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Selection of patients for mailed FIT colorectal cancer screening outreach programs: A Systematic Review

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Keywords:	colon cancer, patient selection criteria, quality indicators, exclusionary factors organized screening
Abstract:	Objectives:Digital health care offers an opportunity to scale and personalize cancer screening programs, such as mailed outreach for CRC screening. However, studies that describe the patient selection strategy and process for CRC screening are limited. Our objective was to evaluate implementation strategies for selecting patients for CRC screening programs in large healthcare systems. Methods:We conducted a systematic review of 30 studies along with key informant surveys and interviews to describe programmatic implementation strategies for selecting patients for colorectal cancer screening. PubMed and Embase were searched since inception through December 2018, and hand searches were performed of the retrieved reference lists. No language exclusions were applied. Results:Common criteria for outreach exclusion included: being up-to-date with routine CRC screening (n=22), comorbidities (n=20), and personal history (n=22) or family history of cancer (n=9). Key informant surveys and interviews were performed (n=28) to understand data sources and practices for patient outreach selection and found that 13 studies leveraged EMR, 10 studies leveraged a population registry (national, municipal, community, health), 4 studies required patient opt-in, and 1 study required PCP referral. Broad ranges in FIT completion were observed in community clinic (n=8, 31.0-59.6%), integrated health system (n=5, 21.2-82.7%), and national regional CRC screening programs (n=17, 23.0-64.7%). Of technical codes, 6 studies used ICD, CPT, HCPCS and LOINC, and 4 studies required patient self-reporting

	from a questionnaire to participate. Conclusions:In conclusion, this systematic review provides health systems the diverse outreach practices and technical tools to support efforts to automate patient selection for CRC screening outreach.

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TITLE: Selection of patients for mailed FIT colorectal cancer screening outreach programs: A Systematic Review

RUNNING HEAD: Patient selection for FIT

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ABBREVIATIONS:

CRC - colorectal cancer

FIT – fecal immunochemical test

AUTHOR CONTRIBUTIONS:

Andrew Wang – drafting of the manuscript; acquisition of data; interview outreach; analysis and interpretation of data; and critical revision of the manuscript.

Briton Lee – acquisition of data.

Shreya Patel – acquisition of data; interview outreach; analysis and interpretation of data; and critical revision of the manuscript.

Evans Whitaker – technical, or material support; study concept and design (search terms).

Rachel B. Issaka – study concept and design; critical revision of the manuscript.

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Ma Somsouk – principal investigator; study concept and design; interview outreach; analysis and interpretation of data; critical revision of the manuscript; and study supervisor.

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ABSTRACT

Objectives: Digital health care offers an opportunity to scale and personalize cancer screening programs, such as mailed outreach for CRC screening. However, studies that describe the patient selection strategy and process for CRC screening are limited. Our objective was to evaluate implementation strategies for selecting patients for CRC screening programs in large healthcare systems.

Methods: We conducted a systematic review of 30 studies along with key informant surveys and interviews to describe programmatic implementation strategies for selecting patients for colorectal cancer screening. PubMed and Embase were searched since inception through December 2018, and hand searches were performed of the retrieved reference lists. No language exclusions were applied.

Results: Common criteria for outreach exclusion included: being up-to-date with routine CRC screening (n=22), comorbidities (n=20), and personal history (n=22) or family history of cancer (n=9). Key informant surveys and interviews were performed (n=28) to understand data sources and practices for patient outreach selection and found that 13 studies leveraged EMR, 10 studies leveraged a population registry (national, municipal, community, health), 4 studies required patient opt-in, and 1 study required PCP referral. Broad ranges in FIT completion were observed in community clinic (n=8, 31.0-59.6%), integrated

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Conclusions: In conclusion, this systematic review provides health systems the diverse outreach practices and technical tools to support efforts to automate patient selection for CRC screening outreach.

KEYWORDS: colon cancer, patient selection criteria, quality indicators, exclusionary factors organized screening

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States[1]. Despite the increase in CRC screening programs around the world and the evidence that fecal immunochemical test (FIT) is a highly effective and commonly-used screening method[2], population level CRC screening can still be greatly improved through increased efforts in population reach, personalization of testing, and integration of interventional research outreach [3,4].

With concerns over screening rates[5] and the digitization of health records leading to accountable precision care[6], there remains opportunities where large health systems that have not yet established a CRC screening program, and as a checklist for those CRC screening is already established, to assess the comprehensiveness of their system by responding to standardized quality metrics to improve strategies for CRC screening[7].

Several clinical trials, systematic reviews, and meta-analyses have identified organized outreach and FIT kit mailing as the most effective strategy[8–16]. However, there is limited data on how patients are selected, including criteria and technical procedural codes used[17,18]. A systematic review evaluating the patient selection process with key informant interviews may help improve organized CRC screening.

Our objective was to evaluate implementation strategies for selecting patients for CRC screening programs in large healthcare systems. To examine this issue, we performed a systematic review and key informant interviews to describe the factors used to exclude patients from population-based CRC screening program.

METHODS

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

Data Source and Literature Searches

We developed our search strategy with a medical librarian (EW) using keywords for immunochemical based fecal tests and cancer screening (Supp. Table 1). We searched PudMed and Embase until December, 31, 2018. This systematic review was conducted according to the methods described in the Cochrane Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standard. A review protocol was registered a priori through PROSPERO, an international database of registered prospective systematic reviews (CRD42018114370).

Study Eligibility and Selection

We sought to evaluate studies with details on how patients were selected for mailed outreach CRC screening programs in community-based healthcare systems. The reviewers (AW, BL) appraised the pertinent studies to determine eligibility and studies were included if they: (1) used mailed FIT or iFOBT, (2) reported > 5000 patients (large CRC screening program). Included articles were grouped by the corresponding authors affiliate

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health organization. The most recent article to date of each institute was selected for descriptive analysis. We included randomized controlled trials and non-randomized controlled trials. Non-English language articles were translated through the publisher's website or Google translator. We excluded studies using gFOBT, out-of-scope review articles, population surveys, simulation model and conference abstracts without accompanying full manuscripts.

