OHSU Health System
Office of Clinical Integration and Evidence-Based Practice
Colorectal Cancer Screening
Evidence Summary

Date started: April 2017
Date completed: October 2017

Content Expert Team Members:

Tara Bergeron, MSN, Quality Improvement Coordinator, Tuality Health Alliance
Mike Doorly, MD, General and Colorectal Surgery, Tuality Healthcare
Alice Fung, MD, Radiolgy/Diagnostic Imaging, OHSU
Daniel Herzig, MD, General Surgery, OHSU
Alan Hodgson, BS, Clinical Reporting, OHSU
Vicki Jakovec, MSN, Nursing, OHSU
Steven Kassakian, MD, Internal Medicine/Informatics, OHSU
Jeremy Lake, MD, Gastroenterology Tuality Healthcare
Mark Lovgren, Patient Representative
David Lieberman, MD, Gastroenterology, OHSU
Christine Mullowney, MD, Family Medicine, OHSU
Lisa Newman, BSN, Nursing, OHSU
Paola Paz, MSN, Quality Improvement Coordinator, Tuality Health Alliance
Moira Ray, MD, MPH, Family Medicine, OHSU
Bruin Rugge, MD, MPH, Family Medicine, OHSU
Mick Scanlan, MD, Pathology
Cheri Warren, MS, Clinical Informatics, OHSU
Daisuke Yamashita, MD, MPH, Family Medicine, OHSU

Office of Clinical Integration and Evidence-Based Practice Team:

Elizabeth Crabtree, PhD, MPH, Director of Clinical Integration and EBP
Marcy Hager, MA, EBP Program Manager
Andrew Hamilton, MS/MLS, Liaison Librarian
Stephanie Halvorson, MD, Clinical Integration Medical Director/Hospital Medicine
Tovah Kohl, MA, EBP Program Manager

Objective for the Review: To critically review the evidence on screening for colorectal cancer in adult patients

Definitions:

Average Risk: Non-African American patients aged 50 years or older with no personal history of CRC or adenomas, no inflammatory bowel disease, and with a negative first-degree family history for CRC.
Increased Risk: African American patients or patients with a personal or first-degree family history of CRC or advanced adenomas, or patients with inflammatory bowel disease.

Review Preparation:

In asymptomatic populations at general risk of CRC

1. What is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?
2. What are the test performance characteristics (e.g., sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Do test performance characteristics vary by important subpopulations?
3. a) What are the adverse effects (i.e., serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (e.g., age)?
4. Does using shared decision-making when determining appropriate screening test increase the rate of completed CRC screens compared to a LIP prescribed test?
5. What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?
6. What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

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7. In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Quality Measures:

Outcome

- Patient satisfaction with CRC screening

Process

- Percentage of patients aged 50-75 years who had appropriate screening for colorectal cancer
- Percentage of patients aged 50-75 years receiving a screening colonoscopy without biopsy or polypectomy and with an adequate prep who had a recommended follow-up -interval of 10 years for repeat colonoscopy documented in their colonoscopy report
- Percentage follow-up for positive screenings for other modalities
- Percentage of patients ≥ 50 years old with ≥ 1 conventional adenoma or sessile serrated polyp or colorectal cancer detected during screening colonoscopy
- Percentage of patients ≥ 18 years old receiving a surveillance colonoscopy, with a history of a prior adenomatous polyp(s) in previous colonoscopy findings, who had an interval of ≥ 3 years since their last colonoscopy
- Utilization of shared decision making tool
- Utilization of clinical scoring system
- Positive test referrals received

Colorectal Cancer Screening
Existing External Guidelines/Pathways/Order Sets

Existing External Guidelines

External Guideline	Organization and Author	Last Update
Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer	U.S. Multi-Society Task Force	2017
National Comprehensive Cancer Network Colorectal Cancer Guidelines	National Comprehensive Cancer Network	2017
Colorectal Cancer: Screening	US Preventative Services Task Force	2016
Colorectal Cancer	Canadian Task Force on Preventative Health Care	2016
Colorectal Cancer Screening	American College of Radiology	2013
Colorectal Cancer Screening	American College of Physicians	2012
American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	American College of Gastroenterology	2008

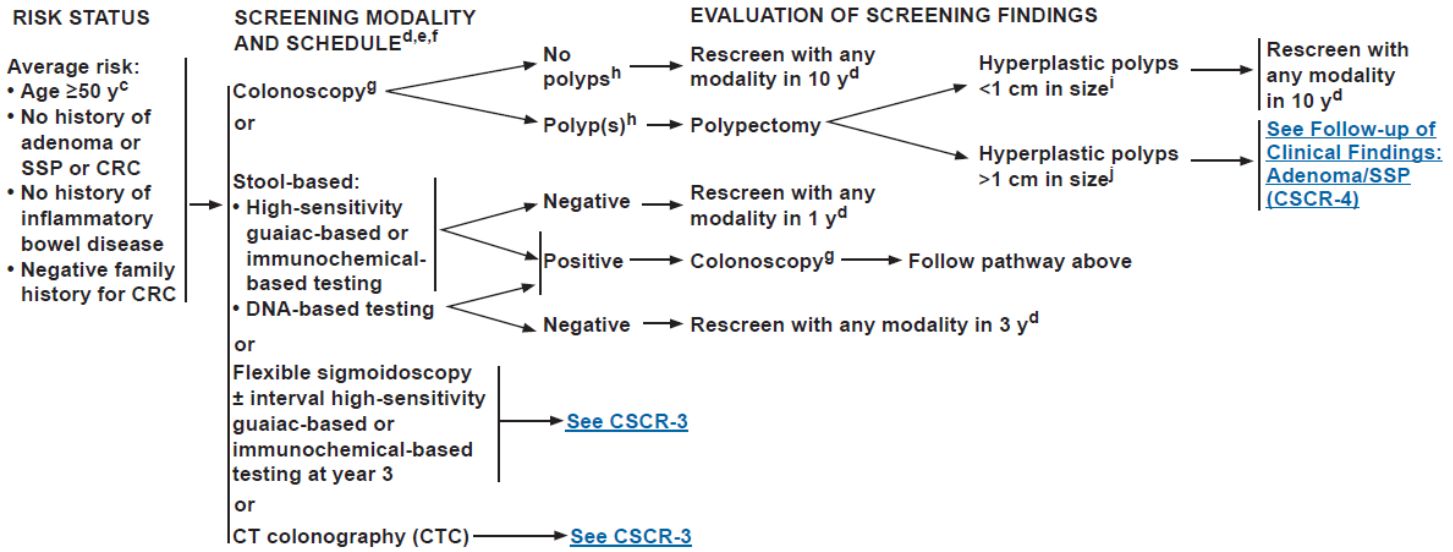
The seven published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale.** The scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

Guideline Issuer	MSTF 2017	NCCN 2017	USPSTF 2016	CTF 2016	ACR 2013	ACP 2012	ACG 2008
1. Transparency	A	B	A	A	C	B	B
2. Conflict of interest	B	NR	A	A	NR	A	NR
3. Development group	C	C	A	NR	B	B	C
4. Systematic Review	A	B	A	A	B	B	B
5. Supporting evidence	A	C	A	A	C	B	A

6. Recommendations	A	C	A	A	C	B	A
7. External Review	B	NR	A	A	NR	B	NR
8. Currency and updates	B	B	A	B	B	B	C

See appendix B for full description of the Trustworthy Guideline grading system.

External Guideline	Screening Recommendations
Multi-Society Task Force 2017	• Recommend that clinicians offer CRC screening beginning at age 50 (strong recommendation, high-quality evidence). • Suggest that sequential offers of screening tests, offering multiple screening options, and risk-stratified screening are all reasonable approaches to offering screening (weak recommendation, low-quality evidence). **Table 4. Multi-Society Task Force ranking of current colorectal cancer screening tests** Tier 1 Colonoscopy every 10 years Annual fecal immunochemical test Tier 2 CT colonography every 5 years FIT-fecal DNA every 3 years Flexible sigmoidoscopy every 10 years (or every 5 years) Tier 3 Capsule colonoscopy every 5 years Available tests not currently recommended Septin 9 1. Recommends colonoscopy every 10 years or annual FIT as first-tier options for screening the average-risk persons for colorectal neoplasia (strong recommendation; moderate quality evidence).

	2. Recommends that physicians performing screening colonoscopy measure quality, including the adenoma detection rate (strong recommendation, high-quality evidence). 3. Recommends that physicians performing FIT monitor quality (strong recommendation, low-quality evidence). 4. Recommends CT colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low-quality evidence) or flexible sigmoidoscopy every 5 to 10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT. 5. Suggests that capsule colonoscopy (if available) is an appropriate screening test when patients decline colonoscopy, FIT, FIT-fecal DNA, CT colonography, and fl exible sigmoidoscopy (weak recommendation, low-quality evidence). 6. We suggest against Septin9 for CRC screening (weak recommendation, low-quality evidence).
National Comprehensive Cancer Network 2017	 - CRC screening is recommended in adults aged 50 – 75 years. Because the risk of colorectal screening increases with age, the decision to screen between ages 76-85 y should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Individuals who have not been previously screened are most likely to benefit in this age group. - Screening should be individualized and include a discussion of the risks and benefits of each modality. - If colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy within 1 year.

<table>
<tr><td>US Preventative Services Task Force 2016</td><td>
<table>
<tr><th>Population</th><th>Recommendation</th><th>Grade
(What's This?)</th></tr>
<tr><td>Adults aged 50 to 75 years</td><td>The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years.
The risks and benefits of different screening methods vary. See the Clinical Considerations section and the Table for details about screening strategies.</td><td>A</td></tr>
<tr><td>Adults aged 76 to 85 years</td><td>The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history.
• Adults in this age group who have never been screened for colorectal cancer are more likely to benefit.
• Screening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy.</td><td>C</td></tr>
</table>
</td></tr>
<tr><td>Canadian Task Force on Preventative Health Care 2016</td><td>• Recommend screening adults aged 60 to 74 for CRC with FOBT (either gFOBT or FIT) every two years OR flexible sigmoidoscopy every 10 years.
(Strong recommendation; moderate quality evidence)
• Recommend screening adults aged 50 to 59 for CRC with FOBT (either gFOBT or FIT) every two years OR flexible sigmoidoscopy every 10 years.
(Weak recommendation; moderate quality evidence)
• Recommend not screening adults aged 75 years and over for CRC.
(Weak recommendation; low quality evidence)
• Recommend not using colonoscopy as a screening test for CRC.
(Weak recommendation; low quality evidence)</td></tr>
<tr><td>American College of Radiology 2013</td><td>ACR's guideline focuses on nonradiologic tests for colorectal cancer screening. Overall, the most appropriate imaging test for colorectal cancer screening is CTC. However, CTC expertise may not be available in all geographic areas. Thus, a Double-Contrast Barium Enema (DCBE) may be the only imaging option in a particular area, despite its lower performance profile. The choice between these 2 tests may ultimately depend on local imaging expertise and on physician and patient preference.

Summary
• CTC has emerged as the leading imaging technique for colorectal cancer screening.
• DCBE remains an imaging test that may be appropriate for colorectal cancer screening, particularly when CTC is not available.
• CTC is the preferred test following an incomplete optical colonoscopy.
• Imaging tests including CTC and barium enema are usually not appropriate for colorectal cancer screening in high-risk patients with hereditary nonpolyposis colorectal cancer and inflammatory bowel disease.</td></tr>
<tr><td>American College of Physicians 2012</td><td>• Guidance Statement 1:
ACP recommends that clinicians perform individualized assessment of risk for colorectal cancer in all adults.</td></tr>
</table>

	• **Guidance Statement 2:** ACP recommends that clinicians screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer. • **Guidance Statement 3:** ACP recommends using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy as a screening test in patients who are at average risk. ACP recommends using optical colonoscopy as a screening test in patients who are at high risk. Clinicians should select the test based on the benefits and harms of the screening test, availability of the screening test, and patient preferences. • **Guidance Statement 4:** ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.
American College of Gastroenterology 2008	**CRC Screening Recommendations** Preferred CRC screening recommendations • Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1 B) Screening should begin at age 45 years in African Americans (Grade 2 C) • Cancer detection test. This test should be offered to patients who decline colonoscopy or another prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1 B) Alternative CRC prevention tests • Flexible sigmoidoscopy every 5-10 years (Grade 2 B) • CT colonography every 5 years (Grade 1 C) Alternative cancer detection tests • Annual Hemoccult Sensa (Grade 1 B) • Fecal DNA testing every 3 years (Grade 2 B) Recommendations for screening when family history is positive but evaluation for HNPCC considered not indicated • Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥ 60 years Recommended screening: same as average risk (Grade 2 B) • Single first-degree with CRC or advanced adenoma diagnosed at age < 60 years or two first-degree relatives with CRC or advanced adenomas. Recommended screening: colonoscopy every 5 years beginning at age 40 years or 10 years younger than age at diagnosis of the youngest affected relative (Grade 2 B) FAP • Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counseling and genetic testing, if they have siblings or children who could potentially benefit from this testing (Grade 2 B) • Patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed) should undergo annual flexible sigmoidoscopy or colonoscopy, as appropriate, until such time as colectomy is deemed by physician and patient as the best treatment (Grade 2 B) • Patients with retained rectum after subtotal colectomy should undergo flexible sigmoidoscopy every 6 – 12 months (Grade 2 B) • Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MYH associated polyposis (Grade 2 C) HNPCC • Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumor or a family member's tumor and/or tumor immunohistochemical staining for mismatch repair proteins (Grade 2 B) • Patients with positive tests can be offered genetic testing. Those with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at age 20 – 25 years, until age 40 years, then annually thereafter (Grade 2 B)

Adverse Effects Guideline Recommendations:

The 2016 United States Preventive Service Task Force states the rate of serious adverse events from colorectal cancer screening increases with age. The harms of screening for colorectal cancer in adults aged 50 to 75 years is small. Thus, the harms of screening for colorectal cancer in adults 76 years and older are small to moderate.

Level of Evidence for recommendations not provided

The 2013 American College of Radiology stated that potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination.

Level of Evidence for recommendations not provided

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢ ☢	0.1-1 mSv	0.03-0.3 mSv
☢ ☢ ☢	1-10 mSv	0.3-3 mSv
☢ ☢ ☢ ☢	10-30 mSv	3-10 mSv
☢ ☢ ☢ ☢ ☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Shared Decision-Making Guideline Recommendations:

The **2017 Multi-Society Task Force** suggests three approaches to offering screening: (1) Multiple Options; (2) Sequential Testing; and (3) Risk stratified approach. When using the multiple option approach with patients, MSTF suggested limited to 2 to 3 preferred options. If patients decline all the offered options, 1 or more of the other options can be offered.

Weak Recommendation, low-quality evidence

Table 1. Approaches to offering screening in the opportunistic setting

Approach	Description
Multiple options	The relative benefits, risks, and costs of 2 or more options are presented
Sequential testing	A preferred test is offered first. If the patients decline another option(s) is offered
Risk stratified approach	Colonoscopy is offered to patients predicted to have a high prevalence of advanced pre-cancerous lesions; other tests are offered to patients predicted at low risk

The 2016 United States Preventive Services Task Force states clinicians should consider engaging patients in informed decision making about the screening strategy that would most likely result in completion, with high adherence over time, taking into consideration both the patient's preferences and local availability.
Level of Evidence for recommendations not provided

Cost-Effectiveness Guideline Recommendations:

The 2017 Multi-Society Task Force cited evidence that colorectal cancer screening by any available modality is cost-effective compared with no screening and in some models screening results in cost savings.
Level of Evidence for recommendations not provided

The 2016 United States Preventive Services Task Force does not consider the costs of providing a service in this assessment.
Level of Evidence for recommendations not provided

The 2013 American College of Radiology demonstrated in a cost-effective analysis that a double-contrast barium enema (DCBE) performed every 5 – 10 years costs less than $22,000 per life-year saved for a possible range of natural history.
Level of Evidence for recommendations not provided

High-Risk Patients Guideline Recommendations:

The 2017 Multi-Society Task Force:

For patients with family history of colorectal cancer and polyps:

- Suggests that persons with 1 first-degree relative with CRC or a documented advanced adenoma diagnosed at age <60 years or with 2 first-degree relatives with CRC and/or documented advanced adenomas undergo colonoscopy every 5 years beginning 10 years younger than the age at which the youngest first-degree relative was diagnosed or age 40, whichever is earlier (weak recommendation, low-quality evidence).
- Suggests that persons with 1 first-degree relative diagnosed with CRC or a documented advanced adenoma at age ≥60 years begin screening at age 40. The options for screening and the recommended intervals are the same as those for average-risk persons (weak recommendation, very-low quality evidence).
- Suggests that persons with 1 or more first-degree relatives with a documented advanced serrated lesion (SSP or traditional serrated adenoma ≥10 mm in size or an SSP with cytologic dysplasia) should be screened according to above recommendations for persons with a family history of a documented advanced adenoma (weak recommendation, very-low-quality evidence).
- Recommends that persons with 1 or more first-degree relatives with CRC or documented advanced adenomas, for whom we recommend colonoscopy, should be offered annual FIT if they decline colonoscopy (strong recommendation, moderate-quality evidence).

Patient considerations regarding age and colorectal cancer risk:

- Recommends that screening begin in non-African American average-risk persons at age 50 years (strong recommendation; moderate-quality evidence).
- Suggests that screening begin in African Americans at age 45 years (weak recommendation, very-low-quality evidence).
- Recommends that adults age <50 years with colorectal bleeding symptoms (hematochezia, unexplained iron deficiency anemia, melena with a negative upper endoscopy) undergo colonoscopy or an evaluation sufficient to determine a bleeding cause, initiate treatment, and complete follow-up to determine resolution of bleeding (strong recommendation, moderate-quality evidence).
- Suggests that persons who are up to date with screening and have negative prior screening tests, particularly colonoscopy, consider stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence).
- Recommends considering stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence).
- Suggests that persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities (weak recommendation, low-quality evidence).

The 2016 United States Preventive Services Task Force recommendations applies to all racial/ethnic groups, with the clear acknowledgement that efforts are needed to ensure that at-risk populations receive recommended screening, follow-up, and treatment.

