

Review Article

Full title: Acceptability of alternative technologies compared with faecal immunochemical test and/or colonoscopy in colorectal cancer screening: A systematic review

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Declarations

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Abstract

Objective: Colorectal cancer (CRC) is the third most common cancer and the second largest cause of cancer-related death worldwide. Current CRC screening in various countries involves stool-based faecal immunochemical testing (FIT) and/or colonoscopy, yet public uptake remains sub-optimal. This review assessed the literature regarding acceptability of alternative CRC screening modalities compared to standard care in average-risk adults.

Method: Systematic searches of MEDLINE, EMBASE, CINAHL, Cochrane and Web of Science were conducted up to February 3rd, 2022. The alternative interventions examined were computed tomography colonography, flexible sigmoidoscopy, colon capsule endoscopy and blood-based biomarkers. Outcomes for acceptability were uptake, discomfort associated with bowel preparation, discomfort associated with screening procedure, screening preferences and willingness to repeat screening method. A narrative data synthesis was conducted.

Results: Twenty-one studies met the inclusion criteria. Differences between **intervention and comparison modalities** in uptake did not reach statistical significance in most of the included studies. The findings do suggest FIT as being more acceptable as a screening modality than flexible sigmoidoscopy. There were no consistent significant differences in bowel preparation discomfort, screening procedure discomfort, screening preference and willingness to repeat screening between the standard care and alternative modalities.

Conclusion: Current evidence comparing standard colonoscopy and stool-based CRC screening with novel modalities does not demonstrate any clear difference in acceptability. Due to the small number of studies available and included in each screening comparison and lack of observed differences, further research is needed to explore factors influencing acceptability of alternative CRC modalities that might result in improvement in population uptake within different contexts.

Keywords: colorectal cancer screening – faecal occult blood test (FOBT) – faecal immunochemical test (FIT) – flexible sigmoidoscopy (FS) – colon capsule endoscopy (CCE) – computed tomography (CT) colonography – blood-based biomarker.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second largest cause of cancer-related death worldwide, with over 1.9 million new cases causing 935,000 deaths in 2020 globally¹. Screening for CRC can be effective at reducing mortality, but uptake remains suboptimal². Several tests can be used to screen for CRC, including stool-based tests and colonoscopy.

The faecal immunochemical test (FIT) is currently most commonly used to screen for CRC and uses antibodies to detect human blood in the stool. Colonoscopy is considered the gold standard of CRC screening due to its ability to examine the whole colon while simultaneously detecting and removing polyps². Population-based colonoscopy screening has not been considered to be practicable in several countries due to the cost, capacity and expertise required³ whilst it has been implemented in others with relatively limited coverage of the population at risk. For example, colonoscopy-based but opportunistic screening is used in the United States and Poland, rather than a population-based screening programme⁴. Stool-based screening may have significant false negatives depending on the threshold used for detection in a particular screening programme³. Hence, there is a need for an effective as well as patient-centred and less invasive screening test that is acceptable to participants⁵.

There are several alternative technologies that have been investigated for colorectal screening, including flexible sigmoidoscopy (FS), computed tomography (CT) colonography, colon capsule endoscopy and blood-based biomarkers⁵, which may have adequate sensitivity and specificity and fulfil criteria⁶ to be used as a screening tool. Most of these are less invasive and/or often perceived as more patient-friendly than colonoscopy⁵. CRC screening uptake is consistently low among the underserved sections of the population⁷. Socioeconomic, ethnic and sociocultural factors also play a role in non-adherence with CRC screening. Individuals from areas with higher levels of social deprivation were less likely to participate in screening⁸. Zhu (2021)⁹ reported that psychosocial barriers such as unpleasantness, embarrassment, pain and fear about a positive result were the most commonly reported barriers to colonoscopy screening among the Hispanic population.

Alternative technologies for CRC screening require systematic investigation of patient acceptability for their efficacy to be translated to effectiveness at a population level. Common parameters used in previous CRC screening studies to determine acceptability have included screening uptake, bowel preparation discomfort, screening procedure discomfort and screening preference¹⁰. There are limited studies assessing the acceptance of alternative technologies among average-risk populations¹¹. Lin and colleagues¹² suggested that participants preferred CT colonography to colonoscopy in 16 of the 19 studies included in the review, but a pooled difference was not calculated. Khalid-de Bakker¹³ reviewed comparative uptake of a range of CRC modalities in average-risk populations. Their study suggested higher uptake for stool-based modalities. Zhu et al¹⁴ conducted a meta-analysis comparing uptake between CT colonography and colonoscopy and found no significant difference. However, their review was limited by comparing one alternative modality to colonoscopy. The purpose of the current systematic review was to examine the acceptability of four alternative CRC screening methods currently available, with published data on their use, compared to standard care (colonoscopy and FIT).

Methods

The systematic review was registered on PROSPERO (reg. no. CRD42020203971) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁵. Throughout all stages of the search, data extraction and quality appraisal, 15% of studies were double-checked for consistency by another member of the team (SG). All discrepancies were resolved through discussion. Data duplication was managed by removing duplications using a reference management software package (EndNote X9) and Rayyan¹⁶, followed by manual checking.

Search strategy

The literature from 1985 to February 3rd, 2022, was searched on electronic databases Medline, Embase, Cochrane, CINAHL and Web of Science using the terms listed in Table 1. A list of the search terms for the different databases are listed in Appendix 1. Studies published before 1985 were not included because the alternative interventions were not used in clinical practice prior to this date.

Eligibility criteria

Inclusion criteria were: (1) participants aged 45-86 years; (2) participants with average risk of CRC; (3) studies that compared colon capsule endoscopy, CT colonography, flexible sigmoidoscopy and/or blood biomarkers (e.g., Septin 9 or Epi proColon) with FOBT, FIT and/or colonoscopy. The exclusion criteria were: (1) studies that used a decision aid to increase CRC uptake; (2) participants who were previously non-adherent to screening and received a tailored intervention to encourage screening; (3) studies that did not report primary study data or used simulation models. This review was not limited to randomised controlled trials (RCTs); it also included studies that reported participants' perceptions and preferences to better understand acceptance of screening tests.