Data Abstraction

Our search strategy is shown in Supplemental Table 1. Titles and abstracts were evaluated for initial screening. Full text articles were assessed for eligibility. Eligible articles were data abstracted for study inclusion. The reviewers (AW, BL) independently abstracted data from the included studies into a Microsoft Excel Spreadsheet (version 2016; Microsoft, Redmond, WA, USA). Information was abstracted on article information, country, primary health organization to corresponding author, program type, number of study patients, FIT brand, intervention type, patient identification sources, patient exclusion criteria's, FIT completion and colonoscopy follow-up after positive FIT completion rate. Any disagreements in eligibility and abstraction were resolved through discussion.

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Data Synthesis

Mailed FIT articles were summarized according to study design, program type (national or regional involvement, community clinic local involvement, integrated health system integrated managed care consortium involvement), country, number of participants (+ = 5000-9999, ++ = 10000-50000, +++ = >50001), type of FIT, outreach intervention type (routine screening, enhanced instructions, enhanced monitoring, enhanced education, added reminder communication), and source of patient selection. Standard mailed FIT kits included notification to participate, brief education pamphlet, FIT device, and manufacturer FIT instructions. Routine screening was defined as annual or biennial testing depending on the accepted practice standards in that country. Enhanced instruction was defined as tutorials, pictorials, low-literacy wordings. Enhanced monitoring was defined as additional navigators and tracking systems for patients. Enhanced education was defined as low-literacy wordings, and psychosocial and racial ethnic modifications. Added reminder communication was defined as the addition of mail, email, text message, or phone call reminders to patients to complete screening. Mailed FIT studies with additional interventional components did not lead to exclusion of the study.

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When available, patient exclusion criteria were abstracted from each article. Patient selection criteria were categorized into the following categories: comorbidities, personal or family history of CRC related conditions, or uncategorized. Comorbidities included CRC related symptoms (blood in stool, bowel obstructions), inflammatory bowel disease (IBD), institutionalization, and terminal diseases. Up to date with routine CRC screening include colonoscopy in the prior 5-10 years, sigmoidoscopy in the prior 5 years, FIT rest in prior year, positive FIT, and colectomy. Personal or family history of related CRC conditions include familial adenomatous polyposis, hereditary nonpolyposis cancer, and other cancers.

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Key Informant Surveys and Interviews

Key informant surveys and interviews were performed by emailing corresponding authors from articles. The survey included questions on program type, location, patient identification source, patient inclusion and exclusion criteria, and technical selection codes (if any). A standard e-mail template was followed, which invited corresponding authors to participate. Authors had two weeks to respond to inquiry before a final reminder email was sent.

Analytical Plan

A mixed methods approach was taken to gather study data. The review focused on summarizing study characteristics, patient identification and selection, FIT completion and CRC follow-up participation, and key informant surveys from articles with patient exclusions. Characteristics, the selection process, and outreach surveys were described as counts and proportions. Participation were described in ranges. Technical procedure codes (International Classification of Disease (ICD), Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), Logical Observation Identifiers Names and Codes (LOINC)) were summarized by patient exclusion categories. Due to the high risk of bias over differences in study characteristics, a meta-analysis was not performed. Our analysis approach was to focus on implementation strategies in mailed FIT outreach that accounted for individual patients, and contextualizing the risks (exclusion criteria) of the screening process. Any disagreements synthesis and analysis were resolved through discussion.

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Compliance with Ethical Standards

All authors had access to the study data and reviewed and approved the final manuscript. The authors have no conflicts of interest to declare.

RESULTS

Summary of Literature Search and Study Selection

After removal of duplicates records, the search identified 2081 articles, of which 434 full-text articles were evaluated (Figure 1). A total of 72 reports remained after stand-alone abstracts, commentaries or guideline articles, duplicates were excluded. Articles that did not distribute FIT by mail, were not relevant, were simulation models, systematic or meta-analysis reviews, or proposal articles were also excluded. We included the most recent article from centers with multiple publications on the same cohort (Supp. Table 3). After limiting articles to those with more than 5000 participants, 43 articles remained. Thirty articles contained documentation of patient exclusion criteria (Table 1) and 13 articles did not (Supp. Table 2). Of the articles with no patient exclusion, 11 studies were from national and regional programs, and 8 studies used population registries as the source of patient outreach.

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Characteristics of Mailed FIT Programs with Patient Exclusion

Of the 30 studies that contained documentation describing patient exclusion (Table 1), 7 studies were randomized control trials and 23 studies were non-randomized observational studies. Fourteen countries were represented and the majority of studies were from the US (n = 8), France (n = 4), Spain (n = 4), and Italy (n = 3). Some countries despite having well-established CRC programs were not included if selection criteria was not defined (Supp.

Table 2, 3). Other excluded studies did not meet study inclusion criteria (Figure 1) or had no published reports.

In the subset of large CRC screening programs that utilized a mailed FIT approach with patient exclusions, 17 studies were at the national or regional level, 8 studies at the community clinic, and 5 studies at the integrated health organization level. The number of patients in the screening program ranged in size: 5000 to 9999 (n = 9), 10000 to 49999 (n = 9), 50000+ patients (n = 12). The cohort used a variety of FIT kits: OC-Sensor (n = 12), OC-Auto (n = 8), OC-Hemodial (n = 1), or not reported (n = 11).