Level of Evidence for recommendations not provided

The 2009 American College of Gastroenterology stated:

- Screening is recommended in African Americans beginning at age 45 years. (Grade 2 C)
- A family history of only small tubular adenomas in first degree relatives is not considered to increase the risk of CRC. (Level of Evidence for recommendation not provided)
- Individuals with a single first-degree relative with CRC or advanced adenomas diagnosed at age >/= 60 years can be screened like average-risk persons. (Level of Evidence for recommendation not provided)

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	PICO Questions 1, 2, 3, 4, 5, 6, 7: See Appendix C
Years Searched - All Questions	PICO Questions 1, 2, 3: January 2015 – May 2017; PICO Questions 4,5,6,7: 2002 – May 2017
Language	English
Age of Subjects	Adults, >/= 18 years

Evidence Found with Searches

Check type of evidence found	Summary of Evidence – All Questions	Number of articles obtained
☒	Systematic reviews/Meta-analysis	16
☒	Randomized controlled trials	3
☒	Non-randomized studies	66
☒	Government/State agency regulations	2
☒	Professional organization guidelines/white papers, etc.	5

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. For more detailed information, see Appendix A.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
CONDITIONAL	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Question #1: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Primary Literature:

USPSTF 2016 Systematic Review Findings:

Overall Summary of Impact of Screening on Colorectal Cancer Incidence and Mortality

Screening test (total #studies, design) (Sample n)		# rounds	CRC incidence	f/u	CRC mortality	f/u
Screening versus no screening	Colonoscopy (k=1, cohort) (n=88,902)	1	*Total* w/polypectomy HR, adj: 0.53 (95% CI, 0.40 to 0.71)* negative colo HR, adj: 0.47 (95% CI, 0.39 to 0.57)* *Distal* w/polypectomy HR, adj: 0.37 (95% CI, 0.23 to 0.61)* negative colo HR, adj: 0.29 (95% CI, 0.21 to 0.39)* *Proximal* w/polypectomy HR, adj: 0.79 (95% CI, 0.52 to 1.19)* negative colo HR, adj: 0.29 (95% CI, 0.21 to 0.39)*	22y	*Total* HR, adj: 0.32 (95% CI, 0.24 to 0.45)* *Distal* HR, adj: 0.18 (95% CI, 0.10 to 0.31)* *Proximal* HR, adj: 0.47 (95% CI, 0.29 to 0.76)†	24 y
	FS (k=4, RCT) (n=458,002)	1-2 Q3-5y	*Total* IRR 0.79 (95% CI, 0.75 to 0.85) *Distal* IRR 0.71 (95% CI, 0.64 to 0.82) *Proximal* IRR 0.92 (95% CI, 0.84 to 1.02)	11-12y	*Total* IRR 0.73 (95% CI, 0.66 to 0.82) *Distal* IRR 0.63 (95% CI, 0.49 to 0.84) *Proximal* IRR 0.90 (95% CI, 0.77 to 1.04)	11-12y
	Hemoccult II (k=5, RCT) (n=404,396)	2-9 Q2y	*Total* RR range from 0.90 (95% CI, 0.77 to 1.04) from 1.02 (95% CI, 0.93 to 1.12) *Distal* NR *Proximal* NR	11-28y	*Total* RR range from 0.78 (95% CI, 0.65, 0.93) to 0.91 (95% CI, 0.84, 0.98)‡ *Distal* NR *Proximal* NR	11-30y

* Adjusted for: age, BMI, family history, smoking status, physical activity, diet, vitamin use, aspirin use, NSAID use, cholesterol-lowering drug use, hormone replacement therapy
‡ Annual RR from one trial only 0.68 (0.56, 0.82), 11 rounds, q1y, 30 y follow-up

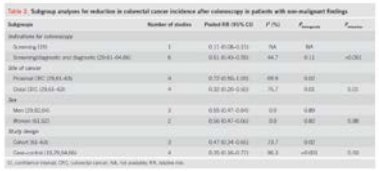
Abbreviations: adj = adjusted; CI = confidence interval; f/u = followup; HR = hazard ratio; IRR = incidence rate ratio; k = number of studies; n = number; NR = not reported; Q = interval; RCT = randomized controlled trial; RR = relative risk; w/ = with; y = years

Overall Summary of Effectiveness of Screening on CRC Mortality

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ1: Effectiveness of screening on CRC mortality	Colonoscopy	k=1 n=88,902 Prospective cohort	After 24 years, CRC specific mortality was lower in persons with self-reported screening colonoscopy (multivariate adjusted HR, 0.32 [95% CI, 0.24-0.45]) compared to those who had never had screening endoscopy. Mortality benefit observed for both proximal and distal CRC.	Single study. No reporting bias.	Fair	Fair- cohort limited to health professionals
	FS	k=4 n=458,002 RCT	FS consistently decreased CRC-specific mortality compared to no screening at 11 to 12 years of followup (IRR, 0.73 [95% CI, 0.66-0.82]). Only 1 trial, PLCO, evaluated more than 1 round of screening. Mortality benefit is limited to distal CRC.	Variation in referral criteria led to differing rates of followup colonoscopy. No reporting bias.	Fair to good	Fair to poor- no longer widely used in US
	gFOBT	k=5 n=419,966 RCT‡	Biennial screening with Hemoccult II compared to no screening (n=404,396) consistently resulted in reduction of CRC-specific mortality, ranging from 9 to 22 percentage points after 2 to 9 rounds of screening with 11 to 30 years of followup (RR, 0.91 [95% CI, 0.84-0.98] at 19.5 years to RR, 0.78 [95% CI, 0.65-0.93] at 30 years).	Variation in number of screening rounds, use of rehydrated samples, definition of "test positive," and recommended diagnostic followup. No reporting bias.	Fair to good	Poor- Hemoccult II no longer widely used
	Comparative effectiveness	k=12 n=94,526 RCT k=3 n=346,494 Prospective cohort	Trials comparing different screening tests do not provide evidence of comparative benefit in CRC incidence or mortality outcomes.	Studies are not designed to assess screening impact on mortality; limited to a single round of screening, low number of cancers detected, and few interval cancers reported.	Poor to fair	Not applicable

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Incidence; **Modality:** Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 4 # of Systematic Reviews: 3 # of RCTs: 0 # of Non-Randomized Studies: 1 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	0 RCTs	No RCTs that met inclusion criteria for the benefits of CRC screening using colonoscopy	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Pan, J., et al, 2016, *American Journal of Gastroenterology*	To evaluate the magnitude of protection against CRC by colonoscopy, with screening and diagnostic indications, in patients with non-malignant findings and further determine the potentially more marked effect of screening over diagnostic colonoscopy in the magnitude or	Systematic Review with meta-analysis	11 observational studies were included in analysis, 5 were cohort studies, 3 prospective and 2 retrospective and 6 were case–control studies. A total of 1,499,521 individuals included, 1,296,605 in the morality meta-analysis	Pooled analysis showed that colonoscopy was associated with a 61% RR reduction in CRC incidence (RR: 0.39; 95% CI: 0.26–0.60; I 2 =93.6%), in patients with non-malignant findings, although there was high heterogeneity for the outcome of CRC incidence. 	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low

	reductions in CRC incidence					
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy	Systematic Review with meta-analysis	2 Systematic Reviews, 2 Prospective Studies, 3 Case-Controlled Studies		Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	
Samadder, N.J., et al, 2016, *Clinical Gastroenterology & Hepatology*	To examine whether exposure to colonoscopy decreases the odds of CRC incidence in Utah	Case-control study; Utah residents, 54 to 90 years old, who received a CRC diagnosis from 2000 through 2010 (cases) were included in analysis. Age- and sex-matched controls with no history of CRC (controls) were selected for each case. We determined receipt of colonoscopy 6 months to 10 years before the reference date for each case and control through administrative claims data. Colonoscopy exposure was compared by using conditional logistic regression	In a database with more than 7.2 million unique individuals, 5,128 cases and 20,512 controls were found and 741 cases (14%) and 5715 controls (28%) received a colonoscopy	Exposure to colonoscopy reduced the odds for a diagnosis of CRC; the odds ratios (ORs) were 0.41 for any CRC (95% confidence interval [CI], 0.38-0.44), 0.58 for proximal colon cancer (95% CI, 0.51-0.65), and 0.29 for distal colon or rectal cancer (95% CI, 0.25-0.33). This finding was consistent among sexes, age groups, and cancer stages.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Pan, J., et al. (2016). "Colonoscopy Reduces Colorectal Cancer Incidence and Mortality in Patients With Non-Malignant Findings: A Meta-Analysis." American Journal of Gastroenterology 111(3): 355-365.
3. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.
4. Samadder, N. J., et al. (2016). "Risk of Incident Colorectal Cancer and Death After Colonoscopy: A Population-based Study in Utah." Clinical Gastroenterology & Hepatology 14(2): 279-286.e271-272.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Incidence; **Modality:** Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 3 # of Systematic Reviews: 3 # of RCTs: 0 # of Non-Randomized Studies: 0 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	3 RCTS; Combined sample of 243,917 (108,234 [I]; 135,683 [C]). All studies included a mixed gender population. Two studies included participants with age ranging from 55 to 64 years and one study with age ranging from 55 to 74 years.	The length of follow-up across four studies ranged from seven years to 11.9 years. There was a reduction in late stage CRC using screening with FS compared to no screen RR 0.75 (95%CI, 0.66, 0.86, I2=23%); ARR 1,733/million (1,011-2,368 fewer, NNS = 577 (95%CI, 422-989)).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies
Holme, O., 2017, *BMJ*	To compare the effectiveness of flexible sigmoidoscopy in screening for colorectal cancer by patient sex and age	Systematic Review with meta-analysis; Pooled analysis of randomised trials (the US Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO), the Italian Screening for Colon and Rectum trial (SCORE), and the Norwegian Colorectal Cancer Prevention trial (NORCCAP)).	287,928 individuals were included in the pooled analysis; 115,139 randomised to screening and 172,789 to usual care.	Screening reduced the incidence of colorectal cancer in men (relative risk 0.76; 95% confidence interval 0.70 to 0.83) and women (0.83; 0.75 to 0.92). No difference in the effect of screening was seen between men younger than 60 and those older than 60. Screening reduced the incidence of colorectal cancer in women younger than 60 (relative risk 0.71; 95% confidence interval 0.59 to 0.84), but not significantly in those aged 60 or older (0.90; 0.80 to 1.02).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☒ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

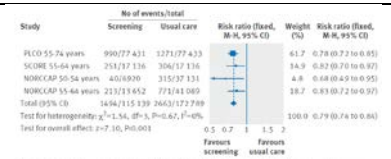
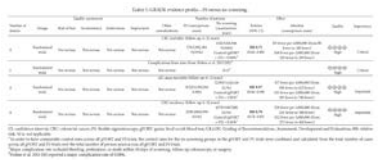
☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low

				 Fig 1 | Colorectal cancer incidence in the three trials comparing flexible sigmoidoscopy screening with usual care. Data from the NORCCAP trial are presented as two separate trials because the control: screening participants ratio was higher in the 50-54 year age group (5.4:1) than the 55-64 year age group (3:1). M-H-Mantel-Haenszel fixed effect model Table 2 | Colorectal cancer incidence and mortality in pooled analysis. Results correspond to overall analysis (50-74 years), and age (≥60 years v <60 years) and sex stratified pairwise comparisons (screening group v control group) using Mantel-Haenszel fixed effect model. P values refer to the interaction terms between age and sex from a metaregression model including age, sex, interaction term, and indicator variables for each trial (see methods section) Screening group v control group Colorectal cancer incidence (relative risk (95% CI)) — P for interaction — Colorectal cancer mortality (relative risk (95% CI)) — P for interaction Colon and rectum Both sexes* 0.79 (0.74 to 0.84) — 0.73 (0.64 to 0.83) Men† 0.76 (0.70 to 0.83) — 0.67 (0.57 to 0.80) ≥60 years‡ 0.76 (0.68 to 0.84) — 0.67 (0.55 to 0.82) <60 years§ 0.76 (0.65 to 0.88) 0.12 0.67 (0.49 to 0.91) 0.55 Women¶ 0.83 (0.75 to 0.92) — 0.82 (0.67 to 1.00) ≥60 years† 0.90 (0.80 to 1.02) — 0.88 (0.69 to 1.12) <60 years§ 0.71 (0.59 to 0.84) — 0.73 (0.53 to 1.02) Distal colon Both sexes* 0.73 (0.66 to 0.80) — 0.60 (0.49 to 0.72) Men† 0.71 (0.63 to 0.80) — 0.51 (0.40 to 0.65) ≥60 years‡ 0.72 (0.62 to 0.84) — 0.48 (0.35 to 0.64) <60 years§ 0.69 (0.56 to 0.85) 0.66 0.58 (0.38 to 0.90) 0.39 Women¶ 0.76 (0.65 to 0.88) — 0.79 (0.58 to 1.09) ≥60 years‡ 0.74 (0.61 to 0.91) — 0.85 (0.57 to 1.27) <60 years§ 0.78 (0.61 to 0.99) — 0.71 (0.42 to 1.18) Proximal colon Both sexes* 0.86 (0.79 to 0.93) — 0.87 (0.73 to 1.04) Men† 0.83 (0.73 to 0.94) — 0.89 (0.70 to 1.13) ≥60 years‡ 0.82 (0.71 to 0.95) — 0.96 (0.73 to 1.28) <60 years§ 0.84 (0.66 to 1.07) 0.04 0.71 (0.44 to 1.14) 0.63 Women¶ 0.91 (0.79 to 1.03) — 0.85 (0.66 to 1.10) ≥60 years‡ 1.03 (0.88 to 1.20) — 0.89 (0.65 to 1.21) <60 years§ 0.65 (0.50 to 0.84) — 0.79 (0.53 to 1.21) Distal colon=rectum and sigmoid, proximal colon=colon proximal to the sigmoid descending junction. *Screening group versus control group, no stratification. †Screening group versus control group, men only, no age stratification. ‡Screening group versus control group, stratification by sex, participants aged 60-74. §Screening group versus control group, stratification by sex, participants aged 50-59. ¶Screening group versus control group, women only, no age stratification.		
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of	Systematic Review with Meta-Analysis	1 Systematic Review and 4 RCTs		Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

	screening over diagnostic colonoscopy					

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Holme, O., et al. (2017). "Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials." BMJ 356: i6673.
3. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Incidence; **Modality:** Fecal Occult Blood Test (FOBT)

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	2 RCTS; Combined sample of 220,283 (110,200 [I]; 110,083[C]). These mixed gender studies included in one study participants aged 45 to 74 years and the other study aged 60 to 64 years.	The length of follow-up across both studies ranged from 9 years to 19.5 years. Screening with gFOBT compared to no screen had a pooled effect on late stage CRC of RR 0.92 (95%CI, 0.85, 0.99, I2=0%); the ARR was 1,141/million (198 fewer to 2,017 fewer). The NNS is 876 (95%CI, 496-5051) for the outcome of incidence of late stage CRC.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:

☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

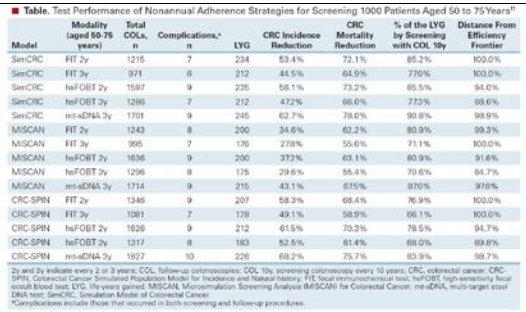
☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

						Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.

Modeling Studies Summaries			
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Outcomes*
Berger, B.M., et al., 2016, *American Journal of Managed Care*	To demonstrate that the US Preventive Services Task Force (USPSTF) modeling screening outcomes included CRC incidence reduction.	Descriptive analysis of USPSTF modeling of the clinical impact of CRC screening strategies. These scenarios involved different modalities (hsFOBT, FIT, and mt-sDNA), intervals (2y, 3y, and every 5 years), and screening age groups (50-75, 50-80, 50-85, 55-75, 55-80, and 55-85 years). All scenarios assumed 100% adherence to the screening modality and interval. Screening scenarios were plotted against life years gained (LYG) and colonoscopies performed to create an "efficiency frontier," a line connecting the most efficient screening scenarios based on the trade-off between LYG and colonoscopies. By excluding annual stool tests, we recreated CISNET's analysis of the "efficiency frontier" and compared these screening scenarios with each other and with 10y colonoscopy screening. Per CISNET, tests were recommended if they were within 98% of the LYG at the equivalent point on the efficiency frontier and generated at least 90% of the LYG generated by 10y screening colonoscopy.	 ■ **Table.** Test Performance of Nonannual Adherence Strategies for Screening 1000 Patients Aged 50 to 75 Years[a] Model | Modality (aged 50-75 years) | Total COLs, n | Complications,* n | LYG | CRC Incidence Reduction | CRC Mortality Reduction | % of the LYG by Screening with COL 10y | Distance From Efficiency Frontier SimCRC | FIT 2y | 1215 | 7 | 234 | 53.4% | 72.1% | 85.2% | 100.0% SimCRC | FIT 3y | 971 | 6 | 212 | 44.5% | 64.9% | 77.6% | 100.0% SimCRC | hsFOBT 2y | 1597 | 9 | 235 | 56.1% | 73.2% | 85.5% | 94.0% SimCRC | hsFOBT 3y | 1286 | 7 | 212 | 47.2% | 66.0% | 77.3% | 88.6% SimCRC | mt-sDNA 3y | 1701 | 9 | 245 | 62.7% | 78.0% | 90.8% | 98.9% MISCAN | FIT 2y | 1243 | 8 | 200 | 34.6% | 62.2% | 80.9% | 99.3% MISCAN | FIT 3y | 995 | 7 | 170 | 27.8% | 55.6% | 71.1% | 100.0% MISCAN | hsFOBT 2y | 1636 | 9 | 200 | 37.2% | 63.1% | 80.9% | 91.6% MISCAN | hsFOBT 3y | 1296 | 8 | 175 | 29.6% | 55.4% | 70.6% | 84.7% MISCAN | mt-sDNA 3y | 1714 | 9 | 215 | 43.1% | 67.5% | 87.6% | 97.8% CRC-SPIN | FIT 2y | 1346 | 9 | 207 | 58.3% | 68.4% | 76.9% | 100.0% CRC-SPIN | FIT 3y | 1081 | 7 | 178 | 49.1% | 58.5% | 66.1% | 100.0% CRC-SPIN | hsFOBT 2y | 1628 | 9 | 212 | 61.5% | 70.3% | 78.5% | 94.7% CRC-SPIN | hsFOBT 3y | 1317 | 8 | 183 | 52.5% | 61.4% | 68.0% | 89.8% CRC-SPIN | mt-sDNA 3y | 1827 | 10 | 226 | 68.2% | 75.7% | 83.9% | 98.7% 2y and 3y indicate every 2 or 3 years; COL, follow-up colonoscopies; COL 10y, screening colonoscopy every 10 years; CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FIT, fecal immunochemical test; hsFOBT, high-sensitivity fecal occult blood test; LYG, life-years gained; MISCAN, Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer; mt-sDNA, multi-target stool DNA test; SimCRC, Simulation Model of Colorectal Cancer. *Complications include those that occurred in both screening and follow-up procedures.
Brenner, 2015, _*Clinical Gastroenterology & Hepatology*	To quantify screening colonoscopy effects on prevention, early detection, and over diagnosis of CRC in the 10 years since it was introduced in Germany	Analyzed data from more than 4.4 million screening colonoscopies (conducted on individuals 55-79 years old from 2003 through 2012) available through the national screening colonoscopy registry. CRCs prevented, detected earlier than they would have been without screening, and overdiagnosed (cancers detected at screening colonoscopy that would not have become clinically manifest during the patient's lifetime) were estimated by Markov models. Model parameters included sex-specific and age-specific findings at screening colonoscopy; mortality; rates of	Overall, approximately 180,000 CRCs (1/28 screening colonoscopies) were estimated to have been prevented, and more than 40,000 CRCs (1/121 screening colonoscopies) were detected earlier than they would have been without screening, compared with approximately 4,500 overdiagnoses (1/1089 screening colonoscopies). Almost all CRCs prevented or detected earlier than they would have been without screening resulted from screening colonoscopies performed on individuals up to 75 years old (97% and 89%, respectively),