Table 1: Population, Intervention, Comparator, Outcomes (PICO) and search terms

PICO	Description	Search terms
Population	Participants aged 45 to 86 years and who were at average risk of CRC	exp Colorectal Neoplasms/ or ((bowel or colorectal or colon) or adj3 (carcinoma* or neoplasm* or cancer)).mp or ("early detection of cancer" or early screening).mp or mass screening/ or (screen* or detection or test*)
Intervention	Colon capsule endoscopy, CT colonography, FS, blood biomarkers	(capsule endoscopy* or colon capsule or virtual camera or video endoscopy).mp or virtual endoscopy.mp or exp Colonography, Computed Tomographic/ or (virtual colonoscopy or CT colonoscopy).mp or Sigmoidoscopy/ or (flexible sigmoid* or flexible sigmoidoscopy).mp or blood test.mp. or Hematologic tests/ or (epi procolon or septins or msept9).mp or septin9.mp or (blood bio* or blood-based or blood-based biomarker or liquid bio*).mp
Comparison	FOBT, FIT, colonoscopy	exp Colonoscopy/ or Occult Blood/ or fecal immunochemical test.mp or faecal immunochemical test.mp
Outcome	Acceptability - uptake, discomfort associated with bowel preparation, discomfort associated with screening procedure, screening preference, willingness to repeat screening modality	(acceptability* or acceptance).mp or (adherence* or attend* or attendance*) or (engage or engagement or interest or willing).mp or (uptake* or screening uptake).mp or (compliance* or complete*).mp or (intend or visit or choice or choose or chose).mp or patient preference/ or patient participation or participate*.mp or (knowledge or understanding or comprehension).mp or (decision making or decide or attitude or belief).mp or (perception or perceive or interest or value or decisional conflict).mp

		or (anxiety/ or discomfort).mp or (embarrassment or pain or experience).mp or satisfaction.mp or Personal Satisfaction/confidence* or fear or worry.mp
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Selection process

Databases were searched with fixed search terms (Table 1) and all results were exported and saved onto EndNote. Articles were cross-referenced to look for relevant articles. Full texts of potentially eligible studies were reviewed. Discrepancies that arose were resolved by agreement between the two reviewers. If no agreement could be reached a third reviewer (SD) was consulted.

Data extraction and synthesis

A standardised form was used to extract the following study details: authors, year of publication, country, study design, screening intervention, screening comparator and study outcomes. Due to the heterogeneity of included studies, a narrative approach was used to synthesise key findings¹⁷. A p-value of <0.05 was used as a cut-off to determine significance of results reported.

Quality assessment

One author assessed the quality of all included studies using the Cochrane risk-of-bias (RoB 2) tool¹⁸ to assess randomised studies and the ROBINS_I tool¹⁹ for non-randomised studies. The Cochrane tool¹⁸ assesses the likelihood of bias in studies across five domains: (1) randomisation bias, (2) intended intervention bias, (3) missing data bias, (4) outcome bias and (5) reporting bias. The risk of bias was judged as low, high or some concerns. Seven domains assessed using the ROBINS_I tool¹⁹ were: (1) confounding bias, (2) participant selection bias, (3) intervention classification bias, (4) deviations from intended intervention bias, (5) missing data bias, (6) outcome bias and (7) reported bias. The risk of bias was judged as low, moderate or high. An RCT was graded higher than an observational study when evaluating the same outcome measure. Evidence from observational studies was used where no RCT data were available.

RESULTS

Study selection

The initial search yielded 19,372 articles (Figure 1). After removing duplicates, 13,188 underwent title and abstract screening. Two-hundred and fifteen articles were assessed for full-text eligibility, of which 21 studies were included in the final analysis. Three of these used the same population cohort to assess uptake and measure acceptability^{31, 34, 36}, but the findings were reported in separate studies.

Study characteristics

Key characteristics of the included studies are outlined in Table 2. Twelve studies were RCTs²⁰⁻³¹ and eight studies were observational³²⁻⁴⁰. To assess acceptability, studies compared participants who had completed a screening intervention or a comparator. Eight studies compared CT colonography and colonoscopy^{20-24, 34-37, 38}, five studies compared FS and FIT^{25-28, 39}, four studies compared FS and colonoscopy^{21, 26, 36-37}, four studies compared blood-based biomarker tests and FIT²⁹⁻³², two studies compared colon capsule endoscopy and colonoscopy^{33, 40}, two studies compared CT colonography and FOBT^{21, 23} and one study compared CT colonography and FIT²⁴.