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Study outreach interventions were diverse. Integrated health organizations and community clinics were more likely to incorporate other interventions in addition to mailed FIT outreach (Table 1). Among community clinics (n = 8), mailed FIT interventions varied with each report using one or a combination of the following: no additional intervention (n = 4), reminder (n =5), enhanced monitoring (n = 1), enhanced education (n = 1), enhanced instructions (n = 3). Among integrated health organizations (n = 5), interventions included one or a combination of the following: routine (n = 5), reminder (n =4), enhanced monitoring (n = 2). Finally, among national or regional

CRC programs (n = 17), interventions included: routine (n = 16), reminder (n = 5), enhanced monitoring (n = 1), enhanced education (n = 2).

Patient Identification and Selection in Programs with Patient Exclusion

Community based programs (n = 8) used various methods for patient outreach and selection (Table 1). Four studies removed patients up-to-date with CRC screening, 6 studies utilized a personal cancer history, 5 studies incorporated patient comorbidities, and 1 study used family history of cancer as reasons to exclude individuals from receiving FIT mailing. Generally, with a smaller number of participants (<1000, n = 5), community-based programs (n = 4) often relied on their own electronic medical care records (EMR) or individual PCP/GP selection (n = 2) as the source for patient identification to then applied subsequent exclusionary criteria.

Integrated health systems (n = 5) used similar methods for patient outreach and selection (Table 1). Three studies removed patients up-to-date with CRC screening, 5 studies utilized a personal cancer history, 3 studies incorporated patient comorbidities, and 1 study used family history of cancer reasons to exclude individuals from receiving FIT mailing. Integrated

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health organizations often had large patient participation (>50000, n = 4) and a study reported relying on internally linked shared EMR as the source for patient identification across the consortium of health clinics in the area.

National or regional programs (n = 17) used similar methods for patient outreach and selection (Table 1). Twelve studies removed patients up-to-date with CRC screening, 11 studies utilized a personal cancer history, 12 studies incorporated patient comorbidities, and 7 studies used family history of cancer as reasons to exclude individuals from receiving FIT mailing. The vast majority of these programs had a higher number of patient participation (>10000, n = 14). While national or regional programs had 3 studies that utilized population registries and 4 studies that utilized local clinics for patient selection, patients were often sent informative leaflets (n = 4) asking to "self-opt out" if they met exclusionary criteria. After inclusion, few programs (n = 2) verified a patient's eligibility through EMR or surveys.

Participation in Programs with Patient Exclusion

From the 30 studies included, broad ranges in FIT completion and colonoscopy follow-up were observed. National and regional programs were more likely to have higher median participation

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rates (Table 1) and reported FIT completion also varied. Completion of mailed FIT in community based programs (n = 7) ranged from 31.0-59.6%, integrated health systems (n = 3) ranged from 21.2-82.7%, and national or regional programs (n = 16) ranged from 23.0-64.7%. In studies with reported colonoscopy follow-up after abnormal FIT: community based programs (n = 5, 70.0-94.0%), integrated health systems (n = 1, 50.8%), and national or regional programs (n = 5, 65.7-97.0%).

Key Informant Surveys and Interviews

Of the 28 studies that responded to survey and interview inquiry (Table 2, Supp. Table 4), responses were from individuals representing national (n = 11) and integrated health systems (n = 17). Corresponding authors identified patients for FIT outreach based on data obtained from the following sources: Electronic medical records (n = 13), population registries (n = 10), patient opt-in (n = 4), and PCP referral (n = 1). In total, 6 studies reported utilizing technical codes (all integrated health systems), 7 studies required self-reporting from a questionnaire to participate (n = 3 national, n = 4 integrated health systems), and 15 studies did not further elaborate on the selection process.

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Common technical codes used to identify patients for outreach include (Table 2): colonoscopy (CPT 44388-44394, 44397, 45355, 45378-45387, 45391, 45392; ICD9 45.22-45.25, 45.42, 45.43; HCPCS G0105, G012), CT colonoscopy (CPT 74261-74263), sigmoidoscopy (CPT 45330-45335, 45337-45342, 45345; ICD9 45.24, 45.42; HCPCS G0104), stool blood (CPT 82270, 82274; ICD9 76.51, 578.xx, V76.51; HCPCS G0107, G0328, G0394; LOINC 2335-8, 12503-9, 12504-7, 14563-1, 14564-9, 14565-6, 27396-1, 27401-9, 27925-5, 27925-7, 29771-3, 50196-5, 56490-6, 56491-4, 57905-2, 58453-2), barium enema (CPT 74270, 74280; HCPCS G0106, G0120, G0122), iron deficiency anemia (ICD9 280.9), chronic diarrhea (ICD9 787.91), total colectomy (CPT 44150-44153, 44155-44156, 44210-44212; ICD9 45.8), history of inflammatory bowel disease (ICD9 211.3, 211.4, 230.3, 230.4, V12.72), history of colorectal polyps (ICD9 153.0-154.8), and history of GI cancer (ICD9 159, 197.5, 197.8, 211.9, 230.3, 230.4, 230.7, 235.2, 239.0, V10.05).

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DISCUSSION

While CRC screening rates have improved globally, they still remain suboptimal and the COVID-19 pandemic has now stalled in-person screening efforts. This review describing population registries and electronic records offers an opportunity for health systems to transform from opportunistic screening to population level screening, which has the potential to reduce CRC incidence and mortality. As health records become increasingly digitized, using algorithmic metrics to identify patients for colorectal cancer screening is an important first step to improving precision population health[6,7]. To our knowledge, our systematic review is the first to describe the methods by which screening programs identify and select patients for mailed FIT outreach programs. We show that while national or regional CRC screening programs typically rely on population registries for patient self-reported exclusion or direct general practitioner or primary

care provider (GP/PCP) recruitment, community clinic and integrated health organization use internal electronic health records to select patients for screening. In addition, many large CRC screening programs around the world that use cancer history and comorbidities as exclusionary criteria.