		transition from nonadvanced to advanced adenoma, advanced adenoma to preclinical cancer, or preclinical cancer to clinically manifest cancer; and protection from screening colonoscopy. 4.4 million screenings, records from almost 2 million men and more than 2.4 million women were included in the database. Slightly more than half of them were between 55 and 64 years of age; only a minority of approximately 2.5% were 80 years or older.	whereas 28% of overdiagnoses occurred from screening colonoscopies of individuals older than 75 years old.
Geurts, S.M., et al., 2015, *British Journal of Cancer*	To project the impact of phasing once-only flexible sigmoidoscopy (FS) at age 55 into the England National Health Service Bowel Screening Programme (NHSBCSP), augmenting biennial gFOBT at ages 60-74, on CRC cases and deaths prevented in England by mid-2030.	Simulated the life-course of English residents reaching age 55 from 2013 onwards. Model inputs included population numbers, invitation rates and CRC incidence and mortality rates. The impact of gFOBT and FS alone on CRC incidence and mortality were derived from published trials, assuming an uptake of 50% for FS and 57% for gFOBT. For FS plus gFOBT, we assumed the gFOBT effect to be 75% of the gFOBT alone impact.	By mid-2030, 8.5 million individuals will have been invited for once-only FS screening. Adding FS to gFOBT screening is estimated to prevent an extra 9,627 (10%) cases by mid-2030. If FS uptake is 38% or 71%, respectively, an extra 7,379 (8%) or 13,689 (15%) cases by mid-2030.
Jeon, J., et al., 2015, *Cancer Causes & Control*	To compute the incremental benefit of colonoscopy over flexible sigmoidoscopy (FSG) using a validated mathematical model, which reflects colorectal neoplasia growth characteristics while allowing uncertainty in endoscopic detection and removal of adenomas.	Calibrated models of CRC incidence within a multistage clonal expansion framework to data from: (1) San Francisco-Oakland SEER registry (reference population) and (2) FSG long-term follow-up data from 50,757 individuals after a negative FSG in the Kaiser Permanente system. Then compared the residual CRC risks after FSG with full-length colonoscopy.	Model mirrored trial data with 10-year CRC risk reductions after FSG screening at age 50 years of approximately one-third; the optimal age for a 'once-only' FSG exam was between ages 50 and 60 years; and the greater benefit was for men compared with women. There were considerable incremental gains in reduction in CRC risk by colonoscopy compared with FSG with the greatest benefit for screening colonoscopy at age 50 years.
Wang, Y.R., et al, 2016, *Digestion*	To determine whether colonoscopy use is associated with a decreased risk of CRC in patients 76-85 years old in the United States.	5,701 patients were identified in the Medicare by pulling a 5% random sample of the Surveillance, Epidemiology and End Results-Medicare linked database 76-85 years old at outpatient colonoscopy between January 1, 1998 and December 31, 2002. Using the Kaplan-Meier method, the cumulative incidence of CRC was estimated in the above-mentioned colonoscopy group and compared with the control group of patients without colonoscopy. All patients were followed until diagnosis of CRC or carcinoma in situ, death or December 31, 2005. The multivariate Cox proportional hazards model was used in statistical analysis.	Of 5,701 patients in the colonoscopy group, 37 (0.65%) patients were diagnosed with CRC, compared to 379 (1.55%) out of 24,437 patients in the control group ($p < 0.001$). The cumulative incidences of CRC were lower in the colonoscopy group compared to those in the control group (5-year distal CRC: 0.26 vs. 0.77%; 5-year proximal CRC: 0.43 vs. 0.79%, both $p < 0.05$). In multivariate Cox regression, colonoscopy was associated with decreased risk of all CRC (hazard ratio ((HR) 0.42, 95% CI 0.28-0.65), distal CRC (HR 0.36, 95% CI 0.18-0.70), and proximal CRC (HR 0.53, 95% CI 0.30-0.92)).

References:

1. Berger, B. M., et al. (2016). "USPSTF colorectal cancer screening guidelines: an extended look at multi-year interval testing." American Journal of Managed Care 22(2): e77-81.
2. Brenner, H., et al. (2015). "Prevention, early detection, and overdiagnosis of colorectal cancer within 10 years of screening colonoscopy in Germany." Clinical Gastroenterology & Hepatology 13(4): 717-723.
3. Geurts, S. M., et al. (2015). "Likely effect of adding flexible sigmoidoscopy to the English NHS Bowel Cancer Screening Programme: impact on colorectal cancer cases and deaths." British Journal of Cancer 113(1): 142-149.
4. Jeon, J., et al. (2015). "Incremental benefits of screening colonoscopy over sigmoidoscopy in average-risk populations: a model-driven analysis." Cancer Causes & Control 26(6): 859-870.
5. Wang, Y. R., et al. (2016). "Decreased Risk of Colorectal Cancer after Colonoscopy in Patients 76-85 Years Old in the United States." Digestion 93(2): 132-138.

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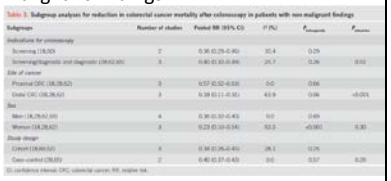
Outcome: Mortality; **Modality:** Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 4 # of Systematic Reviews: 3 # of RCTs: 0 # of Non-Randomized Studies: 1 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	0 RCTs	No RCTs that met inclusion criteria for the benefits of CRC screening using colonoscopy	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Pan, J., et al, 2016, *American Journal of Gastroenterology*	To evaluate the magnitude of protection against CRC by colonoscopy, with screening and diagnostic indications, in patients with non-malignant findings and further determine the potentially more marked effect of screening over diagnostic colonoscopy in the magnitude or	Systematic Review with meta-analysis	11 observational studies were included in analysis, 5 were cohort studies, 3 prospective and 2 retrospective and 6 were case–control studies. A total of 1,499,521 individuals were included, 1,305,419 in the morality meta-analysis	Pooled analysis showed that colonoscopy was associated with a 61% reduction in CRC mortality (RR: 0.39; 95% CI: 0.35–0.43; I 2 =12.0%) in patients with non-malignant findings. 	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

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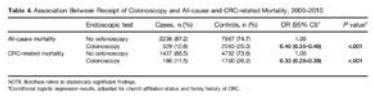
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low

	reductions in CRC mortality					
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy	Systematic Review with Meta-Analysis	2 Systematic Reviews, 2 Prospective Studies, and 1 Retrospective Study	The overall certainty of direct evidence supporting the use of colonoscopy to screen people at average risk for CRC was very low when compared with no screening with a RR 0.32 (0.23-0.43).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	
Samadder, N.J., et al, 2016, *Clinical Gastroenterology & Hepatology*	To examine whether exposure to colonoscopy decreases the odds of incidence CRC and death from CRC in Utah	Case-control study; Utah residents, 54 to 90 years old, who received a CRC diagnosis from 2000 through 2010 (cases) were included in analysis. Age- and sex-matched controls with no history of CRC (controls) were selected for each case. The receipt of colonoscopy was determined at 6 months to 10 years before the reference date for each case and control through administrative claims data. Colonoscopy exposure was compared by using conditional logistic regression	In a database with more than 7.2 million unique individuals, 5,128 cases and 20,512 controls were found and 741 cases (14%) and 5715 controls (28%) received a colonoscopy	12.8% of CRC cases who died of any cause and 11.5% of cases who died of CRC/malignancy underwent colonoscopy versus 25.3% and 26.2% of matched controls for each group, respectively. CRC cases who died (both all-cause and CRC related) were significantly less likely than controls to have undergone colonoscopy (OR, 0.40; 95% CI, 0.35–0.46 for all-cause mortality**; OR, 0.33; 95% CI, 0.28–0.39 for CRC-related mortality**) 	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Pan, J., et al. (2016). "Colonoscopy Reduces Colorectal Cancer Incidence and Mortality in Patients With Non-Malignant Findings: A Meta-Analysis." American Journal of Gastroenterology 111(3): 355-365.
3. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.
4. Samadder, N. J., et al. (2016). "Risk of Incident Colorectal Cancer and Death After Colonoscopy: A Population-based Study in Utah." Clinical Gastroenterology & Hepatology 14(2): 279-286.e271-272.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Mortality; **Modality:** Fecal Immunochemical Test (FIT/iFOBT)

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 4 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 3 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	1 RCT; 192,261 (94,423 [I]; 97,838 [C]) individuals and included a mixed gender population ages 30 years and older. The screening arm received RPHA-FOBT (FIT) test using single screen method. The control group was no screening.	The length of follow-up was eight years. **The effect of iFOBT on CRC mortality was RR 0.88** (95%CI, 0.72, 1.07, I2=NA); ARR 277/million (631 fewer to 151 more).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Chiu, H.M., et al., 2015, *Cancer*	To assess the effectiveness of fecal immunochemical testing (FIT) in reducing colorectal cancer (CRC) mortality in a large, population-based service screening program	Prospective Cohort Study; Follow-up with Taiwanese patients from 2004 to 2009 was conducted to compare CRC morality for an exposed (screened) group and an unexposed (unscreened) group in a population-based CRC screening service targeting community residents of Taiwan who were 50 to 69 years old.	1,160,895 subjects	**The actual effectiveness in reducing CRC mortality attributed to the FIT screening was 62%** (relative rate for the screened group vs the unscreened group, 0.38; 95% confidence interval, 0.35-0.42) with a maximum follow-up of 6 years. The 21.4% coverage of the population receiving FIT led to a significant 10% reduction in CRC mortality (relative rate, 0.90; 95% confidence interval, 0.84-0.95) after adjustments for a self-selection bias.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

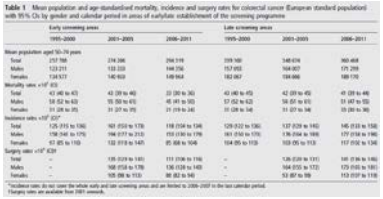
Quality (certainty) of evidence for studies as a whole:

☐ High

☒ Moderate

☐ Low

☐ Very Low

Giorgi Rossi, P., et al, 2015, *Journal of Gastroenterology*	To evaluate the impact of screening with immunochemical FOBT (FIT) on CRC mortality	Observational Study; An organized screening program was implemented in 2005 in the province of Reggio Emilia (Northern Italy). The program invites the resident population aged 50-69 for FIT every 2 years. Subjects who test positive are referred for colonoscopy. People aged 50-74 from 1997 to 2012 were classified for exposure to screening according to age and period. Furthermore, two open cohorts-one never screened (aged 50-69 in 1997) and one invited for screening (aged 50-69 in 2005)-were followed up for 8 years to measure morality.	A total of 171,785 people have been invited, and approximately 70% have undergone FIT at least once (272,197 tests).	The rate of colonoscopy participation was about 90%, and 2,896 cancers were recorded (1237 in the screening period). **Incidence-based mortality decreased by 27% (95% CI, 15-37%).**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Zorzi, M., et al., 2015, *Gut*	To evaluate the impact of FIT-based screening programmes on CRC morality	Observational Study; In the Veneto Region (Italy), biennial FIT-based screening programmes that invited 50–69-year-old residents were introduced in different areas between 2002 and 2009. Study compared CRC mortality rates from 1995 to 2011 between the areas where screening started in 2002–2004 (early screening areas (ESA)) and areas that introduced the screening in 2008–2009 (late screening areas (LSA)) using Poisson regression models. Available data on CRC incidence rates (1995–2007) and surgical resection rates (2001–2012) was also compared.	The 50-74-year-old resident population of the early screening and late screening areas were 274,266 and 348,674 subjects respectively.	Compared with 1995–2000, 2006–2011 mortality rates were 22% lower in the ESA than in the LSA (rate ratio (RR) = 0.78; 95% CI 0.68 to 0.89). **The reduction was larger in women (RR=0.64; CI 0.51 to 0.80) than in men (RR=0.87; CI 0.73 to 1.04).** 	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Chiu, H. M., et al. (2015). "Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program." Cancer 121(18): 3221-3229.
3. Giorgi Rossi, P., et al. (2015). "Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy." American Journal of Gastroenterology 110(9): 1359-1366.
4. Zorzi, M., et al. (2015). "Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test." Gut 64(5): 784-790.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Mortality; **Modality:** Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 4 # of Systematic Reviews: 4 # of RCTs: 0 # of Non-Randomized Studies: 0 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive Health, 2016, *CMAJ Canadian Medical Association Journal*	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review with meta-analysis	4 RCTs; Combined sample of 413,955 14 (165,333 [I]; 248,622 [C]). All studies included a mixed gender population. Three studies included participants with ages ranging from 55 to 64 years and one study included participants with ages 55 to 74 years.	The length of follow-up across four studies ranged from six years to 11.9 years. The meta-analysis of primary screening with flexible sigmoidoscopy showed a relative reduction of 28% in CRC mortality with a pooled RR of 0.72 (95%CI, 0.65, 0.81, I2=0%); the ARR was 1,176/million (830-1,486 fewer). The NNS for the outcome of CRC mortality was 850 (95%CI, 673-1205).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies
Holme, O., 2017, *BMJ*	To compare the effectiveness of flexible sigmoidoscopy in screening for colorectal cancer by patient sex and age	Systematic Review; Pooled analysis of randomised trials (the US Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO), the Italian Screening for Colon and Rectum trial (SCORE), and the Norwegian Colorectal Cancer Prevention trial (NORCCAP)).	287,928 individuals were included in the pooled analysis; 115,139 randomised to screening and 172,789 to usual care.	A total of 373 individuals in the screening group and 740 in the usual care group died from colorectal cancer. Overall, colorectal cancer mortality was reduced by 27% (relative risk 0.73; 95% confidence interval 0.64 to 0.83), 33% in men (0.67; 95% 0.57 to 0.80), and 18% in women (0.82; 0.67 to 1.00, P=0.048). When the analyses were restricted to the 55-64 year age group, colorectal cancer mortality was statistically significantly reduced in men (0.70; 0.57 to 0.86) and in younger women (0.68; 0.47 to	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☒ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

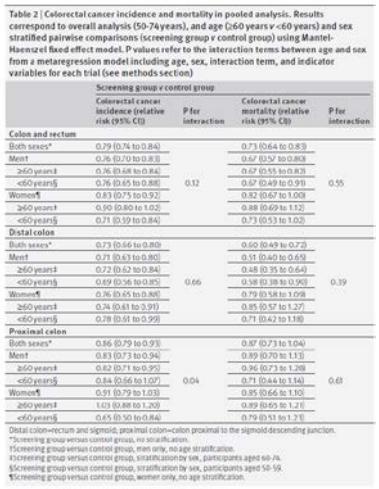
Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

				0.98), but not in women aged 60 years and older (1.07; 0.77 to 1.48).  Table 2 | Colorectal cancer incidence and mortality in pooled analysis. Results correspond to overall analysis (50-74 years), and age (≥60 years v <60 years) and sex stratified pairwise comparisons (screening group v control group) using Mantel-Haenszel fixed effect model. P values refer to the interaction terms between age and sex from a metaregression model including age, sex, interaction term, and indicator variables for each trial (see methods section) Screening group v control group Colorectal cancer incidence (relative risk (95% CI)) / P for interaction / Colorectal cancer mortality (relative risk (95% CI)) / P for interaction Colon and rectum Both sexes* 0.79 (0.74 to 0.84) 0.73 (0.64 to 0.83) Men† 0.76 (0.70 to 0.83) 0.67 (0.57 to 0.80) ≥60 years‡ 0.76 (0.68 to 0.84) 0.67 (0.55 to 0.82) <60 years§ 0.76 (0.65 to 0.88) 0.12 0.67 (0.49 to 0.91) 0.55 Women¶ 0.83 (0.75 to 0.92) 0.82 (0.67 to 1.00) ≥60 years† 0.90 (0.80 to 1.02) 0.88 (0.69 to 1.12) <60 years§ 0.71 (0.59 to 0.84) 0.73 (0.53 to 1.02) Distal colon Both sexes* 0.73 (0.66 to 0.80) 0.60 (0.49 to 0.72) Men† 0.71 (0.63 to 0.80) 0.51 (0.40 to 0.65) ≥60 years‡ 0.72 (0.62 to 0.84) 0.48 (0.35 to 0.64) <60 years§ 0.69 (0.56 to 0.85) 0.66 0.58 (0.38 to 0.90) 0.39 Women¶ 0.76 (0.65 to 0.88) 0.79 (0.58 to 1.09) ≥60 years‡ 0.74 (0.61 to 0.91) 0.85 (0.57 to 1.27) <60 years§ 0.78 (0.61 to 0.99) 0.71 (0.42 to 1.18) Proximal colon Both sexes* 0.86 (0.79 to 0.93) 0.87 (0.73 to 1.04) Men† 0.83 (0.73 to 0.94) 0.89 (0.70 to 1.13) ≥60 years‡ 0.82 (0.71 to 0.95) 0.96 (0.73 to 1.28) <60 years§ 0.84 (0.66 to 1.07) 0.04 0.71 (0.44 to 1.14) 0.61 Women¶ 0.91 (0.79 to 1.03) 0.85 (0.66 to 1.10) ≥60 years‡ 1.03 (0.88 to 1.20) 0.89 (0.65 to 1.21) <60 years§ 0.65 (0.50 to 0.84) 0.79 (0.51 to 1.21) Distal colon=rectum and sigmoid; proximal colon=colon proximal to the sigmoid descending junction. *Screening group versus control group, no stratification. †Screening group versus control group, men only, no age stratification. ‡Screening group versus control group, stratification by sex, participants aged 60-74. §Screening group versus control group, stratification by sex, participants aged 50-59. ¶Screening group versus control group, women only, no age stratification.	
Tang, V., et al., 2015, *BMJ*	To determine the time to benefit of using flexible sigmoidoscopy for colorectal cancer screening	Systematic Review with meta-analysis	Four RCTs, total = 459,814	Studies were similar for patients' age (50-74 years), length of follow-up (11.2-11.9 years), and relative risk for colorectal cancer related mortality (0.69-0.78 with flexible sigmoidoscopy screening). For every 1000 people screened at five and 10 years, 0.3 and 1.2 colorectal cancer related deaths, respectively, were prevented. It took 4.3 years (95% confidence interval 2.8 to 5.8) to observe an absolute risk reduction of 0.0002 (one colorectal cancer related death prevented for every 5000 flexible sigmoidoscopy screenings). It took 9.4 years (7.6 to 11.3) to observe an absolute risk reduction of 0.001 (one colorectal cancer related death prevented for every 1000 flexible sigmoidoscopy screenings).	Study Limitations = ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low