Figure 1: PRISMA flow diagram depicting study selection process

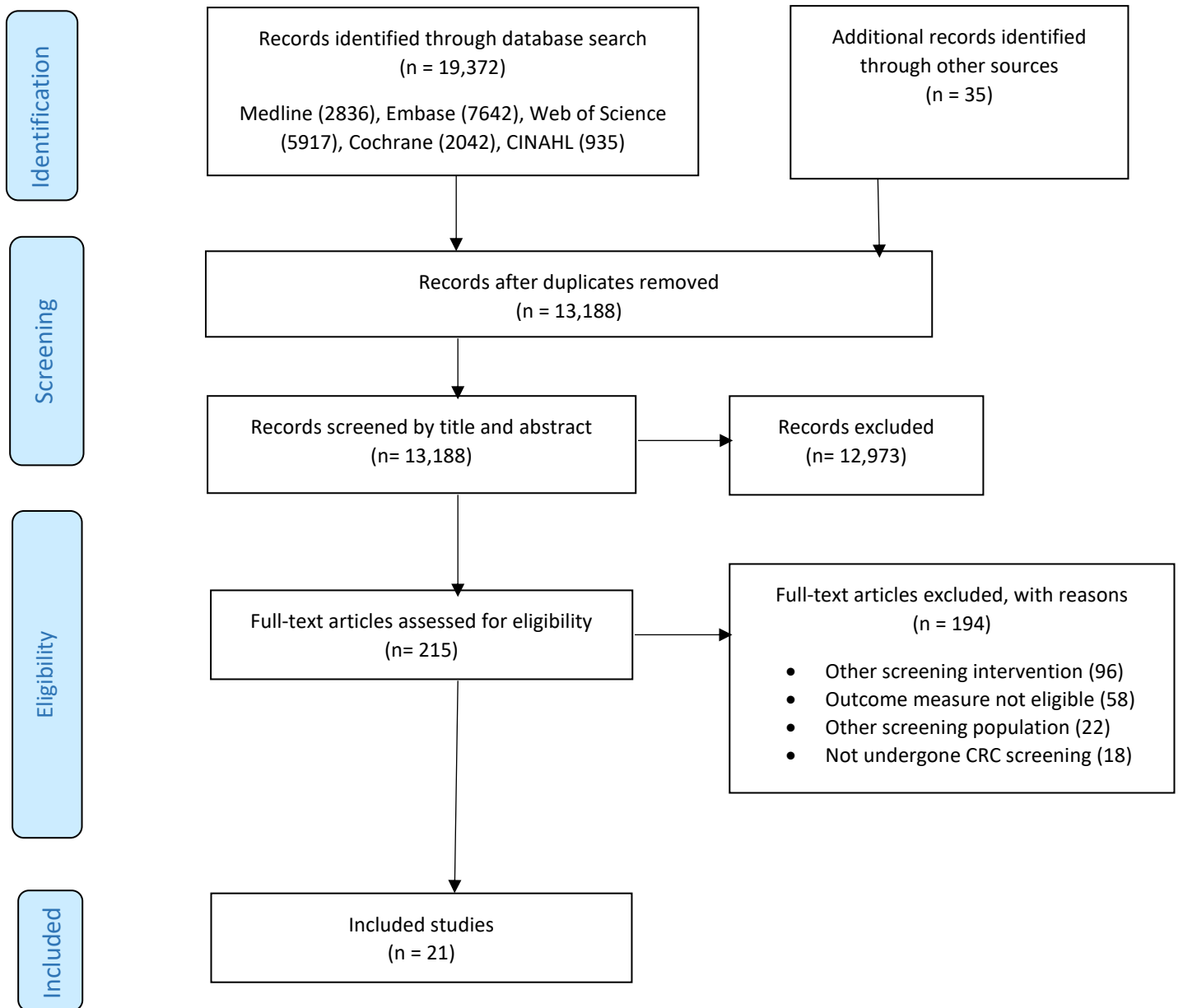


Table 2 – Key characteristics of included studies

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
Scott et al (2004) (Australia) ²⁰	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n=359), colonoscopy (n=350). Age of participants: 50-55 years (53.0%), 65-69 years (47.0%). Gender: male (50.0%), female (50.0%).	Uptake	CT colonography (18.1% 65/359), colonoscopy (16.3%, 57/350), p=0.82, no significant difference.	High risk
Forbes et al (2006) (Australia) ²¹	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n=215), colonoscopy (n=214). Age of participants: 50-54 years (49.5%), 65-69 years (50.5%). Gender: male (50.1%), female (40.9%).	Uptake	CT colonography (16.3%, 35/214), colonoscopy (17.8%, 38/214), no significant difference.	High risk
Stoop et al (2011) (Netherlands) ²²	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n=2920), colonoscopy (n=5924). Age of participants: 50-59 years (45.9%), 60-75 years (54.2%). Gender: male (67.1%), female (32.9%).	Uptake	CT colonography (34%, 982/2920) had highest uptake compared to colonoscopy (22%, 1276/5924), (relative risk [RR] 1.56, 95% CI 1.46–1.68; p<0.001).	High risk
You et al (2015) (Canada) ²³	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n=65), colonoscopy (n=66). Age of participants: 50-70 years. Mean age: 58.7 years. Gender: male (52.5%), female (47.5%).	Uptake	CT colonography (76.9%), colonoscopy (80.3%), no p-value as trial was stopped early.	High risk
Sali et al (2016) (Italy) ²⁴	RCT	CT colonography vs colonoscopy	Sample size invitees: r-CT colonography (n=2395), f-CT colonography (n=2430), colonoscopy (n=1036). Age of participants: 54-60 years (61.5%), 61-65 years (38.5%). Gender: male (46.4%), female (53.6%).	Uptake	r-CT colonography (28.1% 674/2395), f-CT colonography (25.2%, 612/2430), colonoscopy (14.8%, 153/1036). All differences between groups were statistically significant (P< .001).	High risk
Kirkoen et al (2017) (Norway) ²⁵	RCT	FS vs FIT	Sample size invitees: FS (1700), FIT (1439). Age of participants: 50-74	Uptake	FS (52%), FIT (54%), no significant difference.	High risk
Segnan et al (2007) (Italy) ²⁶	RCT	FS vs FIT	Sample size invitees: FIT (6075), FS (6018). Age of participants: 55-59 years (59.5%), 60-64 years (40.5%).	Uptake	FS: 32.3% (1944/6018), FIT: 32.3% (1965/6075), no significant difference.	High risk

Hol et al (2009) (Netherlands) ²⁷	RCT	FS vs FIT	Gender: male (47.7%), female (52.3%) Sample size invitees: FS (5000), FIT (5007). Age of participants: 50-74	Uptake	61.5% (CI, 60.1 to 62.9%) for FIT and 32.4% (CI, 31.1 to 33.7%) for FS screening.	High risk
Randel et al (2021) (Norway) ²⁸	RCT	FS vs FIT	Sample size invitees: FS (69,165) FIT (70,096). Age of participants: 50-74 Gender: male (49.3%), female (50.7%).	Uptake	FIT 1 st round had highest uptake (58.4%) compared to FS (52.1%), p<0.05.	High risk
Symonds et al (2019) (Australia) ²⁹	RCT	Blood-based vs FIT	Sample size invitees: Blood-based (585), FIT (588). Gender: female (50.7%), male (49.3%). Age of participants: 50-74	Uptake	Blood-based test (5.3%, 31/585), FIT (3.6%, 21/588), p>0.05.	High risk
Young et al (2021) (Australia) ³⁰	RCT	Blood-based vs FIT	Sample size invitees: blood test (293), FIT (292). Age of participants: 50-74. Gender: male (53.3%), female (47.7%)	Uptake	Blood-based test (13.3%, 39/293), FIT (12.0%, 35/292), 13.3%, p=0.88.	High risk
Liles et al (2016) (USA) ³¹	RCT	Blood-based vs FIT	Sample size invitees: Epi-proColon (203), FIT (210). Age of participants: 50-75. Gender: male (39.9%), female (60.1%) Ethnicity: Caucasian (85.7%), Others (14.3%).	Uptake	Blood-based test had highest uptake: (99.5%, 202/203), FIT (88.1%, 185.210), p < 0.001.	High risk
Ioannou et al (2021) (USA) ³²	Observational study	Blood-based vs FIT	Sample size invitees: 460. Age of participants: >50 years. Gender: male (39%), female (61%)	Uptake	Of 460 participants, none chose colonoscopy, 30 (6.5%) chose FIT and 430 (93.5%) chose blood-based test. No p-value stated.	Moderate risk
Forbes et al (2006) (Australia) ²¹	RCT	CT colonography vs FOBT	Sample size invitees: CT colonography (215), FOBT (234).	Uptake	FOBT had highest uptake: (27.4%, 64/234), CT colonography (16.3%, 35/215), p=0.005.	High risk
You et al (2015) (Canada) ²³	RCT	CT colonography vs FOBT	Sample size invitees: CT colonography (65), FOBT (67).	Uptake	CT colonography: (76.9%, 50/65), FOBT (64.2%, 43/67).	High risk
Segnan et al (2007) (Italy) ²⁶	RCT	FS vs colonoscopy	Sample size invitees: FIT (6075), FS (6018), colonoscopy (6021).	Uptake	FS: 32.3% (1944/6018), colonoscopy: 26.5% (1597/6021), (OR, 0.74; 95% CI: 0.68–0.80),	High risk
Groth et al (2012) (Germany) ³³	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 2150. Age of participants: >55 years. Gender: male, (49.3%), female (50.7%)	Uptake	Capsule endoscopy: (4.2%, 90/2150), colonoscopy: (1.6%, 34/2150).	Low risk
Sali et al (2016) (Italy) ²⁴	RCT	CT colonography vs FIT	Sample size invitees: r-CT colonography (2617), f-CT colonography (2625), FIT (9288). Age of participants: 54-65.	Uptake	FIT had highest uptake (50.4%), r-CT colonography: (28.1%), f-CT colonography: (25.2%). All differences between groups were statistically significant (P < .001).	High risk