Organized screening programs in large health-care systems has been shown to increase participation, improve patient handling of FIT, reduce disparities, reduce potential harms of screening, and reduce overall care costs[19–21]. And multiple studies have demonstrated the effectiveness and acceptable cost of mailed FIT outreach[8–16,19].In the United States, population health entities within integrated health systems have arisen due to the adoption of electronic health records. To date, they often serve to report on the quality of care in order to obtain payment incentives (references). However, through the data infrastructure, population health entities should also transition to provide clinical services that improve the health of populations. In this review, we also identified multiple publications from Kaiser Permanente in different regions of the United States; they have previously described a centrally organized CRC screening model that includes mailed FIT kits [11,12]. As digitization of health and centrally managed mailed FIT programs become more widespread, these population health entities can enhance overall health care maintenance and cancer prevention. Therefore, a concerted effort should be placed on improving tailored prevention with the goal of refining patient selection criteria for a more personalized and cost-effective outcome[20]. Specifically, to ensure trust between health systems, providers, and patients, organized outreach should offer screening to patients whose provider would have also intended to screen. In this review, while we identified 30 articles and ascertained each of their patient eligibilities with variable cohort definitions, the

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implementation strategies used for mailed FIT outreach were lacking. For example, while we suspect most studies used algorithmic code to identify patients for CRC screening, only 1 study specified ICD/common procedural codes.

While implemented CRC screening practices have historically limited patients by age, risk, and lack of symtpoms[2], this study shows that health organizations often implement different methods for identifying patient comorbidities or history of cancer related conditions, leading to inconsistent CRC screening participation[21]. Moreover, the implementation of screening is markedly different across regions and countries. While not covered in this review, healthcare systems can proactively incorporate data elements used for Healthcare Effectiveness Data and Information Set (HEDIS) performance measures value sets for CRC screening to develop population registries for targeted screening. As an example, the most recent HEDIS measure and technical resource provides guidance on excluding patients from the CRC report when there is use of palliative care or the medication donepezil for dementia. This review summarizes the patient selection criteria and the technical codes that exist in different health care settings, to inform health systems considering implementing mailed FIT outreach.

There are several limitations to this study. First, few studies report patient selection criteria or systems used to identify patients for outreach. Different health organizations may have had internal practices; however, the specified metrics of patient identification and acquisition used in varying clinic practices were not articulated in the manuscript or through contact of the authors. Second, there is a potential for section bias as we only described a subgroup of studies which utilized mailed FIT and published their data. We are aware that multiple national programs exist

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but published data, along with the specified processes around selection of patients for screening, were not publicly available. We may have also missed other patient selection processes because we excluded smaller studies (<5000 participants) from our review. We did so because anecdotally, these studies were more likely to contain patient selection processes that were not economical (e.g., consent of patients, chart review, permission from provider). Third, some CRC programs have begun transitioning from ICD9 to ICD10, and while beyond the scope of this review, the sensitivity and specificity of these code in selecting patients may vary. Finally, we cannot directly compare or perform a meta-analysis on screening outcomes due to heterogeneity in intervention characteristics (e.g., invitations, reminders) and patient selection criteria (e.g., self-report, referrals, population registry, integrated health systems).

In conclusion, our systematic review with key informant interviews describes the patient selection criteria and implementation strategies of 30 studies. We found large CRC screening programs may use heterogenous methods for excluding patients for FIT outreach. This systematic review sought to provide health systems the technical tools to support efforts to automate patient selection for CRC screening outreach. These efforts are particularly timely given the COVID-19 pandemic, which has increased concern for in-person visits and has accelerated the adoption of telehealth and organized outreach services. Optimizing the patient identification process and selection criteria can strengthen preventive care services, improve patient outcomes, and reduce cost.

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DECLARATION OF CONFLICTING INTERESTS

The Authors declares that there is no conflict of interest.

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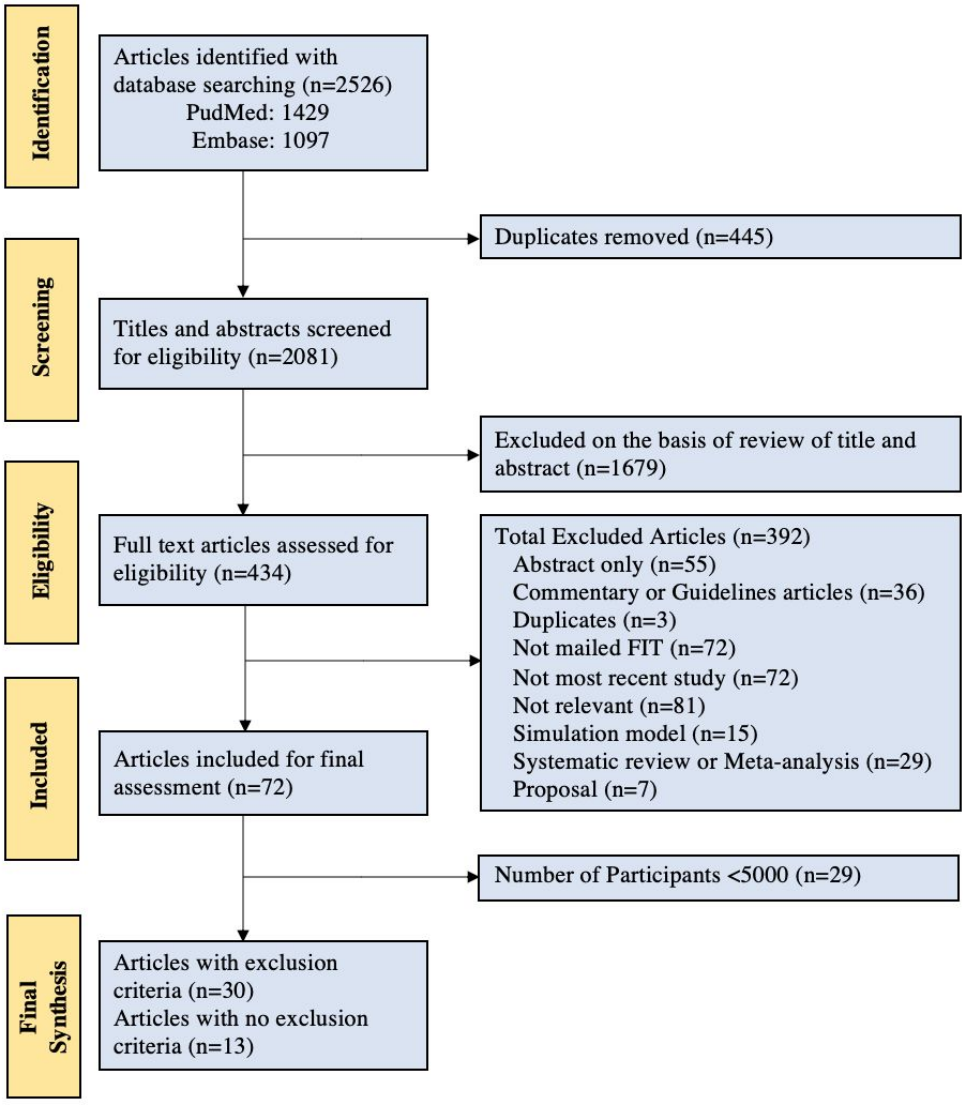
FIGURES