						
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy	Systematic Review with Meta-Analysis	1 systematic review and 4 RCTs	 The magnitude of the effect on CRC mortality (RR, 0.72; 95%CI, 0.65 to 0.80)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Holme, O., et al. (2017). "Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials." BMJ 356: i6673.
3. Tang, V., et al. (2015). "Time to benefit for colorectal cancer screening: survival meta-analysis of flexible sigmoidoscopy trials.[Erratum appears in BMJ. 2015;350:h2228; PMID: 25910493]." BMJ 350: h1662.
4. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Mortality; **Modality:** Fecal Occult Blood Test (FOBT)

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 3 # of Systematic Reviews: 2 # of RCTs: 0 # of Non-Randomized Studies: 1 # of Diagnostic Studies: 0					
Canadian Task Force on Preventive	To synthesize evidence on the benefits and harms	Systematic Review with meta-analysis	4 RCTs; Combined sample of 313,180 (156,737 [I -	For colorectal specific mortality, the meta-analysis for screening with gFOBT compared to no screening found RR 0.82	Study Limitations = ☐ None ***Systematic Review***

Lower Quality Rating if:

☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

Health, 2016, *CMAJ Canadian Medical Association Journal*	of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.		intervention]; 156,443[C - control]). Two studies included participants with ages ranging from 45 to 75 years, one study included participants ages 50 to 80 years and one study included participants ages 60 to 64 years. The	(95%CI, 0.73, 0.92, I2=67%), with an ARR 2,654/ million (1,128-4,010 fewer). The number needed to screen (NNS) was 377 (95%CI, 249-887).	☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy	Systematic Review with Meta-Analysis; PubMed, EMBASE, and conference abstracts were searched through 30 April 2015. The primary outcomes were overall CRC incidence and mortality. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effect models.	2 RCTs	The overall certainty of the evidence was high, suggesting a definite reduction in CRC-related mortality. The magnitude of the effect was small with a RR 0.87; 95% CI 0.82 to 0.92.	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	
Ananda, S., et al., 2016, *Internal Medicine Journal*	To analyze the impact of the National Bowel Cancer Screening Programme (NBCSP) launched in Australia in 2006 that mailed invitations to people turning 55 or 65 years to undertake immunochemical-	Prospective Study; Data on consecutive patients enrolled into a prospective, comprehensive, multidisciplinary database at six Victorian hospitals were examined. Clinicopathologic and outcome data were compared for NBCSP and symptomatic presentation patients.	3,743 patients	Of 1,930 patients aged between 50 and 70 years, 141 (7.3%) had a NBCSP detected cancer, 1441 (74.7%) presented with symptoms and 266 (13.8%) were diagnosed through screening outside of the NBCSP. Based on the American Society of Anaesthesiology score, the NBCSP patients were fitter. They had an earlier stage of diagnosis and were more likely to be female and less likely to have lymphovascular invasion or to present as an emergency. **NBCSP detected patients had a lower rate of recurrence (HR 0.17, P**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

	based FOBT screening.			**= 0.0001) and fewer deaths (HR 0.19, P = 0.005).**		

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348.
2. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.
3. Ananda, S., et al. (2016). "Survival impact of the Australian National Bowel Cancer Screening Programme." Internal Medicine Journal 46(2): 166-171.

PICO Question: In asymptomatic populations at general risk of CRC, what is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Does effectiveness (or comparative effectiveness) vary by important subpopulations?

Outcome: Mortality; **Modality:** Fecal Immunochemical Test (FIT) vs Fecal Occult Blood Test (gFOBT)

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0 # of Diagnostic Studies: 0					
Tinmouth, J., 2016, *Canadian Journal of Gastroenterology & Hepatology*	To conduct a meta-analysis quantifying the magnitude of protection by colonoscopy, with screening and diagnostic indications, against CRC in patients with non-malignant findings and demonstrating the potentially more marked effect of screening over diagnostic colonoscopy	Systematic Review with Meta-Analysis	1 Systematic Review and 10 RCTs	While there were well-designed randomized controlled trials (RCTs) comparing FIT with gFOBT, the outcomes of these trials (participation and detection rates) were considered to be less important than CRC related mortality. However, it was anticipated that the reduction in CRC-related mortality and the complications resulting from screening with FIT would be at least equivalent to those observed from screening with gFOBT.	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

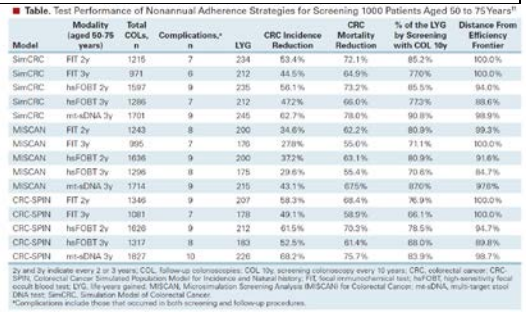
☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

						Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Tinmouth, J., et al. (2016). "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary." Canadian Journal of Gastroenterology & Hepatology 2016: 2878149.

Modeling Studies Summaries			
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Outcomes*
Berger, B.M., et al., 2016, *American Journal of Managed Care*	To demonstrate that the US Preventive Services Task Force (USPSTF) modeling screening outcomes included CRC mortality reduction.	Descriptive analysis of USPSTF modeling of the clinical impact of CRC screening strategies. These scenarios involved different modalities (hsFOBT, FIT, and mt-sDNA), intervals (2y, 3y, and every 5 years), and screening age groups (50-75, 50-80, 50-85, 55-75, 55-80, and 55-85 years). All scenarios assumed 100% adherence to the screening modality and interval. Screening scenarios were plotted against life years gained (LYG) and colonoscopies performed to create an "efficiency frontier," a line connecting the most efficient screening scenarios based on the trade-off between LYG and colonoscopies. By excluding annual stool tests, the CISNET's analysis of the "efficiency frontier" was recreated and compared these screening scenarios with each other and with 10y colonoscopy screening. Per CISNET, tests were recommended if they were within 98% of the LYG at the equivalent point on the efficiency frontier and generated at least 90% of the LYG generated by 10y screening colonoscopy.	■ **Table.** Test Performance of Nonannual Adherence Strategies for Screening 1000 Patients Aged 50 to 75 Years[a]  2y and 3y indicate every 2 or 3 years; COL, follow-up colonoscopies; COL 10y, screening colonoscopy every 10 years; CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural history; FIT, fecal immunochemical test; hsFOBT, high-sensitivity fecal occult blood test; LYG, life years gained; MISCAN, Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer; mt-sDNA, multi-target stool DNA test; SimCRC, Simulation Model of Colorectal Cancer. [a]Complications include those that occurred in both screening and follow-up procedures.
Brenner, H., et al, 2015, *Clinical Gastroenterology & Hepatology*	To quantify the effects of screening colonoscopy on prevention, early detection, and overdiagnosis of colorectal cancer (CRC) in the 10 years since its introduction in Germany	Analyzed data from screening colonoscopies (conducted on individuals 55–79 years old from 2003 through 2012) available through the national screening colonoscopy registry. CRCs prevented, detected earlier than they would have been without screening, and overdiagnosed (cancers detected at screening colonoscopy that would not have become clinically manifest during the patient's lifetime) were estimated by Markov models. Model parameters included sex-specific and age-specific findings at screening colonoscopy; mortality; rates of transition from nonadvanced to advanced adenoma, advanced adenoma to preclinical cancer, or preclinical cancer to clinically manifest cancer; and protection from screening colonoscopy. For each iteration and each transition, mortality was accounted for and obtained from general population life tables for the year 2010.	Overall, approximately 180,000 CRCs (1/28 screening colonoscopies) were estimated to have been prevented, and more than 40,000 CRCs (1/121 screening colonoscopies) were detected earlier than they would have been without screening, compared with approximately 4500 overdiagnoses (1/1089 screening colonoscopies). Almost all CRCs prevented or detected earlier than they would have been without screening resulted from screening colonoscopies performed on individuals up to 75 years old (97% and 89%, respectively), whereas 28% of overdiagnoses occurred from screening colonoscopies of individuals older than 75 years old.

Geurts, S.M., et al., 2015, *British Journal of Cancer*	To project the impact of phasing once-only flexible sigmoidoscopy (FS) at age 55 into the England National Health Service Bowel Screening Programme (NHSBCSP), augmenting biennial gFOBT at ages 60-74, on CRC cases and deaths prevented in England by mid-2030.	Simulated the life-course of English residents reaching age 55 from 2013 onwards. Model inputs included population numbers, invitation rates and CRC incidence and mortality rates. The impact of gFOBT and FS alone on CRC incidence and mortality were derived from published trials, assuming an uptake of 50% for FS and 57% for gFOBT. For FS plus gFOBT, the gFOBT effect was assumed to be 75% of the gFOBT alone impact.	By mid-2030, 8.5 million individuals will have been invited for once-only FS screening. Adding FS to gFOBT screening is estimated to 2,207 (12%) deaths by mid-2030. If FS uptake is 38% or 71%, respectively, an extra 1,691 (9%) or 3,154 (17%) deaths will be prevented by mid-2030.

References:

1. Berger, B. M., et al. (2016). "USPSTF colorectal cancer screening guidelines: an extended look at multi-year interval testing." American Journal of Managed Care 22(2): e77-81.
2. Geurts, S. M., et al. (2015). "Likely effect of adding flexible sigmoidoscopy to the English NHS Bowel Cancer Screening Programme: impact on colorectal cancer cases and deaths." British Journal of Cancer 113(1): 142-149.

Question #2: What are the test performance characteristics (eg, sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Do test performance characteristics vary by important subpopulations?

Primary Literature:

USPSTF 2016 Systematic Review Findings:

Overall Summary of Diagnostic Accuracy of Screening

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ2: Diagnostic accuracy of screening	Colonoscopy	k=4 n=4821 Prospective diagnostic accuracy	In 2 studies (n=1685), colonoscopy missed cancers. In 3 studies (n=2290) comparing colonoscopy to CTC or CTC-enhanced colonoscopy, the per-person sensitivity for adenomas ≥10 mm ranged from 89.1% to 94.7%, and the per-person sensitivity for adenomas ≥6 mm ranged from 74.6% to 92.8%.	Studies are not designed to assess diagnostic accuracy to detect cancer. Limited number of studies with large number of endoscopists, thus applicable to community practice. No reporting bias.	Fair to good	Fair- colonoscopies were conducted or supervised by "experienced" specialists
	FS	None**	Not applicable	Not applicable	Not applicable	Not applicable
	CTC	k=9 n=6497 Prospective diagnostic accuracy	In 1 study (n=2531), CTC missed 1 of 7 cancers. In 7 studies of CTC with bowel prep (n=5328), the per-person sensitivity and specificity to detect adenomas ≥10 mm ranged from 66.7% to 93.5% and 86.0% to 97.9%, respectively; the per-person sensitivity and specificity to detect adenomas ≥6 mm ranged from 72.7% to 98.0% and 79.6% to 93.1%, respectively. Only 3 studies (n=1044) reported sensitivity to detect advanced adenomas, ranging from 87.5% to 100%. In 2 studies (n=1169) of CTC without bowel prep, it appears that sensitivity without bowel prep to detect advanced adenomas, adenomas ≥10 mm, or adenomas ≥6 mm is lower than CTC protocols including bowel prep.	Studies are not designed to assess diagnostic accuracy to detect cancer. Unclear if the variation of test performance is due to differences in study design, populations, bowel prep, CTC imaging itself, or differences in reader experience or reading protocols. No reporting bias.	Fair to good	Fair- mostly single-center studies, the majority of studies (k=7) used 3 or fewer highly trained radiologists, current practice may use lower doses of radiation (therefore different technology and protocols)
	gFOBT	k=3 n=15,969 Prospective diagnostic accuracy	The sensitivity and specificity of Hemoccult SENSA to detect CRC ranged from 61.5% to 79.4% and from 86.7% to 96.4%, respectively.	Verification bias (i.e., screen-negative persons did not receive colonoscopy). No reporting bias.	Fair	Fair to poor- Hemoccult SENSA no longer widely used in US

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
	FIT	**Qualitative** k=6 n=36,808 Prospective diagnostic accuracy **Quantitative** k=7 n=40,134 Prospective diagnostic accuracy	In studies with colonoscopy followup for all, qualitative and quantitative FIT sensitivity varied considerably across different assays for each outcome. Good results were seen from specific FITs with supporting data from more than 1 study, and best results from small studies using more than 1 stool sample or lower than manufacturer-recommended cutoffs. In 4 studies (n=34,857) evaluating 3 FDA-cleared qualitative FITs, OC-Light had the best sensitivity and specificity for CRC (87.5% and 91.0%, respectively, in 1 study, and 78.6% and 92.8% in another). For advanced adenoma, sensitivity and specificity were lower (40.3% and 92.3%, respectively, in 1 study and 28.0% and 93.5% in another). In 9 studies (n=42,310) evaluating 7 quantitative FITs, best results were seen with OC FIT-CHEK, the only FDA-cleared test. Sensitivity and specificity for CRC varied from 73.3% and 95.5%, respectively, to 92.3% and 87.2%. For advanced adenoma, sensitivity and specificity varied from 22.2% and 97.4%, respectively, to 44.1% and 89.8%.	Variation in test performance resulted from the use of 18 different FITs (FIT families), different numbers of stool samples, and to a limited extent, different assay cutoff value. Sparse data on most individual tests limited comparisons. Quantitative FITs included some that are older and now discontinued. In a separate group of studies (k=7), verification bias (i.e., screen-negative persons did not receive colonoscopy) did not change results or conclusions. No reporting bias.	Fair to good	Fair to good- for specific qualitative (OC-Light) and quantitative (OC-FIT CHEK) tests
	mtsDNA	k=1 n=9989 Prospective diagnostic accuracy	mtsDNA assay had better sensitivity but lower specificity compared to a commercial FIT (OC-FIT CHEK) for the detection of CRC and advanced adenoma. The sensitivity and specificity for CRC was 92.3% (95% CI, 84.0 to 97.0) and 84.4% (95% CI, 83.6 to 85.1), respectively; and for advanced adenoma was 42.4% (95% CI, 38.7 to 46.2) and 86.3% (95% CI, 85.5, 87.0), respectively.	Single study. 6% inadequate stool sample. No reporting bias.	Fair	Fair- only 1 mtsDNA test available, incorporates FIT in stool test, Cologuard (Exact Sciences)
	m*SEPT9*	k=1 n=1516 Prospective diagnostic accuracy	Weighted sensitivity and specificity of the m*SEPT9* assay to detect CRC was 48.2% (95% CI, 32.4 to 63.6) and 91.5% (95% CI, 89.7 to 93.1), respectively.	Single study. Large attrition due to incomplete data or inadequate sample. Analyses conducted in random subsample stratified by colonoscopy findings. No reporting bias.	Fair	Poor- only 1 blood test available and not FDA-approved for screening, Epi proColon Assay (Epigenomics AG)

PICO Question: What are the test performance characteristics (eg, sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Do test performance characteristics vary by important subpopulations?

Outcome: FIT Characteristics

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 13 # of Systematic Reviews: 2 # of Non-Randomized Studies: 11					
Canadian Task Force on Preventative Healthcare (2016) CMAJ Canadian Medical Association Journal	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review	40 studies (38 cohorts and 2 case control)	Result are reported in median with range. The overall sensitivity for iFOBT was 81.5% (53.3%-100%) and a specificity of 95.0% (87.2%-96.9%) with median PPV 7.35% (4.0%-10.8%), NPV 100% (99.7%-100%) and NNS 209 (41-430).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Hirai et al. (2016) Alimentary Pharmacology & Therapeutics	To assess in a meta-analysis, the diagnostic accuracy of FOBTs for relative detection of CRC according to anatomical location of CRC.	Systematic Review with meta-analysis	Thirteen studies, with 11 FIT cohorts with 20, 148 patients	Proximal CRC: Pooled Sensitivity: 71.1% (60.9–79.6%) Pooled Specificity: 95.2% (92.1–97.1%) Pooled Positive LR 14.7 (9.5–22.7) Pooled Negative LR 0.3 (0.2–0.4) AUC 91% Distal CRC: Pooled Sensitivity 79.0% (69.2–86.3%) Pooled Specificity 95.2% (92.1–97.1%) Pooled Positive LR 16.4 (10.5–25.5) Pooled Negative LR 0.2 (0.1–0.3) AUC 95%	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

☐ High
☒ Moderate
☐ Low
☐ Very Low

Huang, Y., et al. (2016). European Journal of Cancer Prevention	To evaluate and understand the superiority of quantitative FIT, a representative randomly selected population in China was invited for CRC screening. The performances of five featured screening strategies was compared.	Prospective cohort study where three fecal samples were collected from each participant by one optimized and two common sampling devices, and then tested by both quantitative and qualitative FITS. Colonoscopy was provided independently to all participants.	1020 participants	**Table 4 Performance characteristics of the five screening strategies** CI, confidence interval; FIT, fecal immunochemical test. Quantitative FIT ≥ 40 μg: Patients 20/49, Percentages (95% CI) 40.8 (27.1–54.8); Quantitative FIT ≥ 10 μg: Patients 311/118, Percentages (95% CI) 26.3 (18.3–34.3); Optimized qualitative FIT: Patients 18/61, Percentages (95% CI) 29.5 (18.1–41.0); One qualitative FIT: Patients 19/135, Percentages (95% CI) 14.1 (8.2–19.9); Two qualitative FIT: Patients 27/217, Percentages (95% CI) 12.4 (8.1–16.8) Advanced neoplasia Positive predictive value: 20/49; 40.8 (27.1–54.8); 311/118; 26.3 (18.3–34.3); 18/61; 29.5 (18.1–41.0); 19/135; 14.1 (8.2–19.9); 27/217; 12.4 (8.1–16.8) Sensitivities: 20/51; 39.2 (25.8–52.6); 31/52; 59.6 (46.3–73.0); 18/47; 38.3 (24.4–52.2); 19/51; 37.3 (24.0–50.6); 27/51; 52.9 (39.2–66.6) Specificities: 899/920; 96.8 (95.7–98.0); 802/919; 87.0 (85.0–89.4); 881/924; 95.3 (94.0–96.7); 789/959; 82.3 (79.9–84.8); 841/957; 87.8 (85.7–90.0); 860/957; 89.8 (87.7–92.0) Positive likelihood ratio: -; 12.4; -; 6.3; -; 8.2; -; 3.1; -; 2.7 Screening-relevant neoplasia Positive predictive value: 26/49; 53.1 (38.1–67.0); 60/118; 42.4 (33.5–51.3); 26/61; 42.6 (30.2–55.0); 38/135; 28.1 (20.9–35.7); 62/217; 24.0 (18.3–29.6) Sensitivities: 26/53; 17.0 (11.0–22.9); 50/155; 32.3 (24.9–39.6); 26/141; 18.4 (12.0–24.8); 38/153; 24.8 (18.0–31.7); 50/156; 33.3 (25.9–40.7) Specificities: 795/818; 97.2 (96.1–98.3); 740/816; 91.7 (89.8–93.6); 799/830; 95.7 (94.4–97.2); 689/854; 88.7 (86.5–90.8); 758/855; 89.7 (88.0–93.3) Positive likelihood ratio: -; 6.0; -; 3.9; -; 4.3; -; 2.2; -; 1.7	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☒ Failure to include all patients in analysis	
Shahidi, N., et al. (2016). Canadian Journal of Gastroenterology & Hepatology	To assess FIT performance among average-risk participants of the British Columbia Colon	Prospective cohort study where a single quantitative FIT with a cut-off of ≥10 μg/g (≥50 ng/mL) was used to screen participant. Participants with	20,322 participants with a positive FIT who then underwent a colonoscopy.	At the BCCSP FIT cut-off of ≥10 μg/g (≥50 ng/mL) the PPV for CRC, HRAs, all adenomas, and all neoplasia were 2.3%, 20.4%, 52.0%, and 54.2%, respectively.	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☒ Case-control study	