Wijkerslooth et al (2011) (Netherlands) ³⁴	Observational study	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n=801/982), colonoscopy (n=1009/1276). Age of participants: 50-74 years.	Bowel preparation discomfort	More burdensome in colonoscopy than CT colonography: (61% vs 16%, p<0.001).	High risk
Gareen et al (2015) (USA) ³⁵	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310, participants. Age of participants: 55-86 years. Mean age: 58.4 years.	Bowel preparation discomfort	CT colonography participants reported more discomfort (81.3% vs 27.8%, p<0.001) and more embarrassment (42.5% vs 26.0%, p<0.001).	High risk
Nicholson and Korman (2005) (Australia) ³⁶	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256). Gender: male (45%), female (55%).	Bowel preparation discomfort	BP ranked the worst part of procedure FS: 31%, colonoscopy 78% (p<0.02).	Low risk
Senore et al (2011) (Italy) ³⁷	Observational study	FS vs colonoscopy	Sample size invitees: FS (1696), colonoscopy (1382).	Bowel preparation discomfort	BP symptom moderate/severe: FS (3.8%), colonoscopy (15.1%), not significant.	Moderate risk
Scott et al (2004) (Australia) ²⁰	RCT	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n=56), colonoscopy (n=95).	Screening discomfort	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). Pain: CT computed tomography (23), colonoscopy (7.1). Satisfaction: CT computed tomography (6.5), colonoscopy (4.6). Embarrassment: CT computed tomography (10.2), colonoscopy (7.8).	High risk
Forbes et al (2006) (Australia) ²¹	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n=37/38), colonoscopy (n=62/63). Age of participants: 50-54 years and 65-69 years.	Screening discomfort	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). Pain score: CT colonography (20), colonoscopy (4.5). Satisfaction score: CT colonography (10), colonoscopy (4). Embarrassment score: CT colonography (6), colonoscopy (4).	High risk
Pickhardt et al (2003) (USA) ³⁸	Observational study	CT colonography vs colonoscopy	Sample size invitees: 1233 (81.5% returned post-study questionnaire). Age of participants: 50-79 years	Screening discomfort	CT colonography participants reported more discomfort (54.3% vs 38.1%, p<0.001) and more acceptable in terms of convenience (68.3% vs 24.1%, p<0.001).	Low risk
Wijkerslooth et al (2011) (Netherlands) ³⁴	Observational study	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n=801/982), colonoscopy (n=1009/1276). Age of participants: 50-74 years.	Screening discomfort	CT colonography participants reported more pain (72% vs 47%, p<0.001), more embarrassment (8% vs 5%, p<0.001).	High risk

Forbes et al (2006) (Australia) ²¹	RCT	FS vs colonoscopy	Sample size invitees: FS (39), colonoscopy (63).	Screening discomfort	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). Pain: FS (18), colonoscopy (4.5). Satisfaction: FS (6), colonoscopy (4). Embarrassment: FS (10), colonoscopy (4).	High risk
Nicholson and Korman (2005) (Australia) ³⁶	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256). Gender: male (45%), female (55%).	Screening discomfort	Colonoscopy more comfortable (75% vs 18%; P<0.001), embarrassment score not significantly different. No pain associated with colonoscopy and most individuals had a pain score of less than 3 (11-point scale) for FS.	Low risk
Senore et al (2011) (Italy) ³⁷	Observational study	FS vs colonoscopy	Sample size invitees: FS (1696), colonoscopy (1382).	Screening discomfort	No significant difference with pain and embarrassment levels.	Moderate risk
Hol et al (2010) (Netherlands) ³⁹	Observational study	FS vs FIT	Post-study questionnaire: FS (852/1124), FIT (530/659). Age of participants: 50-74	Screening discomfort	FS participants reported greater discomfort and embarrassment mean scores (p < 0.001).	Moderate risk
Scott et al (2004) (Australia) ²⁰	RCT	CT colonography vs colonoscopy	62 participants returned post-study questionnaire. Age of participants: 50–54 years and 65–69 years.	Screening preference	CT colonography (39%), colonoscopy (61%), p=0.075, not significant.	High risk
Pickhardt et al (2003) (USA) ³⁸	Observational study	CT colonography vs colonoscopy	Sample size invitees: 1233 (81.5% returned post-study questionnaire).	Screening preference	CT colonography participants reported greater preference (49.8% vs 41.1%, p=0.004).	Low risk
Gareen et al (2015) (USA) ³⁵	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310 participants.	Screening preference	CT colonography: 46.6%, (95% confidence interval [CI]: 44.5% -48.7%), colonoscopy: 25.0%, (95% CI: 23.3%–26.9%).	High risk
Groth et al (2012) (Germany) ³³	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 147	Screening preference	Capsule endoscopy (70.6%), colonoscopy (29.4%)	Low risk
Voska et al (2019) (Czech Republic) ⁴⁰	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 225	Screening preference	Capsule endoscopy (47.0%), colonoscopy (53.0%).	Moderate risk
Scott et al (2004) (Australia) ²⁰	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n=56), colonoscopy (n=95).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). Colonoscopy (4.5), CT colonography (11.0).	High risk
Forbes et al (2006) (Australia) ²¹	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n=37/38), colonoscopy (n=62/63).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). CT colonography (10), Colonoscopy (4).	High risk