Figure 1. Flow chart of study selection to evaluate implementation strategies that select patients for colorectal cancer screening program is community-based healthcare systems.



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TABLES

Table 1: Characteristics of the Included Studies Performing Mailed FIT Outreach

Represented Study, Year	Study Design	Country	Primary Health Organization	Program Type	Number of Participants	Type of FIT	Intervention Type	Patient Identification Sources	Up-to-Date	Comorbidities	Personal Cancer History	Family Cancer History	Other	FIT Completion	Colonoscopy Follow-up
650 Duncan et al.[22]	Non-Randomized	Australia	School of Psychology, The University of Adelaide	National/ Regional	+	OC-Sensor	Routine + Enhanced Education + Reminder	Clinic		*X*	*X*	*X*		45.8	n/a
898 Van Roosbroeck et al.[23]	Non-Randomized	Belgium	Research Group Medical Sociology and Health Policy, Department of Epidemiology and Social Medicine, University of Antwerp	Community Clinic	++	OC-Auto	Routine + Enhanced Education + Reminder	Clinic	*X*	*X*	*X*			42.1	72.9
322 Telford et al.[24]	Non-Randomized	Canada	Department of Medicine (Telford) and School of Population and Public Health (Coldman), University of British Columbia	Community Clinic	++	n/a	Routine	n/a	*X*	*X*	*X*			86.0	88.6
236 Larsen et al.[25]	Non-Randomized	Denmark	Department of Public Health Program	National/ Regional	+++	n/a	Routine	n/a	*X*	*X*	*X*			67.2	n/a

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			mes, Randers Regional Hospital												
126 Sportes et al.[26]	Non-Randomized	France	Gastroenterology Unit, Departmental Committee of Cancers-Bondy	National/ Regional	+++	OC-Sensor	Routine	Population registry		***X***				30.0	n/a
131 Pellant et al.[27]	Non-Randomized	France	Cochin teaching Hospital, Paris Descartes University	National/ Regional	+++	OC-Sensor	Routine	Population registry	***X***	***X***				23.0	70.5
34 Koivogui et al.[28]	Non-Randomized	France	Comité Départemental Des Cancers	National/ Regional	+++	OC-Sensor	Routine	n/a	***X***	***X***	***X***	***X***		28.4	65.7
213 Rat et al.[29]	Randomized	France	Department of General Practice, Faculty of Medicine, Nantes	National/ Regional	++	n/a	Routine + Enhanced Education + Reminder	n/a	***X***	***X***	***X***	***X***		24.8	n/a
650 McNamara et al.[30]	Non-Randomized	Ireland	Trinity College Dublin	Community Clinic	+	OC-Sensor	Routine	Clinic	***X***					51.0	87
347 Clarke et al.[31]	Randomized	Ireland	Department of Epidemiology and Public Health, University College Cork	Community Clinic	+	n/a	Enhanced Monitoring + Reminder	n/a			***X***			59.6	n/a
537 Rossi[32]	Non-Randomized	Italy	Inter-institutional Epidemiology Unit,	National/ Regional	+++	n/a	Routine	n/a			***X***			64.0	91.7

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			AUSL Reggio Emilia												
1137 Grazzini et al.[33]	Non-Randomized	Italy	ISPO Cancer Prevention and Research Institute Florence	National/ Regional	++	OC-Hemodial	Routine	Clinic	***X***	***X***	***X***	***X***		52.3	n/a
610 Senore et al.[34]	Randomized	Italy	AOU Città della Salute e della Scienza	National/ Regional	++	n/a	Enhanced Monitoring + Reminder	n/a	***X***	***X***	***X***	***X***		46.1	n/a
594 Santare et al.[35]	Randomized	Latvia	Institute of Mathematics and Computer Science, University of Latvia	National/ Regional	++	OC-Sensor	Routine	n/a			***X***			47.4	n/a
326 Van Der Vlugt et al.[36]	Non-Randomized	Netherlands	Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam	National/ Regional	++	OC-Sensor	Routine + Reminder	n/a	***X***	***X***				63.0	n/a
237 Knudsen et al.[37]	Non-Randomized	Norway	Department of Bowel cancer screening, Cancer Registry of Norway	National/ Regional	+	n/a	Routine	n/a	***X***	***X***	***X***			56.7	n/a
209 Vanacloc	Non-Randomi	Spain	Cancer and	National/ Regional	+++	n/a	Routine + Reminder	Population registry	***X***				***X***	48.7	n/a