	Screening Program (BCCSP)	positive FIT results were referred for colonoscopy.		When comparing a cut-off of ≥10 μg/g (≥50 ng/mL) to ≥20 μg/g (≥100 ng/mL) the PPV for CRC, HRAs, and all neoplasia increased by absolute values of 1.5%, 6.5%, and 5.7%, respectively. The frequency of missed CRCs and HRAs was 61 (13.6%) and 1300 (32.4%), respectively.	☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	
Jensen, C. D., et al. (2016). Annals of Internal Medicine	To asses FIT performance characteristics over 4 rounds of annual screening.	Retrospective cohort study	323,349 participants who completed the first round of FIT and were followed-up for up to 4 screening rounds.	*Table 3.* FIT Sensitivity for CRC Among the Cohort That Completed Round 1 of FIT Screening **CRC Sensitivity in Participants With Positive FIT Results/FIT-Screened Participants, by Screening Round and Overall, *n/N* (%) (*n* = 1192 participants)*** **Variable** / **Round 1** / **Round 2** / **Round 3** / **Round 4** / **Total** KPNC / 322/380 (84.7) / 84/106 (79.2) / 75/97 (77.3) / 71/89 (79.8) / 552/672 (82.1) KPSC / 223/265 (84.2) / 63/89 (70.8) / 63/91 (69.2) / 57/75 (76.0) / 406/520 (78.1) Total / 545/645 (84.5) / 147/195 (75.4) / 138/188 (73.4) / 128/164 (78.0) / 958/1192 (80.4) **CRC Sensitivity in Participants With Positive FIT Results/FIT-Screened Participants, by Total Rounds of Participation, *n/N* (%) (*n* = 1192 participants)*** **1 Round** / **2 Rounds** / **3 Rounds** / **4 Rounds** / **Total** Total / 545/645 (84.5) / 228/290 (78.6) / 123/171 (71.9) / 62/86 (72.1) / - **CRC Sensitivity in Participants With Positive FIT Results Who Had CRC/Total Participants With CRC, by Look-Back Period, *n/N* (%) (*n* = 1411 participants)†** **≤1 y** / **≤2 y** / **≤3 y** / **≤4 y** / **Total** Total / 975/1223 (79.9) / 1024/1342 (76.3) / 1045/1386 (75.4) / 1063/1411 (75.3) / - CRC = colorectal cancer; FIT = fecal immunochemical test; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California. * The percentage of FIT-screened participants with CRC who had positive FIT results in the year before the cancer was diagnosed. † The percentage of FIT-screened participants with CRC who had positive results on FIT up to 1, 2, 3, and 4 y before the CRC diagnosis. This analysis compared 1411 total participants with CRC diagnosed with 1 y of FIT screening, 1 of whom was diagnosed >1 y after the prior FIT screening date, and 101 who had crossed over for endoscopy in subsequent rounds or terminated health plan membership but then rejoined.	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☒ Failure to include all patients in analysis	

Kapidzic, A., et al. (2015). Clinical Gastroenterology & Hepatology	The study assessed FIT performance in men and women.	A prospective cohort study was performed, in which subjects were invited for first-round screening and for second-round screening with a single FIT. Subjects with a hemoglobin (Hb) level of 10 mg hemoglobin (Hb)/g (or ‡50 ng/mL) feces or higher were referred for colonoscopy. The test characteristics were assessed by sex for a range of FIT cut-off values.	10,008 screenees (age, 50–74 y) were approached for first-round screening and 8316 screenees (age, 51–74 y) were approached for second round screening.	In the first round, differences in PPV for advanced neoplasia between men and women were significant only at a cut-off level of 15 mg Hb/g feces (men: 51%; 95% CI, 45–58; women: 40%; 95% CI, 32–48; P= .032) In the second round, no differences in PPV between men and women were observed. The NNscope for advanced neoplasia and CRC was similar in both sexes. **In both rounds, sex was not associated significantly with the PPV for advanced neoplasia after adjusting for age.** A lower NNscreen to detect 1 advanced neoplasia was seen in men at cut-off level of 10 mg Hb/g feces: men, 44; 95% CI, 34–59; women, 66; 95% CI, 50–91; P =.046; cut-off level of 20 mg Hb/g feces: men, 59;95%CI, 44–83; women, 95;95%CI, 67–143; P=.045; cut-off level of 25 mg Hb/g feces: men, 65; 95%CI, 48–91; women, 115; 95%CI, 77–167; P=.028, respectively. A significantly higher FPR in men was found in both rounds at a cut-off level of 10 mg Hb/g feces (FPR round I, 6.3% in men vs 4.1% in women, P < .001; FPR round II, 4.6% in men vs 3.3% in women, P=.017). **No differences were seen when comparing the fecal hemoglobin concentrations between true-positive men and women**	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

Symonds, E. L., et al. (2015). Journal of Medical Screening	Examine whether demographic, pathological, behavioural, and environmental factors affected haemoglobin concentration and positive rates where FIT samples are mailed.	Retrospective cohort study. Participant demographics, temperature on sample postage day, and previous screening were recorded. Outcomes from colonoscopy performed within a year following FIT were collected. Multivariate logistic regression identified significant predictors of test positivity.	13,433 subjects, 21,929 correct screening packs	**Temperature:** with temperature expressed as a continuous variable, a 1degree C increase in temperature decreased the chance of a positive result by 1.8% (OR 0.982, 95% CI 0.973–0.991) **Gender:** Positive rates were higher in males. OR 1.47 (95% CI 1.30-1.65 p<.001) **Colonoscopy Outcome:** Likelihood of significant neoplasia was higher after a positive FIT compared with a negative test result (OR 2.21, 95% CI 1.65–2.98) Multivariate logistic regression analysis indicated that the site of the significant neoplasia was a predictor for FIT positivity, with distal neoplasia significantly more likely to result in a positive FIT than proximal neoplasia (OR 2.10, 95% CI 1.17–3.78)	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☒ Failure to include all patients in analysis	

Wong, M. C., et al. (2015) Gastrointestinal Endoscopy	To identify demographic factors associated with false-positive and false-negative FIT results during CRC screening	Retrospective database review of prospectively collected data.	4482 participants who underwent both FIT and colonoscopy in the first year and 857 underwent colonoscopy after negative FIT results for 3 years.	The sensitivity, specificity, positive predictive values, and negative predictive values for advanced neoplas ia were 33.1%, 91.9%, 19.0%, and 96.0%, respectively. Participants 66 to 70 years of age had higher sensitivity, whereas older age, smoking, and use of aspirin/ nonsteroidal anti-inflammatory drugs were associated with lower specificity. The rates of false-positive and false-negat ive results were 8.1% and 66.9%, respecively. Older age (66-70 years; adjusted odds ratio (AOR 1.95; 95% (CI], 1.35-2.81; P < .001), smoking (AOR 1.68; 95% CI, 1.08-2.61; P = .020) , and the presence of polypoid adenoma (AOR 1.71; 95% CI, 1.14-2.57; P = .009) were associated with false -positive results. Younger participants (AOR for elderly participants 0.31) and the use of aspirin/ nonsteroidal anti-inflammatory drugs (AOR 4.44) in participants with 1 FIT with negative results and the absence of high-grade dysplasia (AOR for presence 0.41) were associated with false-negative results.	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

Wong, M. C., et al. (2015). Clinical Gastroenterology & Hepatology	To compare the accuracy of a qualitative FIT in identifying patients with proximal vs distal advanced neoplasia and evaluate whether analysis of 2 specimens performed better than analysis of 1 specimen.	Prospective cohort study	5343 subjects (50-70 years old) who received 2 FITs (Hemosure; cutoff value, 10 mg hemoglobin/g feces) before colonoscopy	**Sensitivity** FIT detected distal advanced adenoma with 39.7% sensitivity (95% confidence interval [CI], 32.0%-48.0%) vs proximal advanced adenoma with 25.0% sensitivity (95% CI,17.3%-34.6%; P [.014), distal advanced neoplasia with 40.0% sensitivity (95% CI, 32.5%L47.9%) vs proximal advanced neoplasia with 27.9% sensitivity (95% CI, 20.0%-37.4%; P [.039), and any distal adenoma ‡10 mm, irrespective of other lesion characteristics, with 39.5% sensitivity (95% CI,31.0%-48.7%) vs proximal adenoma with 25.3% sensitivity (95% CI, 16.5%-36.6%; P [.038). **Specificity** The specificity of FIT in detecting CRC was similar between the proximal and distal colon. FIT detected distal lesions with higher PPV than proximal lesions. One FIT detected advanced neoplasia with 31.8% sensitivity (95% CI, 25.9%-38.4%) and 92.4% specificity (95% CI, 91.6%-93.2%), whereas 2 FITs detected advanced neoplasia with 34.1% sensitivity (95% CI, 28.0%-40.8%; P [.617) and 91.9% specificity (95% CI, 91.0%-92.7%; P [.327). FIT detected distal advanced neoplasia with greater sensitivity and higher PPV than proximal advanced neoplasia.	Study Limitations = ☒ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☐ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

Bujanda, L., et al. (2015) European Journal of Gastroenterology & Hepatology	To evaluate the characteristics of CRC detected in a second round of FIT screening after negative results in a first round.	Prospective cohort study with two rounds of screening.	A total of 238,647 individuals participated in the first round of FIT screening and 69,193 individuals in the second round after a first negative result.	Multivariate analysis confirmed that, in the second round, CRC diagnosed was more often proximal (hazard ratio vs. first round, 2.4; 95% confidence interval, 1.3–4.4; P =0.003) and the concentration of Hb/g faeces was lower (hazard ratio vs. first round, 2.1; 95% confidence interval, 1.3–3.5; P =0.003).	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☒ Failure to include all patients in analysis	

Chausserie, S., et al. (2015). International Journal of Cancer	To compare the seasonal variation performance of FIT and gFOBT for CRC screening	Prospective cohort study. Each patient sent in 3 consecutive stool samples. gFOBT was performed on all 3 samples and FIT was performed on the last 2 samples.	18,290 subjects	The performance of tests for detection of advanced neoplasia was compared according to seasons using Receiver Operating Characteristics (ROC) curves, at various FIT cut-off values. The positivity rate of FIT was significantly lower in the summer compared with other seasons (2.3% versus 3.0%, p = 0.03), whilst the positivity rate of gFOBT increased in the autumn (1.8% versus 1.5%, p = 0.11). **FIT was clinically more effective than gFOBT over the four season-specific ROC curves**. At the cut-off concentration used in the study, the season-specific FIT/ gFOBT ratios for true positive rates were: 2.8 (Autumn), 2 . 5 (Winter), 3.0 (Spring), 3.7 (Summer), and for false positive rates: 1.2 (Autumn), 1.5 (Winter), 1.8 (Spring), 0 .9 (Summer). **The seasonal variations of performance of FIT led to improved gain in specificity in the summer, without a decrease in gain in sensitivity compared with gFOBT.**	Study Limitations = ☒ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☐ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

Redwood, D. G., et al. (2016). Mayo Clinic Proceedings	To assess the accuracy of a multitarget stool DNA test (MT-sDNA) compared with FIT for detection of screening-relevant colorectal neoplasia (SRN) in Alaska Native people	Prospective, cross-sectional study of asymptomatic adults undergoing screening colonoscopy.	661 participants	Sensitivity by MT-sDNA increased with adenoma size (to 80% for lesions 2:3 cm; P=.01 for trend) and substantially exceeded FIT sensitivity at all adenoma sizes. For sessile serrated polyps larger than 1 cm (n= 9), detection was 67% by MT-sDNA vs 11 % by FIT (P= .07) For CRC (n= l O) , detection was 100% by MT-sDNA vs 80% by FIT (P= .48). Specificities were 93% and 96%, respectively (P= .03).	Study Limitations = ☒ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☐ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

Jin, P., et al. (2015). Journal of Gastroenterology & Hepatology	Evaluate the performance of the second-generation SEPT9 assay for the detection of colorectal neoplasm, and compared it with FIT.	Prospective cohort study. Patients with CRC, adenomatous polyps, hyperplastic polyps, and a healthy control group were included. The clinical status of all patients was verified by colonoscopy. In all patients, peripheral blood samples were taken for SEPT9 testing. For 177 patients, both SEPT9 and FIT were performed.	476 patients	**The sensitivity and specificity of SEPT9 for CRC were 74.8% (95% confidence interval [CI]: 67.0–81.6%) and 87.4% (vs non-CRC, 95% CI: 83.5–90.6%), respectively**. SEPT9 was positive in 66.7% of stage I, 82.6% of stage II, 84.1% of stage III, and 100% of stage IV CRCs. **The sensitivity of SEPT9 for advanced adenomas was 27.4% (95% CI:18.7–37.6%).** **SEPT9 showed better performance in CRC detection than FIT, but similar among advanced adenomas.**	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☐ Case-control study ☒ No independent, blind comparison between index test and reference test ☐ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition ☐ Failure to include all patients in analysis	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)
2. Hirai, H. W., et al. (2016). "Systematic review with meta-analysis: faecal occult blood tests show lower colorectal cancer detection rates in the proximal colon in colonoscopy-verified diagnostic studies." Alimentary Pharmacology & Therapeutics 43(7): 755-764.
3. Huang, Y., et al. (2016). "Optimizing sampling device for the fecal immunochemical test increases colonoscopy yields in colorectal cancer screening." European Journal of Cancer Prevention 25(2): 115-122.
4. Shahidi, N., et al. (2016). "Correlating Quantitative Fecal Immunochemical Test Results with Neoplastic Findings on Colonoscopy in a Population-Based Colorectal Cancer Screening Program: A Prospective Study." Canadian Journal of Gastroenterology & Hepatology 2016: 4650471.
5. Jensen, C. D., et al. (2016). "Fecal Immunochemical Test Program Performance Over 4 Rounds of Annual Screening: A Retrospective Cohort Study." Annals of Internal Medicine 164(7): 456-463.
6. Kapidzic, A., et al. (2015). "Gender Differences in Fecal Immunochemical Test Performance for Early Detection of Colorectal Neoplasia." Clinical Gastroenterology & Hepatology 13(8): 1464-1471.e1464.
7. Symonds, E. L., et al. (2015). "Factors affecting faecal immunochemical test positive rates: demographic, pathological, behavioural and environmental variables." Journal of Medical Screening 22(4): 187-193.
8. Wong, M. C., et al. (2015). "Factors associated with false-positive and false-negative fecal immunochemical test results for colorectal cancer screening." Gastrointestinal Endoscopy 81(3): 596-607.
9. Wong, M. C., et al. (2015). "Diagnostic Accuracy of a Qualitative Fecal Immunochemical Test Varies With Location of Neoplasia But Not Number of Specimens." Clinical Gastroenterology & Hepatology 13(8): 1472-1479.
10. Bujanda, L., et al. (2015). "Colorectal cancer in a second round after a negative faecal immunochemical test." European Journal of Gastroenterology & Hepatology 27(7): 813-818.
11. Chausserie, S., et al. (2015). "Seasonal variations do not affect the superiority of fecal immunochemical tests over guaiac tests for colorectal cancer screening." International Journal of Cancer 136(8): 1827-1834.
12. Plumb, A. A., et al. (2015). "Effect of faecal occult blood positivity on detection rates and positive predictive value of CT colonography when screening for colorectal neoplasia." Clinical Radiology 70(10): 1104-1109.
13. Redwood, D. G., et al. (2016). "Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People." Mayo Clinic Proceedings 91(1): 61-70.
14. Jin, P., et al. (2015). "Performance of a second-generation methylated SEPT9 test in detecting colorectal neoplasm." Journal of Gastroenterology & Hepatology 30(5): 830-833.

PICO Question: What are the test performance characteristics (eg, sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Do test performance characteristics vary by important subpopulations?

Outcome: gFOBT Test Characteristics

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews: 1 # of Non-Randomized Studies: 1					
Canadian Task Force on Preventative Healthcare (2016). CMAJ Canadian Medical Association Journal	To synthesize evidence on the benefits and harms of screening and the test properties of effective screening methods for asymptomatic adults who are not at high risk for colorectal cancer.	Systematic Review	40 studies (38 cohorts and 2 case control)	Result are reported in median with range. The overall sensitivity of gFOBT is 47.1% (12.9%-75.0%) and median specificity of 96.1% (90.1%-98.1%) with PPV of 7.5 (1.5%-15%), NPV of 99.55% (99.5%-99.6%) and NNS 597 (239-936).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Azimafousse Assogba, G. F., et al. (2015). Cancer Epidemiology	Evaluate the impact of repeated gFOBT screening on the PPV for advanced colorectal neoplasia and their distribution according to atomic subsite.	Analysis of a cross-sectional study focused on people with a positive gFOBT who were followed up with a colonoscopy.	98,031 people	The PPV for detection of advanced neoplasia was 24.5%, substantially higher in men than women (30.7% vs 17.7%), and it increased with age. Advancing age (RR1.28, 95% CI 1.19- 1.39 for every 10-year increase in age),female gender (RR 1.31,95 % CI 1.19- 1.44),and subsequent screening (RR 1.15, 95 % CI 1.04-1.27) were significantly and independently associated with detection of proximal adenocarcinoma. The latter was also detected at an advanced stage more often (RR.1.24, 95 % CI: 1.09- 1.42). Early stages of invasive adenocarcinoma (stages I and II) was more	Study Limitations = ☐ None ***Diagnostic Studies*** ☐ Patients not enrolled in consecutive or random manner ☒ Case-control study ☒ No independent, blind comparison between index test and reference test ☒ Not all patients received reference test ☐ Reference test not likely to correctly classify target condition

Lower Quality Rating if:

☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

☐ High
☒ Moderate
☐ Low
☐ Very Low

				likely to be detected in a subsequent than an initial screening (RR 1.07, 95% CI 1.01- 1.13)	☐ Failure to include all patients in analysis	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)
2. Azimafousse Assogba, G. F., et al. (2015). "Impact of subsequent screening episodes on the positive predictive value for advanced neoplasia and on the distribution of anatomic subsites of colorectal cancer: A population-based study on behalf of the French colorectal cancer screening program." Cancer Epidemiology 39(6): 964-971.