Wijkerslooth et al (2011) (Netherlands) ³⁴	Observational study	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n=801/982), colonoscopy (n=1009/1276).	Willingness to repeat	CT colonography (93%), colonoscopy (96%), p=0.99, not significant.	High risk
Gareen et al (2015) (USA) ³⁵	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310 participants.	Willingness to repeat	Colonoscopy participants reported greater willingness to screen (96.6% vs 79%, p<0.001).	High risk
Kirkoen et al (2017) (Norway) ²⁵	RCT	FS vs FIT	Post-study questionnaire: FS (528), FIT (356) Age of participants: 50-74	Willingness to repeat	FS (90%), FIT (95%), not statistically significant.	High risk
Hol et al (2010) (Netherlands) ³⁹	Observational study	FS vs FIT	Post-study questionnaire: FS (852/1124), FIT (530/659). Age of participants: 50-74	Willingness to repeat	FIT (94.0%), FS (83.8%).	Moderate risk
Forbes et al (2006) (Australia) ²¹	RCT	FS vs colonoscopy	Sample size invitees: FS (39), colonoscopy (63).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0=most favourable, 100=least favourable). FS (5), Colonoscopy (4).	High risk
Nicholson and Korman (2005) (Australia) ³⁶	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256).	Willingness to repeat	FS (97.5%), colonoscopy (99.5%).	Low risk
Groth et al (2012) (Germany) ³³	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 147	Willingness to repeat	Capsule endoscopy (87%), colonoscopy (94%).	Low risk

CT: computed tomography, BP: bowel preparation, r-CT: reduced computed tomography, f-CT: full computed tomography, FS: flexible sigmoidoscopy, FIT: faecal immunochemical test.

Study quality

All of the randomised studies obtained a high risk of bias from the Cochrane RoB 2 tool¹⁸, as shown in Table 3a, since participants were aware of their assigned intervention during the study. According to the ROBINS_I tool¹⁹ shown in Table 3b, two studies were assessed to be at high risk³⁴⁻³⁵, four studies moderate risk^{32, 37, 39-40} and three studies low risk^{33, 36, 38}. In two studies, participants were informed of their screening result prior to completing the questionnaire, which might have influenced the responses³⁹⁻⁴⁰.

Table 3a: Risk of bias in randomised studies assessed by Cochrane Risk of bias 2.

	Randomisation bias	Intended intervention bias	Missing data bias	Outcome bias	Reporting bias	Overall bias
Scott 2004 ²⁰	+	-	+	+	+	-
Forbes 2006 ²¹	+	-	+	+	+	-
Stoop 2011 ²²	+	-	+	+	+	-
You 2015 ²³	+	-	-	-	-	-
Sali 2016 ²⁴	+	-	+	+	+	-
Kirkoen 2017 ²⁵	+	-	+	+	+	-
Segnan 2007 ²⁶	+	-	+	+	+	-
Hol 2009 ²⁷	+	-	+	+	+	-
Randel 2021 ²⁸	+	-	+	+	+	-
Symonds 2019 ²⁹	+	-	+	+	+	-
Young 2021 ³⁰	+	-	+	+	+	-
Liles 2016 ³¹	+	-	+	+	+	-

+ = Low risk, - = High risk

Table 3b: Risk of bias in non-randomised studies assessed by ROBINS_I tool.

	Confounding bias	Participant selection bias	Intervention classification bias	Deviations from intervention bias	Missing data bias	Outcome bias	Reported bias	Overall bias
Ioannou ³² 2021	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Groth ³³ 2012	Low	Low	Low	Low	Low	Low	Low	Low
Wijkerslooth ³⁴ 2011	Low	Low	Low	Low	Low	Low	High	High
Gareen ³⁵ 2015	Low	Low	Low	Low	Low	Low	High	High
Nicholson ³⁶ 2005	Low	Low	Low	Low	Low	Low	Low	Low
Senore ³⁷ 2011	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Pickhardt ³⁸ 2003	Low	Low	Low	Low	Low	Low	Low	Low
Hol ³⁹ 2010	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Voska ⁴⁰ 2019	High	Low	Low	Low	Low	Low	Moderate	Moderate

Uptake

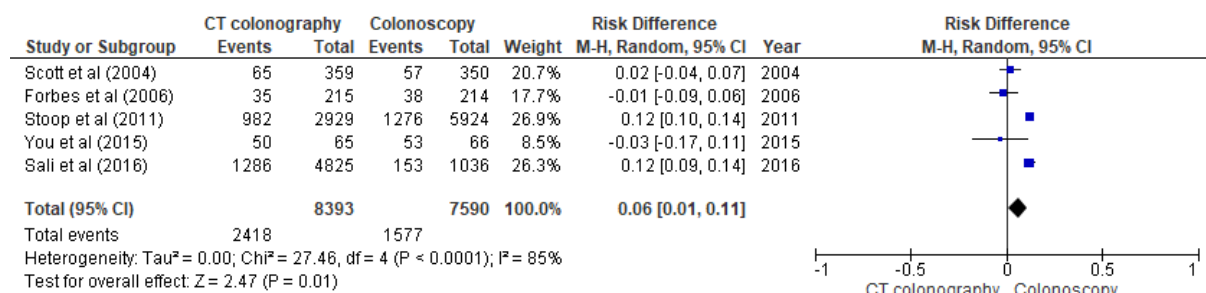
Five RCT studies compared uptake between CT colonography and colonoscopy²⁰⁻²⁴ (Figure 2a). In two studies²⁰⁻²¹, differences in observed uptake were not statistically significant. In a third study by You²³, the trial was stopped early; there was insufficient statistical power to detect relevant differences in uptake. In Stoop's study²², differences in observed uptake were statistically higher in CT colonography than colonoscopy (34% vs 22%, $p < 0.001$). Similarly, differences in observed uptake in Sali's study²⁴ were significantly higher in both reduced (28.1%, $p < 0.001$) and full-preparation (25.2%, $p < 0.001$) CT colonography over colonoscopy (14.8%).

Four RCT studies compared uptake of FS and FIT²⁵⁻²⁸ (Figure 2c). Uptake was higher with FIT compared to FS in two studies²⁷⁻³⁰, which totalled 150,000 participants. The other two studies²⁵⁻²⁸ found no significant differences, but their combined sample size only accounted for a tenth of the total. In this review, Hol's study²⁷ was the only comparator of FS and FIT which included socio-economic status as a baseline characteristic. The results found participants from a higher socio-economic group were more likely to take part in both FS and FIT screening ($p < 0.05$). Three RCTs²⁹⁻³¹ and one observational³² study compared uptake of blood-based test and FIT (Figure 2b). In two of these studies²⁹⁻³⁰, differences in observed uptake were not significant. In the third study, by Liles³¹, differences in observed uptake were higher in blood-based test than FIT (99.5% vs 88.1%, $p < 0.001$). In the fourth study, by Ioannou³², there was no p-value stated to determine statistical difference.

