-income (47%), uninsured (25%), African American (59%), Asian (52%), Native American (48%), and Hispanic (47%) populations.[2] These rates fall short of the 70% and 80% targets for Healthy People 2020 and National Colorectal Cancer Round Table. Net health care costs in the first year after CRC diagnosis range from $36 000 for stage I to $74 000 for stage IV disease.[3] Colorectal cancer survivors also experience high out-of-pocket costs and lost productivity.[4] In short, optimal and equitable CRC screening would improve health outcomes and produce cost-savings.[5]

In pursuit of optimal and equitable CRC control, multiple federal agencies, advocacy groups, and initiatives (eg, from the National Cancer Institute, Centers for Disease Control and Prevention, American Cancer Society) have sponsored numerous trials