PICO Question: What are the test performance characteristics (eg, sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? Do test performance characteristics vary by important subpopulations?

Outcome: MtDNA Test Characteristics

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1					
Zhai, R. L., et al. (2016). Medicine	To evaluate the diagnostic performance of stool DNA for CRC.	Systematic Review with meta-analysis	53 studies with 7524 patients	**Single-gene test:** sensitivity 48%, specificity 97%, pooled DOR 20.35 (95% CI: 17.63-23.49), ROC curve .908 (std error .013), LR 9.17 **Multi-gene test:** sensitivity 78%, specificity 93%, pooled DOR 31.64 (95% CI: 25.13-39.84), ROC .934(std. error .011), LR 7.94	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

						☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

References:

1. Zhai, R. L., et al. (2016). "The Diagnostic Performance of Stool DNA Testing for Colorectal Cancer: A Systematic Review and Meta-Analysis." Medicine 95(5): e2129.

Question #3: a) What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Primary Literature:

USPSTF 2016 Systematic Review Findings:

Overall Summary of Serious Adverse Events of Screening

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
KQ3: Serious adverse events of screening	Screening program	k=13 n=45,867 RCT	We found no evidence for any serious harms resultant from stool testing other than false-negative results and risk of serious adverse events associated with diagnostic colonoscopy. The rate of perforation in colonoscopies for positive FOBT may be higher, the pooled estimate was 8 perforations (k=6) per 10,000 (95% CI, 2 to 32). Likewise, rates of serious adverse events from followup diagnostic/therapeutic colonoscopy post FS (k=6) is estimated at 14 perforations per 10,000 (95% CI, 9 to 26), and 34 major bleeds per 10,000 (95% CI, 5 to 63).	Serious adverse events not reported in comparator arms (persons without endoscopy). Likely reporting bias of serious harms other than perforation and bleeding. No studies report differential harms by age groups.	Fair	Fair to good- reflects community practice, limited studies in US
	Colonoscopy	k=55 n=10,398,876 24 prospective cohorts or trials, 31 retrospective studies	Serious adverse events from screening colonoscopy or colonoscopy in asymptomatic persons is estimated at 4 perforations (k=26) per 10,000 procedures (95% CI, 2 to 5) and 8 major bleeds (k=22) per 10,000 procedures (95% CI, 5 to 14). Other serious harms were not consistently reported. Risk of perforations, bleeding and other serious harms increase with age.	Only 2 studies reported serious adverse events in persons without colonoscopy (no difference in serious harms other than perforation and bleeding. Likely reporting bias of serious harms other than perforation and bleeding.	Fair	Good- reflects community practice
	FS	k=18 n=331,181 13 prospective cohorts or trials, 5 retrospective studies	Serious adverse events from screening FS are estimated at 1 perforation (k=16) per 10,000 procedures (95% CI, 0.4 to 1.4) and 2 major bleeds (k=10) per 10,000 procedures (95% CI, 1 to 4).	No studies reported serious adverse events in persons without FS. Likely reporting bias of serious harms other than perforation and bleeding. Only 1 study reported differential harms by age groups (no difference with increasing age).	Fair	Good- reflects community practice
	CTC harms	k=15 n=75,354 11 prospective cohorts or trials, 4 retrospective studies	Serious harms from CTC in asymptomatic persons are uncommon. Risk of perforation for screening CTC was less than 2 per 10,000 exams. The range of low-dose ionizing radiation per exam is 1 to 7 mSv.	No studies reported serious adverse events in persons without CTC. More limited evidence in true average-risk screening populations. Likely reporting bias of serious harms other than perforation. No studies report differential harms by age groups.	Fair	Fair to good- radiation exposure per exam may be decreasing over time

KQ	Test	# Studies (k), sample size (n), Design	Summary of Findings*	Body of Evidence Limitations†	Quality	Applicability
	CTC ECF	k=21 n=38,193 retrospective studies	Extracolonic findings, which could be a benefit or harm, are estimated to occur in 41% to 69% of examinations. Similarly, the estimated proportion of these findings that necessitate actual diagnostic followup varies widely from 5% to 37%, with a very small proportion that require any type of definitive treatment (up to 3%). Higher prevalence of ECF with increasing age.	No studies able to quantify net benefit/harms of ECF findings. Varying levels of followup, few studies with final disposition of ECF. Some variation in definition of clinical importance of ECF. Very limited studies comparing ECF by age groups.	Fair	Fair to good-categorization of ECF using C-RADS

* Includes consistency and precision
† Includes reporting bias
‡ Total 6 RCTs identified, but 1 trial (from Finland) has not yet reported mortality outcomes
** No studies meeting inclusion criteria requiring comparison against criterion standard of colonoscopy

Abbreviations: CI = confidence interval; C-RADS = Computed Tomographic Colonography Reporting and Data System; CRC = colorectal cancer; CTC = computer tomographic colonography; ECF = extracolonic findings; k = number of studies; FDA = Food and Drug Administration; FIT = fecal immunochemical test; FS = flexible sigmoidoscopy; FOBT = fecal occult blood test; HR = hazard ratio; IRR = incidence rate ratio; m*SEPT9* = circulating methylated septin 9 gene deoxyribonucleic acid; mSv = millisievert; mtsDNA = multi-target stool deoxyribonucleic acid; n = number; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RCT = randomized controlled trial; RR = relative risk

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Major Bleeding
Modality: Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews: 2					
Canadian Task Force on Preventative Health et al. (2016) *CMAJ*	To synthesizes the benefits and harms of screening for colorectal	A systematic review of literature with meta-analysis.	16 studies which included a total of	**Screening Colonoscopy** One uncontrolled study reported no cases of bleeding that resulted in hospitalization by number of colonoscopies 0/324 events; proportion of 0.0/1,000 (95%CI, 0.0-11.72). Reported by	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

Canadian Medical Association Journal	cancer (CRC) in asymptomatic adults.		254,530 patients and 14,703 colonoscopies	number of patients, bleeding that required hospitalization occurred in 94 of 79,486 patients 1.08/1,000 (0.85-1.32). **Follow-up Colonoscopy** Three uncontrolled observational studies reported bleeding requiring hospitalization by number of colonoscopies. The total events were 68/14,379, 4.73/1,000 (95%CI, 3.59-5.87). Seven papers reported this outcome by number of patients finding 28 bleeds requiring hospitalization for 25,178, 1.11/1,000 (95%CI, 0.62-1.57).	☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Vermeer, N.C., et al. (2017) *Cancer Treatment Reviews*	To evaluate potential harm as a result of mass colorectal cancer screening in terms of complications after colonoscopy, morbidity and mortality following surgery, psychological distress and inappropriate use of the screening test.	A systematic review of all literature with a meta-analysis to examine the pooled incidence of major complications of colonoscopy.	24 studies. 2,531,186 total colonoscopies	The pooled overall risk of major bleeding after colonoscopy was 0.8/1000 (95% CI .18-1.63)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)
2. Vermeer, N. C., et al. (2017). "Colorectal cancer screening: Systematic review of screen-related morbidity and mortality." Cancer Treatment Reviews 54: 87-98.

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Major Bleeding
Modality: Flexible Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1					
Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values	A systematic review of literature with meta-analysis.	2 studies with 149,866 flexible sigmoidoscopies	**Flexible Sigmoidoscopy (FS)** Major bleeding requiring hospitalization from primary screening with FS was reported by number of patients in two papers. The total events were 14/149,866, 0.00/1,000 (95%CI, 0.04-0.15).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Anxiety and Depression
Modality: Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews: 1					
Vermeer, N.C., et al. (2017) *Cancer Treatment Reviews*	To evaluate potential harm as a result of mass colorectal cancer screening in terms of complications after colonoscopy, morbidity and mortality following surgery, psychological distress and inappropriate use of the screening test.	A systematic review	11 studies, 15,447 patients	Five out of seven prospective studies reported an adverse effect on psychological well-being in participants who received a positive test result. Largest effects were observed before the screenings test, in anticipation of and shortly after being informed about a positive test result. One study reported no clinically relevant psychological effect of participation in the mass CRC screening, even a decreased anxiety and improvement in some dimensions of health related quality of life because of receiving a negative result. The largest prospective study (n = 3828) reported that patients experienced some psychological distress up to six weeks after the colonoscopy. In two studies the same pattern of declining scores during follow- up were observed when comparing participants tested positive with positive findings at work-up (true positives) and participants tested positive with negative findings at work-up (false positives).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Vermeer, N. C., et al. (2017). "Colorectal cancer screening: Systematic review of screen-related morbidity and mortality." Cancer Treatment Reviews 54: 87-98.

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Anxiety and Depression
Modality: Flexible Sigmoidoscopy and FIT

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of RCTs: 1					
Kirkoen B, et al. (2016) *British Journal of Cancer*	To evaluate the psychological effects of participation in the Bowel Cancer Screening in Norway pilot program	RCT. Participants were invited to either flexible sigmoidoscopy (FS) screening, (FIT), or no screening (control). Participants were asked to complete a Hospital Anxiety and Depression Scale and a health related quality of life scale questionnaire when invited to screening and again when receiving screening result. Control group was invited to complete questionnaire only.	3,216 participants completed both screening and questionnaire (1,839 in Flexible Sigmoidoscopy group and 1,377 in FIT group) and 2,618 participants in the control group	**Anxiety :**The interaction effect for anxiety of time (baseline and result), screening group (FIT and FS), and screening result (positive and negative) was not statistically significant (P = 0.89). **No significant increase in anxiety with positive test results (P= .29 for FS and .40 for FIT)**. Negative test results had a significant decrease in anxiety from baseline (P<.01 for FIT and FS) **Depression:** Participants receiving positive or negative screening test did not report a statistically significant change in depression from baseline. (P=.14 for posFS and .07 for posFIT and P= .09 for negFS and .63 for negFIT) **No changes observed in the study reached the criteria of clinical relevance.**	***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline studies

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Kirkoen, B., et al. (2016). "Do no harm: no psychological harm from colorectal cancer screening." British Journal of Cancer 114(5): 497-504.

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Perforation
Modality: Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews 2					
Vermeer, N.C., et al. (2017) *Cancer Treatment Reviews*	To evaluate potential harm as a result of mass colorectal cancer screening in terms of complications after colonoscopy, morbidity and mortality following surgery, psychological distress and inappropriate use of the screening test.	A systematic review of all literature with meta-analysis	22 studies. 2,456,349 colonoscopies	The pooled risk of perforation after colonoscopy was .07/1000 (95% CI .0006-.17)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient

Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.	Systematic review of the literature with meta-analysis	16 studies: 39,235 colonoscopies; 116,680 sigmoidoscopies; 340,869 patients	**Colonoscopy**: Eight uncontrolled observational studies reported perforation data for screening colonoscopy; three of those by number of colonoscopies. There were total of 16 events for 39,235 colonoscopies 0.41/1,000 (95%CI 0.19-0.62). For the five papers that reported by number of patients, there were 45 events in 84,850 patients 0.53/1,000 (95%CI 0.37-0.69).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)
2. Vermeer, N. C., et al. (2017). "Colorectal cancer screening: Systematic review of screen-related morbidity and mortality." Cancer Treatment Reviews 54: 87-98.

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Perforation
Modality: Flexible Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews 1					

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in

Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.	Systematic review of the literature with meta-analysis	16 studies: 39,235 colonoscopies; 116,680 sigmoidoscopies; 340,869 patients	**Flexible Sigmoidoscopy:** Seven uncontrolled observational studies reported perforation for screening with FS. For the three papers that reported number of sigmoidoscopies, there were three perforations for 116,680 sigmoidoscopies, with the proportion of perforations being 0.03/1,000 (95%CI, 0.0-0.07). Four papers reported perforations by number of patient this event rate was 4 for 277,421 patients with the proportion 0.01/1,000 (95%CI, 0.0-0.03)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	*regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?	<u>Lower Quality Rating if:</u> ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations,*
Outcome: Perforation **Modality: CT Colonography**	

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	*interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Total # of Studies: 1 # of Systematic Reviews 1						
Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.	Systematic review of the literature with meta-analysis	1 study, 11,707 CT colonography	**Screening CT Colonography:** One paper reported no perforations for screening with CT colonography with 0 events for 11,707 tests 0.0/1,000 (95%CI, 0.0- 0.33)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?						Lower Quality Rating if: ☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect
Outcome: Mortality **Modality: Colonoscopy**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Systematic Reviews 2						
Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.	Systematic review of the literature with meta-analysis	4 studies. 111,160 patients and 38,472 colonoscopies	**Colonoscopy**: Death as a result of colonoscopy screening was reported in one study by number of colonoscopies; total events were 12 deaths for 38,472 colonoscopies 0.31/1,000 (95%CI, 0.18-0.55). For the two studies reporting this outcome by number of patients, total events were 2/70,828, resulting in a proportion of 0.02/1,000 (95%CI, 0.0-0.06).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	

Vermeer, N.C., et al. (2017) *Cancer Treatment Reviews*	To evaluate potential harm as a result of mass colorectal cancer screening in terms of complications after colonoscopy, morbidity and mortality following surgery, psychological distress and inappropriate use of the screening test.	A systematic review of all literature.	8 studies. 204,640 participants.	Reported mortality rates ranged from 0-3.3% with the largest study reporting no mortality rates at 30 days.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)
2. Vermeer, N. C., et al. (2017). "Colorectal cancer screening: Systematic review of screen-related morbidity and mortality." Cancer Treatment Reviews 54: 87-98.

PICO Question: a)What are the adverse effects (ie, serious harms) of the different screening tests (either as single application or in a screening program)? b) Do adverse effects vary by important subpopulations (eg, age)?

Outcome: Mortality
Modality: Flexible Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews 1					

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in

Canadian Task Force on Preventative Health et al. (2016) *CMAJ Canadian Medical Association Journal*	This systematic review synthesizes the benefits and harms of screening for colorectal cancer (CRC) in asymptomatic adults; provides diagnostic properties for screening tests that show a positive impact on mortality or incidence of late stage CRC; and answers contextual questions such as patient preferences and values.	Systematic review of the literature with meta-analysis	4 studies. 111,160 patients and 38,472 colonoscopies	**Flexible Sigmoidoscopy:** Death resulting from screening with FS was reported in one study by the number of patients. There were 6 deaths in 40,332 patients 0.15/1,000 (95%CI, 0.07-0.32).	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies ☐ Differences in important prognostic factors at baseline	*regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Canadian Task Force on Preventive Health, C., et al. (2016). "Recommendations on screening for colorectal cancer in primary care." CMAJ Canadian Medical Association Journal 188(5): 340-348. (Systematic Review)

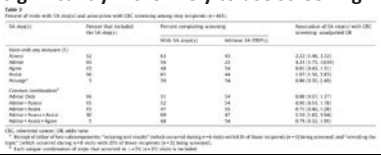
Modeling Studies Summaries			
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Outcomes*
Knudsen et al., 2016, *Clinical Review and Education*	To inform the USPTF by modeling the benefits, burden, and harms of CRC screening strategies.	Three models were used (SimCRC, MISCAN, and CRC-SPIN) Each model consisted of a natural history component and a screening component, which were used to simulate individual life histories from birth to death under alternative CRC screening strategies.	The lifetime number of harms from screening was low, with at most 23 per 1000 40-year-olds with colonoscopy screening every 5 years from ages 45-85.

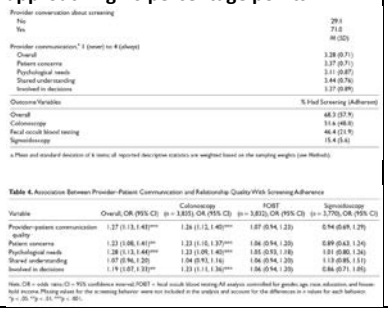
Question #4: Does using shared decision-making when determining appropriate screening test increase the rate of completed CRC screens compared to a LIP prescribed test?