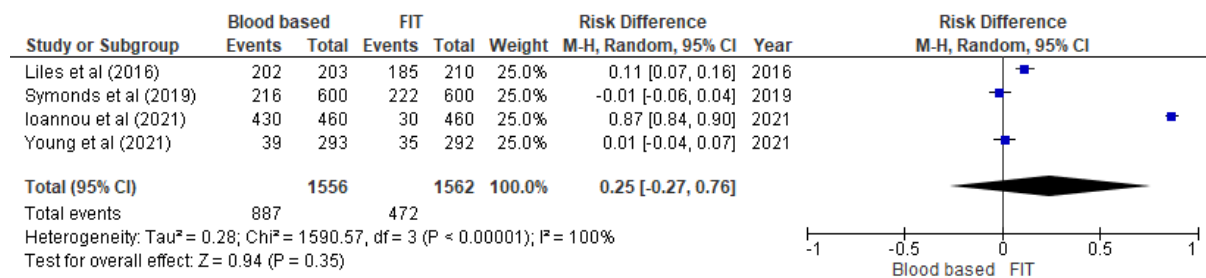
Two RCTs compared uptake of CT colonography and FOBT^{21, 23}. Differences in observed uptake were not significant in Forbes²¹ study and in You's study²³ the trial was stopped early. Segnan's RCT²⁶ was the only study that compared FS and colonoscopy uptake. After adjustment for demographic variables, the uptake was significantly higher in FS than colonoscopy (OR, 0.74; 95 percent CI: 0.68–0.80). Groth's observational study³³ was the only study that compared colon capsule endoscopy and colonoscopy uptake. The differences in observed uptake were not significant. Sali's RCT²⁴ was the only study that compared CT colonography and FIT. The differences in observed uptake were higher with FIT (50.4%, $p < 0.001$) than both reduced (28.1%) and full-preparation (25.2%) CT colonography.

Figure 2 (a) Pooled results of uptake for computed tomography (CT) colonography and colonoscopy. (b) Pooled results of uptake for blood based and faecal immunochemical test (FIT). (c) Pooled results of uptake for flexible sigmoidoscopy (FS) and FIT.

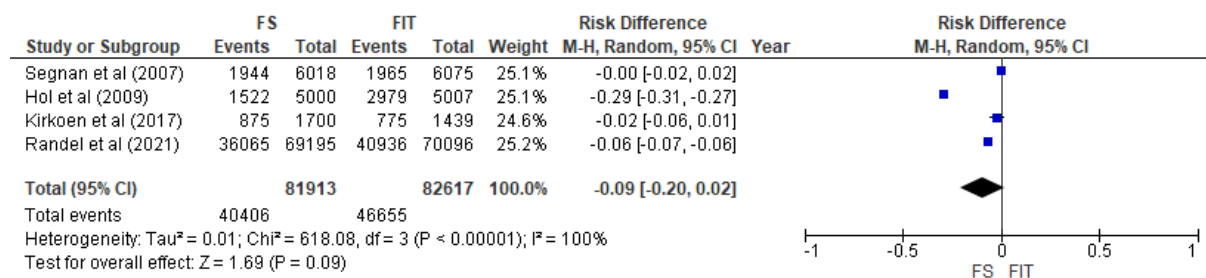
(a)



(b)



(c)



Bowel preparation associated discomfort

Two observational studies³⁴⁻³⁵ compared bowel preparation discomfort associated with CT colonography and colonoscopy. In Wijkerslooth's study³⁴, bowel preparation burdensome was significantly higher for colonoscopy than CT colonography (73% vs 32%, p<0.001). They suggest this may be due to the increased fluid intake before colonoscopy, as opposed to the limited bowel preparation in CT colonography. In Gareen's study³⁵, differences in bowel preparation discomfort were not statistically significant. Two observational studies³⁶⁻³⁷ compared bowel preparation discomfort of FS and colonoscopy. In Nicholson's study³⁶, bowel preparation discomfort was ranked the worst aspect in both colonoscopy (78%) and FS (31%) procedures (p<0.02). In Senore's study³⁷, differences in bowel preparation discomfort scores were not statistically significant.

Screening procedure associated discomfort

Four studies compared screening procedure discomfort between CT colonography and colonoscopy^{20-21, 34, 38}. In two studies, discomfort was significantly higher for CT colonography than colonoscopy (p value<0.001)^{34, 38}. In the other two studies, differences in median pain scores were not statistically significant²⁰⁻²¹. Three studies compared screening procedure discomfort between FS and colonoscopy^{21, 36-37}. In two studies, differences in pain scores were not significant^{21, 37}. In Nicholson's study³⁶, differences in discomfort were significantly higher for FS than colonoscopy (p<0.001). Hol's study³⁹ was the only study that compared pain scores between FS and FIT. The mean pain score was unsurprisingly significantly higher with FS than FIT (p<0.001).

Screening preference

Three studies compared screening preference between CT colonography and colonoscopy^{20, 35, 38}. In two studies^{20, 35}, differences in screening preference were not significant. A questionnaire was used to capture participants' reasons for choosing a certain modality^{20, 33}. The reasons participants chose colonoscopy in Scott's study²⁰ included there was no obligation for a second procedure, they expected a more detailed examination and a preference for sedation. Conversely, the reasons participants chose CT colonography in Scott's study²⁰ included they expected it to take less time, be less painful,

be less risky and not require sedation. In Pickhardt's study³⁸, differences in screening preference were significantly higher for CT colonography than colonoscopy ($p=0.004$).

Two studies compared screening preference between capsule endoscopy and colonoscopy^{33, 40}. In both studies, differences in screening preference were not statistically significant. In Groth's study³³, the reasons participants preferred capsule colonoscopy were captured from questionnaires, and included that it sounded more pleasant, were afraid of colonoscopy pain, were afraid of sedation, and were afraid of colonoscopy problems. The reasons participants favoured colonoscopy were because it allowed for biopsy and polypectomy in a single procedure and is the standard method.