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ha-espi et al.[38]	zed		Public Health Area-FISABIO												
225 Guirigu et al.[39]	Non-Randomized	Spain	Unitat de Suport a la Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol	National/ Regional	++	n/a	Routine	n/a	X	X		X		48.0	n/a
59 Binefa et al.[40]	Non-Randomized	Spain	Cancer Prevention and Control Programme, Instituto Catalán de Oncología, Hospitalet de Llobregat	Community Clinic	+++	OC-Sensor	Routine	n/a	X	X	X	X		n/a	94.0
921 Quintero et al.[41]	Randomized	Spain	Department of Gastroenterology, Hospital Universitario de Canarias,	National/ Regional	++	OC-Sensor	Routine	Clinic	X	X	X	X		34.2	86.4
459 Chen et al.[42]	Non-Randomized	Taiwan	Digestive Disease Center, Show-Chwan Memorial Hospital	National/ Regional	+++	OC-Sensor	Routine	n/a			X			n/a	n/a
143 Vleugels	Non-Randomi	UK	Cancer Screening	National/ Regional	+	OC-Auto	Routine	n/a	X					64.7	97.0

Proof

et al.[43]	zed		and Prevention Research Group, Department of Surgery and Cancer, Imperial College London												
29 Kemper et al.[44]	Non-Randomized	USA	Center for Health Research, Kaiser Permanente Northwest	Community Clinic	+	OC-Auto	Enhanced Instructions + Reminder	Clinic	***X***					31.0	70.0
50 Ghai et al.[11]	Non-Randomized	USA	Kaiser Foundation Health Plan, Department of Regional Clinical Effectiveness	Integrated Health System	+++	OC-Auto	Routine + Reminder	Health Maintenance Organization		***X***	***X***		***X***	n/a	n/a
62 Yu et al.[45]	Non-Randomized	USA	David Geffen School of Medicine	Integrated Health System	+	OC-Auto	Routine + Enhanced Monitoring	n/a	***X***		***X***		***X***	21.2	50.8
137 Corley et al.[46]	Non-Randomized	USA	Kaiser Permanente Walnut Creek	Integrated Health System	+++	OC-Sensor	Routine + Reminder	n/a	***X***	***X***	***X***			82.7	n/a
277 Fedewa et al.[47]	Non-Randomized	USA	Emory University School of Medicine	Integrated Health System	+++	n/a	Routine + Reminder	n/a		***X***	***X***	***X***		n/a	n/a
362 Mehta et al.[48]	Non-Randomized	USA	Division of Gastroenterology, Departme	Integrated Health System	+++	n/a	Routine + Enhanced Monitoring + Reminder	n/a	***X***		***X***		***X***	44.0	n/a

Proof

			nt of Medicine, Perelman School of Medicine												
447 Luthgens et al.[49]	Randomized	USA	Division of Gastroenterology, Zuckerberg San Francisco General Hospital	Community Clinic	+	OC-Sensor	Enhanced Instructions + Reminder	Clinic	*X*	*X*	*X*			38.7	n/a
212 Singal et al.[50]	Randomized	USA	Department of Internal Medicine, UT Southwestern Medical Center	Community Clinic	+	OC-Auto	Enhanced Instructions + Reminder	n/a	*X*	*X*	*X*		*X*	28.0	n/a

Table 2. Technical Codes Identified and Used to Optimize Patient Selection for Colorectal Cancer Screening

Exclusion Criteria Categories	Current Procedural Terminology (CPT) (n=5)	International Classification of Disease (ICD9) (n=6)	Healthcare Common Procedure Coding System (HCPCS) (n=1)	Logical Observation Identifiers Names and Codes (LOINC) (n=1)
Colonoscopy	44388-44394, 44397, 45355, 45378-45387, 45391, 45392	45.22-45.25, 45.42, 45.43	G0105, G0121	
CT-Colonography	74261-74263			
Sigmoidoscopy	45330-45335, 45337-45342, 45345	45.24, 45.42	G0104	
Stool Blood	82270, 82274	76.51, 578.xx, V76.51	G0107, G0328, G0394	2335-8, 12503-9, 12504-7, 14563-1, 14564-9, 14565-6, 27396-1, 27401-9, 27925-5, 27925-7, 29771-3, 50196-5, 56490-6, 56491-4, 57905-2, 58453-2
Barium Enema	74270, 74280		G0106, G0120, G0122	
Iron Deficiency Anemia		280.9		
Chronic Diarrhea		787.91		
Total Colectomy	44150-44153, 44155-44156, 44210-44212	45.8		

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History of Inflammatory Bowel Disease		555-555.2, 555.9, 556-556.6, 556.8, 556.9		
History of Colorectal Polyps		211.3, 211.4, 230.3, 230.4, V12.72		
History of Cancer		153.0-154.8		
History of GI Cancer		159, 197.5, 197.8, 211.9, 230.3, 230.4, 230.7, 235.2, 239.0, V10.05		

*2 studies reported utilizing ICD10, however, codes were unspecified.