Primary Literature:

PICO Question: Does using shared decision-making when determining appropriate screening test increase the rate of completed CRC screens compared to a LIP prescribed test?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole:
Outcome: CRC Screening Completed						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 7 # of RCTs: 2 # of Non-Randomized Studies: 5						
Schroy, P.C., et al., 2014, *Am J Prev Med*	To assess the impact of decision aid-assisted shared decision making (SDM) on CRC screening uptake	RCT; Asymptomatic, average-risk patients aged 50-75 participants from an urban, academic safety-net hospital and community health center between were randomized to one of two intervention arms (decision aid plus personalized risk assessment [*YourDiseaseRisk YDR]* or decision aid alone) or control arm. The interventions took place just prior to a routine office visit with their primary care providers.	825 participants; 280 decision aid + YDR, 269 decision aid alone, and 276 control	**Patients in the decision aid–alone group were more likely to have a test ordered than the control group at the 1-month (69.1% vs 60.5%, p<0.035); 3-month (71.8% vs 62.3%, p=0.019); 6-month (77.0% vs 65.2%, p=0.002); and 12-month (80.7% vs 71.4%, p=0.011) time points**. The decision aid–alone group also was more likely to have a test ordered than the decision aid plus YDR group at each of these points, but here the differences were only significant at 1 month (69.1% vs 60.4%, p<0.031); 6 months (77.0% vs 67.1%, p<0.010); and 12 months (80.7% vs 73.6%, p=0.048). The pattern of test ordering was similar for the three groups; regardless of patient preferences, colonoscopy was the most commonly ordered test (range, 79%–81%) followed by FOBT (13%–19%); flexible sigmoidoscopy (<2%); and barium enema (<2%).	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Reuland, D.S., et al., 2017, *JAMA Intern Med*	To determine the combined effect of a CRC screening decision aid and patient navigation compared with usual care on CRC	RCT; Average risk patients between 50 – 75 years in two community health center practices, 1 in North Carolina and 1 in New Mexico, were randomized 1:1 to intervention or control arms. Intervention participants viewed a CRC	265 participants	**Intervention participants were more likely to complete CRC screening within 6 months (68% vs 27%); adjusted-difference, 40 percentage points (95% CI, 29-51 percentage points).** The intervention was more effective in women than in men (50 vs 21 percentage point increase, interaction *P* = .02).	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☐ Lack of allocation concealment ☐ Stopped early for benefit	

	screening completion	screening decision aid immediately before their clinician encounter. The decision aid promoted screening and presented colonoscopy and fecal occult blood testing as screening options. After the clinician encounter, intervention patients received support for screening completion from a bilingual patient navigator. Control participants viewed a food safety video before the encounter and otherwise received usual care.			☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	☐ High ☐ Moderate ☒ Low ☐ Very Low
Hoffman, R.M., et al., 2014, *Am J Prev Med*	To describe decision making processes and outcomes for cancer screening discussions	National Internet Survey Study; Adults aged >/= 50 years who made cancer screening decisions (breast, BrCa; colorectal, CRC; prostate, PCa) within the previous 2 years were invited to complete internet survey. Participants were asked about their perceived cancer risk; how informed they felt about cancer tests; whether their healthcare provider addressed pros/cons of testing, presented the option of no testing, and elicited their input; whether they were tested; and their confidence in the screening decision.	1,134 CRC participants; 477 men and 657 women.	For all cancer screening decisions, providers usually (63%-71%) explained that testing was optional, but less often asked women (43%-57%) than men (70%-71%) whether they wanted testing**. Only 27%-38% of participants reported SDM.** Perceived high/average cancer risk and feeling highly informed were associated with confidence in the screening decision. Among participants discussing CRC screening, men had slightly higher decision process scores than women (2.3 vs 2.0, *p*=0.03) and were more likely to report being asked by the healthcare provider whether they wanted testing (71% vs 57%, *p*=0.02). Overall, men and women (71% vs 69%, *p*<0.01) were equally likely to undergo CRC screening and indicate that they would definitely make the same decision again (men = 69.6% vs women = 63%).	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Lafata, J.E., 2014, *Patient Education and Counseling*	To evaluate the association of the 5As (Assess, Advise, Agree, Assist and Arrange) discussion during the primary care	Observational Study; Audio-recording of health exams among insured patients aged 50-80 years and due for CRC screening were joined with pre-visit patient surveys and screening use data from an electronic medical record.	443 patients	93% (OR 2.22; 1.48-3.32) of patients received a recommendation for screening (Advise) and 53% were screened in the following year. **The likelihood of screening increased as the number of 5A steps increased: compared to patients whose visit contained no 5A step, those whose visit contained 1-2 steps (OR =**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome	

	office visits with patients' subsequent colorectal cancer (CRC) screening use			**2.96 [95% CI 1.16, 7.53]) and 3 or more steps (4.98 [95% CI 1.84, 13.44]) were significantly more likely to use screening.** 	☐ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Laiyemo, A.O., et al., 2014, *Prev Med*	To evaluate provider-patient communication about CRC screening with and without specific screening modality recommendation on patient compliance with screening guidelines	Cohort Study; 2007 Health Information National Trends Survey (HINTS) was used to identify respondents who were at least 50 years of age and answered questions about their communication with their care providers and CRC screening uptake. Respondents were tracked to see if compliant with CRC screening as the use of FOBT within 1 year, sigmoidoscopy within 5 years, or colonoscopy within 10 years.	4,283 respondents included in analysis	CRC screening discussions occurred with 3,320 (76.2%) respondents. Approximately 95% of these discussions were with physicians. Overall, 2,793 (62.6%) respondents were current with CRC screening regardless of the screening modality. **Discussion about screening (OR = 8.83; 95% CI: 7.20-10.84) and providers making a specific recommendation about screening modality rather than leaving it to the patient to decide (OR = 2.04; 95% CI: 1.54-2.68) were associated with patient compliance with CRC screening guidelines.**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Mosen, D.M., 2013, *Am J Manag Care*	To examine association of comprehensiveness of CRC screening discussion by PCPs with completion of CRC screening	Observational Study; Conducted at Kaiser Permanente Northwest. Participants overdue for CRC screening received an automated telephone call (ATC) encouraging CRC screening. Participants completed a survey on PCPs' discussion of CRC screening and patient beliefs regarding screening. Primary outcome measure: receipt of CRC screening (assessed by EMR, 9 months after ATC). Primary independent variable: comprehensiveness of CRC	883 participants	Average scores for comprehensives of CRC discussion and perceived benefits were 0.4 (range 0-1) and 4.0 (range 1.5), respectively. 28.2% (n = 249 (completed screening, 84% of whom had surveyed assessments after their screening date. Of screeners, 95.2% completed the FIT. **More comprehensive discussion of CRC screening was associated with increased screening (OR = 1.51, 95% CI 1.03 – 2.21).** Higher perceived benefits (OR = 1.46, 95% CI = 1.13 – 1.90) and one or more PCP visits (OR = 5.82, 95% CI = 3.87 – 8.74) were also associated with increased screening.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

		screening discussion by PCPs (7-item scale). Secondary independent variables: perceived benefits of screening (4-item scale assessing respondents' agreement with benefits of timely screening) and primary care utilization (EMR; 9 months after ATC).				
Underhill, M.L. and M.T. Kiviniemi, 2012, *Health Education & Behavior*	To assess how provider-patient communication and characteristics of the patient-provider relationship may related to screening behavior	Cross-Sectional Study; The association of provider communication quality, relationship, and colorectal cancer screening was examined within data from the 2007 Health Information National Trends Survey.	7,674 individuals	Perceived provider communication and relationship quality were associated with both adherence to colonoscopy and with ever having been screened**. Predictive margins analyses indicated that increasing perceptions from lowest to highest levels of communication and relationship quality would be associated with increases in screening rates approaching 16 percentage points.** 	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Hoffman, R. M., et al. (2014). "Lack of Shared Decision Making in Cancer Screening Discussions." American Journal of Preventive Medicine 47(3): 251-259.
2. Lafata, J. E., et al. (2014). "Patient-physician colorectal cancer screening discussion content and patients' use of colorectal cancer screening." Patient Education & Counseling 94(1): 76-82.
3. Laiyemo, A. O., et al. (2014). "Influence of provider discussion and specific recommendation on colorectal cancer screening uptake among U.S. adults." Preventive Medicine 67: 1-5.
4. Mosen, D. M., et al. (2013). "More comprehensive discussion of CRC screening associated with higher screening." Am J Manag Care 19(4): 265-271. l
5. Reuland, D. S., et al. (2017). "Effect of Combined Patient Decision Aid and Patient Navigation vs Usual Care for Colorectal Cancer Screening in a Vulnerable Patient Population: A Randomized Clinical Tria." JAMA Intern Med 177(7): 967-974.
6. Schroy, P. C., 3rd, et al. (2012). "Aid-assisted decision making and colorectal cancer screening: a randomized controlled trial." American Journal of Preventive Medicine 43(6): 573-583.
7. Underhill, M. L. and M. T. Kiviniemi (2012). "The association of perceived provider-patient communication and relationship quality with colorectal cancer screening." Health Educ Behav 39(5): 555-563.

Question #5: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Primary Literature:

PICO Question: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Modality: SEPT9 Test vs. Stool Screening Test

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 2					
Adler et al (2014) *BMC Gastroenterology*	This study assessed patient willingness to use non-invasive stool or blood based screening tests after refusing colonoscopy.	Prospective Cohort Study. Participants were recruited during regular consultations. All subjects were advised to undergo screening by colonoscopy. Subjects who refused colonoscopy were offered a choice of non-invasive tests. Subjects who selected stool testing received a collection kit and instructions; subjects who selected plasma testing had a blood draw during the office visit. Patients who were positive for either were advised to have a diagnostic colonoscopy	172 subjects. 63 of 172 subjects were compliant to screening colonoscopy (37%). **106 of the 109 subjects who refused colonoscopy accepted an alternative non-invasive method (97%). 90 selected the Septin9 blood test (83%), 16 selected a stool test (15%) and 3 refused any test (3%).**	**The top three reasons for rejecting colonoscopy were being uncomfortable with the bowel preparation for colonoscopy (54%), fear of colorectal cancer itself (44%) and fear that colonoscopy would be painful (32%).** These results were corroborated in a follow-up question asking what would convince subjects to be screened by colonoscopy where 38% indicated an improved bowel preparation, 29% indicated cancer prevention by polypectomy and 24% indicated that overcoming fears would change their choice. **In addition, when asked why they chose one of the screening tests, 78% and 81% of subjects who had a blood and stool test respectively, indicated ease of getting the test**. For those choosing the blood test, primary reasons for not choosing the stool test related to being uncomfortable with specimen handling. For those choosing the stool test, the primary reason related to having used a stool test in the past**. As only 3 subjects rejected any form of testing, limited survey data is available.**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

						☐ High ☐ Moderate ☐ Low ☒ Very Low
Benning, T. M., et al. (2014). Acta Oncologica	To elicit individuals' preferences for different non-invasive CRC screening tests in a Dutch screening campaign.	Survey with Non-randomized discrete choice experiment (DCE).	815 individuals aged 55-75 years	**The combi-test (blood+stool) was generally preferred over the blood and stool test and all three were preferred over the option not to participate in screening.** The alternative specific constant for the combi-test had the highest value followed by the constants of the blood and stool tests, respectively. The differences between the tests are all significant and indicated a clear order in screening test preference. There was significant negative effects for the sensitivity and risk reduction dummies (baseline is highest attribute level) and a positive effect of strong level of evidence (baseline is limited scientific evidence) for all screening tests. **This indicates that as expected, more sensitive tests, tests that lead to a higher risk reduction of CRC death, and tests that are supported by strong scientific evidence are more likely to be chosen.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Taber et al (2014) *American Journal of Health Behavior*	To examine attitudes of a diverse community-based sample toward SEPT9 for CRC screening.	Prospective Cohort Study. Participants eligible for CRC screening completed cross-sectional surveys of their screening preferences following group discussions of colonoscopy, sigmoidoscopy, FOBT, and SEPT9.	100 participants aged 50-74 years with average CRC risk.	The respondents assigned screening modalities a specific rank as well as average rankings. **SEPT9 was ranked first or second by 91% of respondents overall, with 58% ranking it first, 10% tied for first, and 23% second.** Preferences differed sharply by race/ethnicity and screening status, such that 92.9% of unscreened Whites ranked SEPT9 as their first choice, in contrast to only 31.3% of unscreened Blacks. Colonoscopy was ranked first by 31% of participants, tied for first by 9%, and ranked second by 39%. **FOBT was ranked first by only 1%.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Adler, A., et al. (2014). "Improving compliance to colorectal cancer screening using blood and stool based tests in patients refusing screening colonoscopy in Germany." BMC Gastroenterology 14: 183 .
2. Benning, T. M., et al. (2014). "Preferences for potential innovations in non-invasive colorectal cancer screening: A labeled discrete choice experiment for a Dutch screening campaign." Acta Oncologica 53(7): 898-908 .
3. Taber, J. M., et al. (2014). "Preferences for blood-based colon cancer screening differ by race/ethnicity." American Journal of Health Behavior 38(3): 351-361 .

PICO Question: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Modality: FIT vs colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 6 # of Systematic Reviews: 1 # of RCTs: 2# of Non-Randomized Studies: 3					
Bonello et al. (2016) *BMC Gastroenterology*	To assess public preferences for colorectal cancer (CRC) surveillance tests for intermediate-risk adenomas, using a hypothetical scenario.	Survey. A postal survey was carried out during a separate study on preferences for different first-line CRC screening modalities (non- or full-laxative computed tomographic colonography, flexible sigmoidoscopy, or colonoscopy). Individuals were allocated at random to receive a pack containing information on one first-line test, and a paragraph describing CRC surveillance recommendations for people who are diagnosed with intermediate-risk adenomas during screening. All participants received a description of two surveillance options: annual single-sample, home-based stool testing (consistent with Faecal Immunochemical Tests; FIT) or triennial colonoscopy. Invitees were asked to imagine they had	491 participants returned eligible questionnaires	**A small proportion of participants had no preference between the options (n = 40; 8.1 %; 95 % CI [6.1 %, 10.9 %)). The majority stated a preference for surveillance with the stool test (n = 298; 60.8 %; 95 % CI [56.4 %, 65.0 %)) with colonoscopy preferred less frequently (n = 152; 31.0 %; [27.1 %, 35.3 %]).** There was evidence of gender differences in surveillance preferences with women more likely to prefer the stool test than men (66.7 % vs. 53.6 %, x2 [2, N = 490] = 9.028, p = .011). They did not find evidence to suggest differences in surveillance preferences by ethnicity, employment status, level of education, or in-direct experience of CRC (all p-values > .05) The majority of the participants who stated a prefer-ence for surveillance with the stool test stated that they did so because they would be tested more frequently (62.1 %) and the test was more convenient (51.7 %). A large proportion also said they believed that it was less likely to cause side	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

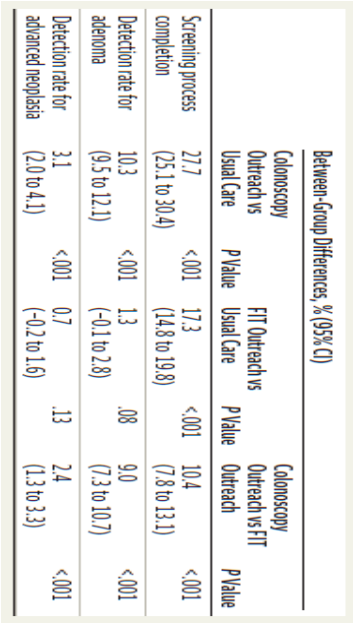
		been diagnosed with intermediate-risk adenomas, and then complete a questionnaire on their surveillance preferences.		effects (39.9 %) and less likely to cause harm (32.6 %). The majority of participants who stated a preference for colonoscopy said that they believed the test was better at finding polyps or cancer (77.6 %) and also more thorough (53.9 %). Almost one in three who preferred a colonoscopy gave the reason that they would have already had one and so would be more familiar with the test (29.6 **%**).		Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Bowyer et al. (2013) *Journal of Medical Screening*	To examine attitudes towards an annual faecal immunochemical test for haemoglobin (FIT) versus three-yearly colonoscopic surveillance of individuals at intermediate risk of colorectal cancer (CRC).	Qualitative Study. Five semi-structured discussion groups were conducted with 28 adults with different levels of CRC risk and *experience* of colonoscopy or colonoscopic surveillance. Information was presented sequentially using a step-by-step discussion guide. Results were analyzed using thematic analysis	28 adults	When evaluating FIT in the context of a surveillance program, all respondents readily made comparisons with related tests that they had been exposed to previously. Those with no experience of surveillance were enthusiastic about an annual FIT to replace three-yearly colonoscopy, because they felt that the higher testing frequency could improve detection of advanced lesions. Those with experience of colonoscopic surveillance did not perceive FIT to be as accurate as colonoscopy, and therefore either preferred colonoscopy on its own or wanted an annual FIT in addition to three-yearly colonoscopy.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	
Daskalakis, C., et al. (2014). *Cancer Epidemiology, Biomarkers & Prevention*	To investigate how CRC screening test preference operates together with test access and navigation to influence screening adherence in primary care.	Randomized Controlled Trial. Participants ages 50 to 79 years who were not up to date with colorectal cancer screening were randomized into one of three groups: (i) a usual case control group; (ii) a standard intervention (SI) group that received non-tailored mailed access to both stool blood test and colonoscopy; and (iii) a tailored navigation intervention (TNI) group that was provided mailed access and navigation	945 participants	Preference was not associated with overall screening, but **individuals who preferred FIT were more likely to complete FIT screening (P = 0.005), whereas those who preferred colonoscopy were more likely to perform colonoscopy screening (P = 0.032).**	Study Limitations = ☐ None ***RCTS*** ☒ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline	

		based on self-reported screening test preference.				

Table 3. Independent effects of test preference, test access, and navigation on colorectal cancer screening adherence ($N = 933^a$)

	Overall screening		FIT screening vs. none		CX screening vs. none	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Test preference		0.940		0.005		0.032
FIT	1.02 (0.61–1.71)	0.930	1.33 (0.70–2.53)	0.384	0.59 (0.25–1.39)	0.226
Equal FIT/CX	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
CX	0.94 (0.60–1.46)	0.787	0.44 (0.23–0.84)	0.013	1.61 (0.93–2.81)	0.091
Test access						
Usual care	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Mailed FIT kit + CX number	2.64 (1.79–3.90)	0.001	29.1 (10.3–82.0)	0.001	0.71 (0.42–1.19)	0.194
Navigation						
No navigation	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Navigation FIT + CX	2.09 (1.26–3.49)	0.005	1.53 (0.85–2.76)	0.157	3.22 (1.52–6.82)	0.002

Abbreviation: CX, colonoscopy.
[a]Final multivariable results based on 933 participants with full covariate data. The model included the three variables shown in the table, and controlled for primary care practice, age, sex, race, education, marital status, perceptions of colorectal cancer and screening, and baseline screening decision stage.

Singal A. G., et al (2017) *JAMA*	To compare the effectiveness of FIT outreach and colonoscopy outreach to increase completion of CRC screening process within 3 years.	RCT. Participants were randomly assigned to a mailed FIT outreach, mailed colonoscopy outreach, or usual care with clinic based screening.	5999 participants aged 50-64		Study Limitations = ☐ None ***RCTS*** ☐ Lack of blinding ☒ Lack of allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline	
Wortley, S., et al. (2014). *The Patient: Patient-Centered Outcomes Research*	A systematic review of discrete choice experiments (DCEs) of CRC screening.	Systematic review	3 studies, 4902 participants	One included study reported that both screened and screening-naive subjects preferred flexible sigmoidoscopy and colonoscopy to FOBT screening. Another found that fecal DNA testing, colonoscopy, and virtual colonoscopy (CT colonography) were the most preferred tests. The third study reported similar results, with respondents preferring newer tests such as virtual colonoscopy. In most studies, FOBT was reported as the least preferred option despite being the test most commonly adopted in national screening programs.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Xu, Y., et al. (2015). *BMC*	To compare patient	Prospective Cohort study. Patients scheduled for a	954 patients	In the AHP analysis, the test accuracy was given the highest priority (0.457), followed	Study Limitations = ☒ None	

Between-Group Differences, % (95% CI)

	Colonoscopy Outreach vs Usual Care	*P* Value	FIT Outreach vs Usual Care	*P* Value	Colonoscopy Outreach vs FIT Outreach	*P* Value
Screening process completion	27.7 (25.1 to 30.4)	<.001	17.3 (14.8 to 19.8)	<.001	10.4 (7.8 to 13.1)	<.001
Detection rate for adenoma	10.3 (9.5 to 12.1)	<.001	1.3 (−0.1 to 2.8)	.08	9.0 (7.3 to 10.7)	<.001
Detection rate for advanced neoplasia	3.1 (2.0 to 4.1)	<.001	0.7 (−0.2 to 1.6)	.13	2.4 (1.3 to 3.3)	<.001

Health Services Research	preferences for FIT or colonoscopy	colonoscopy were asked to complete a FIT before colonoscopy prep. Following both tests, patients completed a questionnaire which was based on analytic hierarchy process decision-making model.		by complications (0.321), and test preparation (0.223). **Patients preferred colonoscopy (0.599) compared with FIT (0.401) when considering accuracy; preferred FIT (0.589) compared with colonoscopy (0.411) when considering avoiding complications; and preferred FIT (0.650) compared with colonoscopy (0.350) when considering test preparation**. **The overall aggregated priorities were 0.517 for FIT, and 0.483 for colonoscopy, indicating patients slightly preferred FIT over colonoscopy**. Patients' preferences were significantly different before and after provision of detailed information on test features ($p < 0.0001$).	***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Bonello, B., et al. (2016). "Using a hypothetical scenario to assess public preferences for colorectal surveillance following screening-detected, intermediate-risk adenomas: annual home-based stool test vs. triennial colonoscopy." BMC Gastroenterology 16: 113.
2. Bowyer, H. L., et al. (2013). "Patient attitudes towards faecal immunochemical testing for haemoglobin as an alternative to colonoscopic surveillance of groups at increased risk of colorectal cancer." Journal of Medical Screening 20(3): 149-156.
3. Daskalakis, C., et al. (2014). "The effects of test preference, test access, and navigation on colorectal cancer screening." Cancer Epidemiology, Biomarkers & Prevention 23(8): 1521-1528.
4. Singal, A. G. et. Al. (2017) "Effect of Colonoscopy Outreach vs Fecal Immunochemical Test Outreach on Colorectal Cancer Screening Completion." JAMA 318(9); 806-815.
5. Wortley, S., et al. (2014). "Assessing stated preferences for colorectal cancer screening: a critical systematic review of discrete choice experiments." The Patient: Patient-Centered Outcomes Research 7(3): 271-282.
6. Xu, Y., et al. (2015). "Comparison of patient preferences for fecal immunochemical test or colonoscopy using the analytic hierarchy process." BMC Health Services Research 15: 175.