Willingness to repeat screening modality at recommended screening interval

Four studies compared willingness to repeat screening between CT colonography and colonoscopy^{20-23, 34-35}. In three of the studies, there was no significant difference in willingness to repeat^{20-21, 34}. In Gareen's study³⁵, the willingness to repeat colonoscopy was significantly higher than CT colonography (96.6% vs 79%, $p<0.001$). Two studies compared willingness to repeat screening between FS and FIT^{25, 29} and neither study found a significant difference. Two studies compared willingness to repeat screening between FS and colonoscopy^{21, 36} and found no significant difference. The only study that evaluated willingness to repeat screening between colon capsule endoscopy and colonoscopy was Groth's³³ and showed no significant difference.

Discussion

This systematic review suggests that though there was no significant overall difference in acceptability between alternative modalities of screening, FIT seemed more acceptable than FS as evidenced by higher uptake and less discomfort experienced by participants. This review's findings are in agreement with Stracci⁴¹, who indicated FIT as being a more widely accepted screening test than FS.

The findings of Hol's study²⁷ are comparable to those of the English Bowel Screening Programme study⁴², which found those participants in the least deprived areas were more likely to participate (53.2%) in FS screening than those in the most deprived areas (32.7%). Previous synthesis of evidence has included these modalities in non-screening cohorts, e.g. for early detection of CRC in symptomatic patient groups where other factors may motivate patient preference, anxiety and willingness to accept discomfort¹⁴⁻¹⁵. Mutneja's meta-analysis⁴³ did not include Kirkoen's study²⁵ and compared an additional two studies that were not eligible in this review. The bowel preparation requirement was found to be a common barrier to completing a colonoscopy. The percentage of participants in Wijkerslooth's study³⁴, who declined screening due to inconvenience of bowel preparation was significantly higher for colonoscopy than for CT colonography. This review's findings are similar to those of Cash's randomised trial⁴⁵, which found no significant differences in screening preference between colonoscopy, colon capsule endoscopy and CT colonography.

This systematic review has a number of strengths. Firstly, a range of alternative screening modalities were compared to current standard of care screening by colonoscopy and FIT. Secondly, this review compared several parameters of acceptability measures, which included uptake, bowel preparation, screening discomfort, screening preference and willingness to repeat modality. Thirdly, this review focused on average-risk CRC individuals to understand their views of screening as opposed to those at high risk, who may be more motivated and consequently more likely to participate in screening anyway. Lastly, this review focused on studies of actual screening participants rather than studies of hypothetical screening scenarios or discrete choice experiments.

There are some limitations to this systematic review. There can be no definitive conclusion drawn on acceptability of alternative modality, because only a limited number of studies that fitted the inclusion criteria were possible to analyse. Secondly, the 21 studies included in the review were heterogeneous in study design, screening comparison and sample size, which were all limiting factors for why a meta-analysis was not conducted. Thirdly, studies differed as to where participants completed the post-screening questionnaire: at their homes or in hospital. Completing the questionnaire in a hospital setting may potentially influence a participant's response. Studies varied as to whether or not they informed participants of their screening result before completing the questionnaire, which could potentially influence participants' responses. Finally, there was no uniform reporting on the acceptability measures, which included use of a Likert scale, percentages and median 100-point analogue score. This made it difficult to interpret the significance of the results.

Due to the limited number of studies in each screening comparison, no definitive conclusion can be drawn on most acceptable alternative modality. The lack of significance in the study outcomes could be due to the specific nature of study population, small study sample sizes, mixture of study designs, different healthcare systems and limited context of demographic differences in the populations studied (different countries, ages, and socio-economic status). Other factors such as insurance status in some jurisdictions may also have an influence on screening modality preference⁴⁶⁻⁴⁷. However, this research adds to the limited evidence regarding bowel preparation acceptance, screening preference and willingness to repeat modality for non-invasive modalities. In the future, larger well-designed studies are needed comparing alternative CRC modalities with FIT and/or colonoscopy in order to facilitate meaningful comparison and complete a meta-analysis. Further qualitative studies are needed to explore compliance with bowel preparation, participants' screening preferences, and reasons for non-uptake in standard screening and alternative modality. In addition, future studies should include qualitative research analysing the acceptability of alternative screening modalities among individuals who are less likely to engage in routine CRC screening.

Several factors need to be considered before the consideration of colon capsule endoscopy and blood-based screening as population-based screening. These include a cost-effectiveness analysis, resource availability, views of healthcare organisations, practical implementation, need for subsequent second procedures and patient preferences. We believe this review is relevant to inform the context when there is increasing focus on blood-based cancer screening (including multiple cancer screening and early detection) tests as well as colon capsule endoscopy as potential screening modalities for CRC. It highlights the complex interplay between the effectiveness and acceptability of various tests and in different populations.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *J Clin* 2021; 71(3): 209-249.
2. Issa IA and Noureddine M. Colorectal cancer screening: An updated review of the available options. *J Gastro* 2017; 23(28): 5086-5096.
3. Katsoula A, Paschos P, Haidich AB, et al. Diagnostic Accuracy of Fecal Immunochemical Test in Patients at Increased Risk for Colorectal Cancer. *J Am Med Ass* 2017; 177(8): 1110-1118.
4. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; 64(10): 1637-1649.
5. Tepus M and Yau T. Non-Invasive Colorectal Cancer Screening: An Overview. *Gast Tum* 2020; 7(3): 62–73.
6. Wilson, JMG and Jungner G. Principles and practice of screening for disease. World Health Organization 1968.
7. Huang JL, Fang Y, Liang M, et al. Approaching the Hard-to-Reach in Organized Colorectal Cancer Screening: an Overview of Individual, Provider and System Level Coping Strategies. *AIMS Pub Health* 2017; 4(3): 289-300.
8. Mayhand, KN, Handorg EA, Gonzalez ET, et al. Effect of Neighborhood and Individual-Level Socioeconomic Factors on Colorectal Cancer Screening Adherence. *Int J Environ* 2021; 18(9): 4398.
9. Zhu X, Parks PD, Weiser E, et al. Barriers to utilization of three colorectal cancer screening options – Data from a national survey. *Prev Med Rep* 2021; 24.
10. Ferrari A, Neefs, I, Hoeck, S, et al. Towards Novel Non-Invasive Colorectal Cancer Screening Methods: A Comprehensive Review. *Cancers*, 13(8), p.1820.
11. Ghanouni, A, Smith, SG, Halligan S, et al. Public perceptions and preferences for CT colonography or colonoscopy in colorectal cancer screening. *Patient Educ Couns* 2012; 89(1): 116-121.
12. Lin OS, Kozarek RA, Gluck M et al. Preference for Colonoscopy Versus Computerized Tomographic Colonography: A Systematic Review and Meta-analysis of Observational Studies. *J Gen Intern Med* 2012; 27(10): 1349-1360.
13. Khalid-de Bakker C, Jonkers, D, Smits, K, et al. Participation in colorectal cancer screening trials after first-time invitation: a systematic review. *Endoscopy* 2011; 43(12): 1059–1086.
14. Zhu H, Li F, Tao K, et al. Comparison of the participation rate between CT colonography and colonoscopy in screening population: a systematic review and meta-analysis of randomized controlled trials. *Br J Radiol* 2020; 93 (1105).