Proof

SUPPLEMENTARY TABLES AND FIGURES

Supplemental Table 1: Search Strategy

Search Engine	Search Terms through 12/31/2018
PubMed	((((FIT) AND (fecal OR colon OR colonic OR "colorectal neoplasms"[mh])) OR ((fecal OR faecal OR feces OR faeces OR "feces"[mh]) AND (immunochemical OR "immunochemistry"[mh])) AND (Mass screening[mh] OR screen OR screening OR "early detection of cancer" OR "early detection of cancer"[mh]) AND ("high risk" OR organized OR "increased risk" OR selection OR inclusion OR exclusion OR organized OR outreach OR population OR quality OR intervention)
Embase	(screen OR 'screening'/exp OR screening OR 'early detection of cancer'/exp OR 'early detection of cancer' OR 'early cancer diagnosis'/exp OR 'early cancer diagnosis' OR 'mass screening'/exp OR 'mass screening') AND ((fit AND ('colon'/exp OR colon OR colonic OR 'colorectal cancer'/exp OR 'colorectal cancer')) OR (('feces'/exp OR feces OR fecal OR faecal) AND ('immunochemistry'/exp OR immunochemistry OR immunochemical)) OR ('fecal immunochemical testing'/exp OR 'fecal immunochemical testing')) AND [humans]/lim AND [english]/lim AND [clinical study]/lim

Supplementary Table 2: Characteristics of CRC Programs with No Stated Process to Exclude Patients from Screening

Represented Study, Year	Study Design	Country	Primary Health Organization	Program Type	Number of Participants	Type of FIT	Type of Intervention	Patient Identification Sources	FIT Screening Outcomes	Colonoscopy Follow-up
1006 Ward et al.[51]	Non-Randomized	Australia	Discipline of Public Health, Flinders University, South Australia	National/Regional	+++	n/a	Routine + Reminder	Population Registry	46.1	n/a
619 Crouse et al.[52]	Non-Randomized	Canada	Department of Pathology and Laboratory Medicine, University of Calgary	National/Regional	++	OC-Sensor	Routine	Population Registry	25.8	n/a

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18 Amitay et al.[53]	Non-Randomized	Germany	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center	National/Regional	+	FOB Gold	Routine	Clinic	96.0	89.0
8 O'Donoghue et al.[54]	Non-Randomized	Ireland	BowelScreen, National Screening Service	National/Regional	+++	OC-Sensor	Routine + Enhanced Education + Enhanced Instruction	Population Registry	40.2	82.4
528 Turrin et al.[55]	Non-Randomized	Italy	Veneto Tumour Registry, Veneto Region	National/Regional	+++	OC-Sensor	Routine	n/a	68.0	n/a
563 Van Roon et al.[56]	Randomized	Netherlands	Department of Gastroenterology and Hepatology, Erasmus University Medical Centre	National/Regional	+	OC-Sensor	Enhanced Education + Enhanced Instruction	n/a	64.4	n/a
809 Tan et al.[57]	Non-Randomized	Singapore	Department of Colorectal Surgery, Singapore General Hospital	National/Regional	++	n/a	Routine	Population Registry	38.9	75.0
642 Quintero et al.[41]	n/a	Spain	Universidad de La Laguna, Hospital Universitario de Canarias	National/Regional	+++	OC-Sensor	Routine	Population Registry	96.0	87.0
417 Moss et al.[58]	Non-Randomized	UK	Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London	National/Regional	++	OC-Sensor	Routine	Population Registry	66.4	85.7
683 Steele et al.[59]	Non-Randomized	UK	Department of Surgery,	National/Regional	+++	OC-Sensor	Enhanced Education +	Population Registry	60.6	86.3

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			Ninewells Hospital and Medical School				Enhanced Instruction			
772 Digby et al.[60]	Non-Randomized	UK	Scottish Bowel Screening Research Unit, University of Dundee, Dundee, Scotland.	National/Regional	+++	OC-Sensor	Enhanced Education + Enhanced Instruction	Population Registry	58.7	n/a
55 Berry et al.[61]	n/a	USA	Moncrief Cancer Institute	Community Clinic	++	n/a	Reminder	Clinic	54.0	54.0
979 Cha et al.[62]	Non-Randomized	Korea	Department of Medicine, Graduate School, Kyung Hee University	Community Clinic	++	OC-Sensor	Reminder	Clinc	73.1	90

Supplementary Table 3: Represented Study and their Associated Studies and Linked Primary Health Organizations

Represented Study, Year	Country	Primary Health Organization	Associated Study
O'Donoghue et al.[54]	Ireland	BowelScreen, National Screening Service	
Amitay et al.[53]	Germany	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center	
Kemper et al.[44]	USA	Center for Health Research, Kaiser Permanente Northwest	Coronado et al.[16], Thompsonh et al.[63], Coronado et al.[64], Liles et al.[65]
Koivogui et al.[28]	France	Comité Départemental Des Cancers	
Ghai et al.[11]	USA	Kaiser Foundation Health Plan, Department of Regional Clinical Effectiveness	
Berry et al.[61]	USA	Moncrief Cancer Institute	
Binefa et al.[40]	Spain	Cancer Prevention and Control Programme, Instituto Catalán de Oncología, Hospitalet de Llobregat	Sanz-et al.[66]
Yu et al.[45]	USA	David Geffen School of Medicine	
Sportes et al.[1]	France	Gastroenterology Unit, Departmental Committee of Cancers-Bondy	