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an Updated Guideline for Reporting Systematic Reviews. *BMJ* 2021; 372(71).
16. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan — a web and mobile app for systematic reviews. *Systematic Reviews* 2016; 5(210).
17. Popay J, Roberts H, Sowden A et al. *Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC Methods Programme*. Lancaster, UK: University of Lancaster, 2006.
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366(4898).
19. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355(4919).
20. Scott RG, Edwards JT, Fritschi L, et al. Community-Based Screening by Colonoscopy or Computed Tomographic Colonography in Asymptomatic Average-Risk Subjects. *Am J Gastroenterol* 2004; 99(6): 1145-1151.
21. Forbes GM, Mendelson RM, Edwards JT, et al. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. *Med J Aust* 2006; 184(11): 546-550.
22. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol* 2012; 13(1): 55–64.
23. You JJ, Liu Y, Kirby J, et al. Virtual colonoscopy, optical colonoscopy, or fecal occult blood testing for colorectal cancer screening: results of a pilot randomized controlled trial. *Trials* 2015; 16(1).
24. Sali L, Mascialchi M, Falchini M, et al. Reduced and Full-Preparation CT Colonography, Fecal Immunochemical Test, and Colonoscopy for Population Screening of Colorectal Cancer: A Randomized Trial. *J NCI* 2015; 108(2).
25. Kirkøyen B, Berstad P, Botteri E, et al. Acceptability of two colorectal cancer screening tests: pain as a key determinant in sigmoidoscopy. *Endoscopy* 2017; 49(11): 1075–1086.
26. Segnan N, Senore C, Andreoni B, et al. Comparing Attendance and Detection Rate of Colonoscopy With Sigmoidoscopy and FIT for Colorectal Cancer Screening. *Gastroenterology* 2007; 132(7): 2304–2312.
27. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2009; 59(01): 62–68.
28. Randel KR, Schult AL, Botteri E, et al. Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. *Gastroenterology* 2021; 160(4): 1085-1096.

29. Symonds EL, Hughes D, Flight I, et al. Woodman R, Chen G, Ratcliffe J, et al. A Randomized Controlled Trial Testing Provision of Fecal and Blood Test Options on Participation for Colorectal Cancer Screening. *Cancer Prev Res* 2019; 12(9): 631–640.
30. Young GP, Chen G, Wilson CJ, et al. “Rescue” of Nonparticipants in Colorectal Cancer Screening: A Randomized Controlled Trial of Three Noninvasive Test Options. *Cancer Prev Res* 2021; 14(8): 803–810.
31. Liles EG, Coronado GD, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: A randomized trial. *Cancer Treat Res Commun* 2017; 10: 27-31.
32. Ioannou S, Sutherland K, Sussman DA, et al. Increasing uptake of colon cancer screening in a medically underserved population with the addition of blood-based testing. *BMC Cancer* 2021; 21(1).
33. Groth S, Krause H, Behrendt R, et al. Capsule colonoscopy increases uptake of colorectal cancer screening. *BMC Gastroenterol* 2012; 12(1).
34. de Wijkerslooth TR, de Haan MC, Stoop EM, et al. Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening programme: randomised controlled trial. *Gut* 2011; 61(11): 1552–1559.
35. Gareen I, Siewert B, Vanness D, et al. Patient willingness for repeat screening and preference for CT colonography and optical colonoscopy in ACRIN 6664: the National CT Colonography trial. *Patient Prefer Adherence* 2015; 9: 1043-1051.
36. Nicholson FB and Korman MG. Acceptance of flexible sigmoidoscopy and colonoscopy for screening and surveillance in colorectal cancer prevention. *J Med Screen* 2005; 12(2): 89–95.
37. Senore C, Correale L, Regge D, et al. Flexible Sigmoidoscopy and CT Colonography Screening: Patients’ Experience with and Factors for Undergoing Screening - Insight from the Proteus Colon Trial. *Radiology* 2018; 286(3): 873–83.
38. Pickhardt PJ, Choi JR, Hwang I, et al. Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults. *NEJM* 2003; 349(23): 2191–2200.
39. Hol L, de Jonge V, van Leerdam ME, et al. Screening for colorectal cancer: Comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. *EJC* 2010; 46(11): 2059–2066.
40. Voska M, Zavoral M, Grega T, et al. Accuracy of Colon Capsule Endoscopy for Colorectal Neoplasia Detection in Individuals Referred for a Screening Colonoscopy. *Gastroenterol Res Pract* 2019; 1-8.
41. Stracci F, Zorzi M and Grazzini G. Colorectal Cancer Screening: Tests, Strategies, and Perspectives. *Public Health Front* 2014; 2.
42. Koo S, Neilson LJ, Von Wagner C, et al. The NHS Bowel Cancer Screening Program: current perspectives on strategies for improvement. *Risk Manag Healthc Policy* 2017; 10: 177-187.

43. Mutneja H, Agrawal R, Bhurwal A, et al. Comparative Effectiveness of Fecal Immunochemical Tests versus Flexible Sigmoidoscopy for Colorectal Cancer Screening: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *JGLD* 2021; 30(2): 267-273.
44. Deding U, Valdivia PC, Koulaouzidis A, et al. Patient-Reported Outcomes and Preferences for Colon Capsule Endoscopy and Colonoscopy: A Systematic Review with Meta-Analysis. *Diagnostics* 2021; 11(9):1730.
45. Cash BD, Fleisher MR, Fern S, et al. Multicentre, prospective, randomised study comparing the diagnostic yield of colon capsule endoscopy versus CT colonography in a screening population (the TOPAZ study). *Gut* 2020; 70 (11): 2115–2122.
46. Zhu X, Parks PD, Weiser E, et al. National Survey of Patient Factors Associated with Colorectal Cancer Screening Preferences. *Cancer Prev Res* 2021; 14(5): 603–614.
47. Wolf RL, Basch CE, Zybert P, et al. Patient Test Preference for Colorectal Cancer Screening and Screening Uptake in an Insured Urban Minority Population. *J Community Health* 2015; 41(3), 502–508.