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Pellant et al.[27]	France	[67]Cochin teaching Hospital, Paris Descartes University	
Cha et al.[62]	Korea	Department of Medicine, Graduate School, Kyung Hee University	
Vanaclocha-espi et al.[38]	Spain	Cancer and Public Health Area-FISABIO	
Rat et al.[29]	France	Department of General Practice, Faculty of Medicine, Nantes	
Guirigu et al.[39]	Spain	Unitat de Suport a la Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol	
Larsen et al.[25]	Denmark	Department of Public Health Programmes, Randers Regional Hospital	Njor et al.[67]
Knudsen et al.[37]	Norway	Department of Bowel cancer screening, Cancer Registry of Norway	Knudsen et al.[37], Knudsen et al.[68]
Castaneda et al.[69]	USA	South Bay Latino Research Center, Graduate School of Public Health, San Diego State University	
Fedewa et al.[47]	USA	Emory University School of Medicine	
Telford et al.[24]	Canada	Department of Medicine (Telford) and School of Population and Public Health (Coldman), University of British Columbia	
Van Der Vlugt et al.[36]	Netherlands	Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam	Kallenberg et al.[70], Vlugt et al.[36], Stegeman et al.[71], Stegeman et al.[72], Denters et al.[73], Denters et al.[74], Stegeman et al.[75]
Clarke et al.[31]	Ireland	Department of Epidemiology and Public Health, University College Cork	
Mehta et al.[48]	USA	Division of Gastroenterology, Department of Medicine, Perelman School of Medicine	
Crosby et al.[76]	USA	College of Public Health and the Rural Cancer Prevention Center, University of Kentucky	
Shokar et al.[77]	USA	Department of Family and Community Medicine and Biomedical Sciences, Texas Tech University Health Sciences Center-El Paso	Shokar et al.[78]
Moss et al.[58]	UK	Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London	
Luthgens et al.[49]	USA	Division of Gastroenterology, Zuckerberg San Francisco General Hospital	Vogelaar et al.[79]
Chen et al.[42]	Taiwan	Digestive Disease Center, Show-Chwan Memorial Hospital	

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Singal et al.[50]	USA	Department of Internal Medicine, UT Southwestern Medical Center	Skinner et al.[80], Gupta et al.[81], Halm et al.[82], Pruitt et al.[83], Singal et al.[84]
Rossi[32]	Italy	Inter-institutional Epidemiology Unit, AUSL Reggio Emilia	
Wieten et al.[85]	Netherlands	Department of Gastroenterology and Hepatology, Erasmus University Medical Centre	Meulen et al.[86], Grobbee et al.[87], Hoeck et al.[88], Kapidzic et al.[89], Kapidzic et al.[90]
Santare et al.[35]	Latvia	Institute of Mathematics and Computer Science, University of Latvia	
Wong et al.[91]	China	Institute of Digestive Disease, Faculty of Medicine, Chinese University of Hong Kong	Wong et al.[91], Wong et al.[92], Ng et al.[93], Wong et al.[94]
Senore et al.[34]	Italy	AOU Città della Salute e della Scienza	
Crouse et al.[52]	Canada	Department of Pathology and Laboratory Medicine, University of Calgary	
Quintero et al.[41]	Spain	Universidad de La Laguna, Hospital Universitario de Canarias	
Duncan et al.[1]	Ireland	Trinity College Dublin	Leen et al.[95]
Turrin et al.[55]	Italy	Veneto Tumour Registry, Veneto Region	
Steele et al.[59]	UK	Department of Surgery, Ninewells Hospital and Medical School	McDonald et al.[96]
Digby et al.[60]	UK	Scottish Bowel Screening Research Unit, University of Dundee, Dundee, Scotland.	
Tan et al.[57]	Singapore	Department of Colorectal Surgery, Singapore General Hospital	Fu et al.[97], Chew et al.[98]
Van Roosbroeck et al.[23]	Belgium	Research Group Medical Sociology and Health Policy, Department of Epidemiology and Social Medicine, University of Antwerp	Hal et al.[99]
Ward et al.[51]	Australia	Discipline of Public Health, Flinders University, South Australia	
Grazzini et al.[33]	Italy	ISPO Cancer Prevention and Research Institute Florence	

Supplementary Table 4: Key Informants Targeted to Surveys and Interviews

Key Informant Interview Contributors	Country	Primary Health Organization/Institution
Walker JG	Australia	Victorian Comprehensive Cancer Centre, The University of Melbourne
Wilson C	Australia	Bowel Health Service and Flinders Centre for Innovation in Cancer

Telford J	Canada	Department of Medicine (Telford) and School of Population and Public Health (Coldman), University of British Columbia
Larsen MB	Denmark	Department of Public Health Programmes, Randers Regional Hospital
Koïvogui A	France	Comité Départemental Des Cancers
Amitay EL	Germany	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center
Wong, M	China	Institute of Digestive Disease, Faculty of Medicine, Chinese University of Hong Kong
O'Donoghue DP	Ireland	BowelScreen, National Screening Service
Zorzi M	Italy	Veneto Tumour Registry, Veneto Region
Dekker E	Netherlands	Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam
Quintero, E	Spain	Universidad de La Laguna, Hospital Universitario de Canarias
Fraser CG	UK	Scottish Bowel Screening Research Unit, University of Dundee
Gupta S	USA	Moncrief Cancer Institute
Arnold C	USA	Health Sciences Center, Louisiana State University
Baker DW	USA	Division of General Internal Medicine and Geriatrics, Department of Medicine, Feinberg School of Medicine
Charlton M	USA	Central Region and the Comprehensive Access and Delivery Research and Evaluation (CADRE) Center at the Iowa City VA Healthcare System
Coronado GD	USA	Center for Health Research, Kaiser Permanente Northwest
Daly JM	USA	Department of Family Medicine, University of Iowa
Daskalakis C	USA	Division of Biostatistics, Department of Pharmacology & Experimental Therapeutics, Thomas Jefferson University
Dominitz JA	USA	VA Puget Sound Health Care System
Doubeni CA	USA	Division of Gastroenterology, Department of Medicine, Perelman School of Medicine
Fleming TJ	USA	Touro University, California College of Osteopathic Medicine
Hannon PA	USA	University of Washington School of Public Health
Hendren S	USA	Department of Surgery, University of Michigan
Levin TR	USA	Kaiser Permanente Walnut Creek

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Somsouk M	USA	Division of Gastroenterology, Zuckerberg San Francisco General Hospital
Singal A	USA	Department of Internal Medicine, UT Southwestern Medical Center
Shokar NK	USA	Department of Family and Community Medicine and Biomedical Sciences, Texas Tech University Health Sciences Center-El Paso

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