PICO Question: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Modality: FIT vs gFOBT

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Systematic Reviews: 1# of RCTs: # 0 of Non-Randomized Studies: 1					

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect

Deutekom, M., et al. (2010). *Scandanavian Journal of Gastroenterology*	The aim of the present study was to study differences in patient perception between i-FOBT and g-FOBT and differences in perception and participation rates among relevant subgroups in a population based study	Prospective cohort study. All invited received a FOBT kit, including an invitation letter, information leaflet, and a FOBT without costs for invitees. From the municipal databases, random samples were taken according to postal address and randomized to receive a 3-day guaiac-based FOBT (g-FOBT) or an automated semi-quantitative FIT. A questionnaire was sent by mail 2 weeks after initial invitation to all invitees, accompanied by a letter, which explained the purpose of the survey.	20,623 participants invited, 10,972 invitees participated	Table I. Differences in perception of g-FOBT and i-FOBT. g-FOBT / i-FOBT / *p*-Value Did you find the fecal occult blood test easy to use? [number of positive answers (yes) (%)] 3721 (91) 4772 (97) <0.01 Did you find the collection of stool easy to perform? [number of positive answers (yes) (%)] 3493 (87) 4523 (93) <0.01 I found the test disgusting [number of positive answers (yes) (%)] 915 (23) 405 (8) <0.01 I found the test shameful [number of positive answers (yes) (%)] 191 (5) 124 (3) <0.01 Not easy to use, not easy to perform, disgusting or shameful [number of positive answers (yes) (%)] 1275 (32) 742 (16) <0.01	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*
Wortley, S., et al. (2014). The Patient: Patient-Centered Outcomes Research	A systematic review of discrete choice experiments (DCEs) of CRC screening.	Systematic Review	1 study, 1920 participants	The study that only considered gFOBT vs FIT, did not provided enough detail to permit conclusions about the specific type of FOBT test respondents preferred.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	<u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Deutekom, M., et al. (2010). "Comparison of guaiac and immunological fecal occult blood tests in colorectal cancer screening: the patient perspective." Scandinavian Journal of Gastroenterology 45(11): 1345-1349 .
2. Wortley, S., et al. (2014). "Assessing stated preferences for colorectal cancer screening: a critical systematic review of discrete choice experiments." The Patient: Patient-Centered Outcomes Research 7(3): 271-282.

PICO Question: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Modality: CT Colonography vs. Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 4 # of Systematic Reviews: 1# of RCTs: 0 # of Non-Randomized Studies: 3					
Ghanouni, A., et al. (2012). *Patient Education and Counseling*	To examine public perceptions of and preferences for colonoscopy vs. CT colonography (CTC) as technologies for colorectal cancer (CRC) screening..	Quantitative Study. Six discussion groups were carried out with 30 adults aged 49–60 years (60% female). Information about different aspects of the tests (e.g. sensitivity, practical issues) was presented sequentially using a semi-structured, step-by-step topic guide. Discussions were recorded and analyzed using framework analysis.	30 adults	CTC was favored on the parameters of invasiveness, extra-colonic evaluation and interference with daily life, whereas sensitivity, avoiding false-positives and the capacity to remove polyps immediately were perceived to be important advantages of colonoscopy. **There was no strong preference for either test: with 46% preferring colonoscopy vs. 42% for CTC.**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline
Imaeda, A., et al. (2010). *Journal of General Internal Medicine*	To assess patient experiences with a Maximum Differences Scaling (MDS) tool for eliciting values about CRC screening test characteristics and determine whether patients vary in how they prioritize test characteristics and whether this variation relates to test preferences	Survey Study. MDS survey to elicit patients' values for characteristics related to fecal occult blood testing, sigmoidoscopy, colonoscopy, CT colonography and colon capsule endoscopy.	92 patients enrolled in primary care clinics at a VA hospital and associated university.	After completing the computer task, patients were asked to choose their preferred screening test**: 62% chose colonoscopy, 23% chose colon capsule, 10% CT colonography, 4% FOBT and 1% sigmoidoscopy.** Subjects preferring colonoscopy assigned greater importance to the sensitivity of the CRC screening test (median importance=21.5 versus 19.6, p=0.01) compared to those preferring less invasive procedures. There were no other statistically significant differences in importance ratings between those preferring colonoscopy and subjects preferring less invasive procedures.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

☐ High

☐ Moderate

☒ Low

☐ Very Low

Lin, O. S., et al. (2012). *Journal of General Internal Medicine*	A systematic review and meta-analysis on patient preference for CTC versus colonoscopy.	Systematic Review	23 studies (comprising 5616 subjects)	Amongst the included studies, 16 (comprising 3573 subjects) showed a statistically significant preference for CTC, three (927 subjects) showed a preference for colonoscopy, and four (1116 subjects) showed no difference in preference. Stratified analysis revealed that studies published in radiology journals (preference difference 0.590 [95 % CI 0.485, 0.694]) seemed more likely than studies in gastroenterology (0.218 [-0.015-0.451]) or general medicine journals (-0.158 [-0.389-0.072]) to report preference for CTC ($p<0.001$). Studies by radiology authors showed a trend towards stronger preference for CTC compared with studies by gastroenterology authors.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Moawad, F. J., et al. (2010). *American Journal of Roentgenology*	The aim of this project was to assess patient preferences between colonoscopy and CTC in an open access system.	Survey Study. Average-risk patients undergoing CRC screening completed a survey that assessed reasons for choosing CTC in lieu of colonoscopy, compliance with CRC screening if CTC was not offered, and which of the two tests they preferred.	250 patients	The most common reasons for undergoing CTC included convenience (33.6%), recommendation by referring provider (13.2%), and perceived safety (10.8%). Had CTC not been an available option, 91 of the 250 patients (36%) would have foregone CRC screening. Among the 57 patients who had experienced both CTC and colonoscopy 95% (n = 54) preferred CTC.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Ghanouni, A., et al. (2012). "Public perceptions and preferences for CT colonography or colonoscopy in colorectal cancer screening." Patient Education & Counseling 89(1): 116-121 .
2. Imaeda, A., et al. (2010). "What is most important to patients when deciding about colorectal screening?" Journal of General Internal Medicine 25(7): 688-693 .
3. Lin, O. S., et al. (2012). "Preference for colonoscopy versus computerized tomographic colonography: a systematic review and meta-analysis of observational studies." Journal of General Internal Medicine 27(10): 1349-1360 .
4. Moawad, F. J., et al. (2010). "CT colonography may improve colorectal cancer screening compliance." AJR. American Journal of Roentgenology 195(5): 1118-1123 .

PICO Question: What is the comparative patient acceptance of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood-screening test, methylated SEPT9 DNA?

Modality: FOBT vs colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 6 # of Systematic Reviews: 1 # of RCTs: 0# of Non-Randomized Studies: 5					
Hawley, S., et al. (2014). *American Journal of Managed Care*	To evaluate associations between patients' preferences for attributes of different colorectal (CRC) screening modalities, physician CRC screening recommendations during periodic health exams, and subsequent utilization of screening 12 months later in a large health maintenance organization (HMO). hypothetical scenario.	Multi-method study including baseline surveys from average-risk HMO members joined with audio recordings of 415 periodic health exams (PHEs) and electronic medical record (EMR) data. Methods Patient ratings of test attributes were used to create an algorithm reflecting type and strength of CRC screening modality preference at baseline. Physician recommendations were obtained from audio recordings. Attribute-based test preferences and physician recommendations were compared with CRC test use using chisquare tests. Associations between attribute-based preferences and physician recommendations were assessed using logistic regression.	64 physicians and 500 patients	**Based on attribute rankings, most participants had a weak preference for colonoscopy (COL) (41%), an unclear preference (22.4%), or a weak preference for fecal occult blood testing (FOBT) (18.6%).** About half (56%) of patients were screened at 12 months and there was no statistical association between attribute preferences and type of test received. Patients were significantly more likely to receive a recommendation including a test other than COL when they had an attribute-based test preference for FOBT (odds ratio [OR]: 2.17; 95% CI, 1.26-3.71; P < .01)	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline
Hawley, S. T., et al. (2008). *Medical Care*	To describe variation in CRC screening preferences among racially/ ethnically diverse	Survey Study. Patients completed a preference assessment instrument. Participants were asked to rate 8 hypothetical CRC screening test scenarios comprised of different combinations of 5 attributes and 6 scenarios designed to depict	212 patients	**Of the guideline-recommended tests, 37% preferred colonoscopy, 31 % FOBT, 15% barium enema, and 9% flexible sigmoidoscopy. Ratings of new technology tests (virtual colonoscopy and FIT) were significantly (P < 0.05) higher than ratings of guideline-recommended tests.** The order of the importance of	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome

Lower Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

	primary care patients.	guideline-recommended CRC screening tests (eg, fecal occult blood test, flexible sigmoidoscopy, colonoscopy, and double contrast barium enema) including new technology (eg, virtual colonoscopy, fecal immunochemical test). Responses were used to calculate the overall importance of test attributes, the relative importance of attribute levels, and to identify factors associated with preferences.		attributes was: what the test involved (37%), accuracy (19%), frequency (17%), discomfort (15%), and preparation (13%). Part-worth utilities for 1 attribute showed that collecting a stool sample was most preferable and endoscopy without sedation least preferable. **Multivariate regression found that race/ethnicity and specific test attributes were independently associated (P < 0.05) with test preferences.**	☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Hawley, S. T., et al. (2012). *Cancer*	The purpose of this study was to identify factors associated with colorectal cancer (CRC) screening test preference and examine the association between test preference and test completed.	Survey Study. After administration of a baseline survey, participants were randomized to 1 of 3 study groups stratified by sex and past CRC screening status (ever screened vs overdue for screening). The tailored intervention group participated in an interactive, tailored computer program; the web site group viewed general information about CRC screening from a publicly available web site, Screen for Life, which is the national CRC awareness campaign from the Centers for Disease Control and Prevention; and the survey-only control group received no additional information about CRC screening. As part of the study, all participants completed a wellness visit and exam. At the 12-month follow-up, medical records were reviewed to collect CRC screening utilization data.	1224 patients	**Most patients stated a test preference: 34.7% indicated a preference for FOBT, 41.1% for COL, 12.7% for SIG, 5.7% for BE, and 5.8% did not report a preference.** Factors statistically significantly associated at P<.10 with baseline test preference for COL, SIG, or FOBT in univariable analyses were family history, ever had CRC screening with SIG, physician recommendation for any CRC test, FOBT, and COL, preference for decision-making stage of readiness for CRC screening, test-specific self-efficacy for FOBT, COL or SIG, comparative perceived risk, worry, and perceived pros of CRC screening	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

Imaeda, A., et al. (2010). *Journal of General Internal Medicine*	To assess patient experiences with a Maximum Differences Scaling (MDS) tool for eliciting values about CRC screening test characteristics and determine whether patients vary in how they prioritize test characteristics and whether this variation relates to test preferences	Survey Study. MDS survey to elicit patients' values for characteristics related to fecal occult blood testing, sigmoidoscopy, colonoscopy, CT colonography and colon capsule endoscopy.	92 patients enrolled in primary care clinics at a VA hospital and associated university.	After completing the computer task, patients were asked to choose their preferred screening test**: 62% chose colonoscopy, 23% chose colon capsule, 10% CT colonography, 4% FOBT and 1% sigmoidoscopy.** Subjects preferring colonoscopy assigned greater importance to the sensitivity of the CRC screening test (median importance=21.5 versus 19.6, p=0.01) compared to those preferring less invasive procedures. There were no other statistically significant differences in importance ratings between those preferring colonoscopy and subjects preferring less invasive procedures.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

Palmer, R. C., et al. (2010). *Journal of Cancer Education*	To understand how characteristics of CRC screening tests influence preferences and CRC screening test choice.	In-depth personal interviews were conducted with 60 Americans to understand if CRC test preferences exist and to identify what attributes of screening tests influence test preferences.	60 participants	Colonoscopy preference (n=34) Reason (n) More revealing or thorough 27 More accurate test 22 Diagnose and treat polyps 19 Better/more effective test 16 Can do biopsy 16 FOBT is messy/unclean 12 Other test is old/obsolete 9 Test done by a professional 7 Checks internally 5 FOBT preference (n=26) Reason (n) Ease of test/simplicity 23 Non-invasiveness of the test 21 Low risk associated with test 19 Fear of sedation 18 No fluid preparation 16 Can do at home 14 Low cost 12 No benefit for colonoscopy/same results 10 Able to do test by self 8 Fear of hospital/clinical setting 5	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	

Wortley, S., et al. (2014). *The Patient: Patient-Centered Outcomes Research*	A systematic review of discrete choice experiments (DCEs) of CRC screening.	Systematic Review	4 studies, 4843 participants	Four studies included alternatives that described a variety of CRC screening techniques One study reported that both screened and screening- naive subjects preferred flexible sigmoidoscopy and colonoscopy to FOBT screening. Another found that fecal DNA testing, colonoscopy, and virtual colonoscopy (CT colonography) were the most preferred tests. A third, reported similar results, with respondents preferring newer tests such as virtual colonoscopy. **In most studies, FOBT was reported as the least preferred option despite being the test most commonly adopted in national screening programs.**	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

References:

1. Hawley, S., et al. (2014). "Managed care patients' preferences, physician recommendations, and colon cancer screening." American Journal of Managed Care 20(7): 555-561 .
2. Hawley, S. T., et al. (2008). "Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients." Medical Care 46(9 Suppl 1): S10-16
3. Hawley, S. T., et al. (2012). "Preferences for colorectal cancer screening tests and screening test use in a large multispecialty primary care practice." Cancer 118(10): 2726-2734 .
4. Imaeda, A., et al. (2010). "What is most important to patients when deciding about colorectal screening?" Journal of General Internal Medicine 25(7): 688-693 .
5. Palmer, R. C., et al. (2010). "Colorectal cancer screening preferences among African Americans: which screening test is preferred?" Journal of Cancer Education 25(4): 577-581 .
6. Wortley, S., et al. (2014). "Assessing stated preferences for colorectal cancer screening: a critical systematic review of discrete choice experiments." The Patient: Patient-Centered Outcomes Research 7(3): 271-282 .

Question #6: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Primary Literature:

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☒ Studies are indirect
Modality: FIT vs. Colonoscopy						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1						

<table>
<tr>
<td>Wong et al., 2015, Scientific Reports</td>
<td>To evaluate the cost effectiveness of FIT and colonscopy to detect colorectal neoplastic lesions based on data from a 5-year community screening service</td>
<td>Economic Evaluation; the incremental cost-effectiveness ratio (ICER) was assessed based on the detection rates of neoplastic lesions, and costs including screening compliance, polypectomy, colonoscopy complications, and staging of CRC detected</td>
<td>5,863 patients received yearly FIT and 4,869 received colonoscopy in China</td>
<td>
<table>
<tr><th></th><th>FIT</th><th>Colonoscopy</th></tr>
<tr><td>Overall</td><td></td><td></td></tr>
<tr><td>Screening related cost</td><td>1,225,369</td><td>4,916,415</td></tr>
<tr><td>Treatment cost</td><td>244,494</td><td>254,826</td></tr>
<tr><td>Screening related cost/ Treatment cost</td><td>5.0</td><td>19.3</td></tr>
<tr><td>Moderate Risk</td><td></td><td></td></tr>
<tr><td>Screening related cost</td><td>1,026,448</td><td>3,792,324</td></tr>
<tr><td>Cost of treatment</td><td>151,001</td><td>116,578</td></tr>
<tr><td>Screening related cost/ Treatment cost</td><td>6.8</td><td>32.5</td></tr>
<tr><td>High Risk</td><td></td><td></td></tr>
<tr><td>Screening related cost</td><td>199,184</td><td>1,119,993</td></tr>
<tr><td>Cost of treatment</td><td>93,900</td><td>138,248</td></tr>
<tr><td>Screening related cost/ Treatment cost</td><td>2.1</td><td>8.1</td></tr>
</table>
Using FIT scheme as a control, the incremental Cost-Effectiveness Ratio of screening colonoscopy was US$3,489, US$27,962, US$922,762 and US$23,981 to detect one adenoma, advanced neoplasia, CRC, and a composite endpoint of advanced neoplasia or stage I CRC respectively. The respective incremental cost effectiveness ratio (ICER) of screening colonoscopy to detect these lesions in lower-risk subjects was US$3,597, US$39,513, -US$2,765,876 (dominated) and US$32,297 for lower-risk subjects. The corresponding ICER was US$3,153, US$14,852, US$184,162 and US$13,919 for high-risk individuals
</td>
<td>Study Limitations =
☒ None
Economic Evaluation
☐ The research question is not clearly stated
☐ The perspective of interest is not clear (ie., societal, patient, health system, payer)
☐ The source(s) of effectiveness estimates are not clearly stated
☐ The primary outcome measures are not clearly stated
☐ The methods for the estimation of quantities and unit costs are not described</td>
<td>(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

<u>Increase Quality Rating if:</u>
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low</td>
</tr>
</table>

References:

1. Wong, M. C., Ching, J. Y., Chan, V. C., & Sung, J. J. (2015). The comparative cost-effectiveness of colorectal cancer screening using faecal immunochemical test vs. colonoscopy. *Scientific Reports, 5*, 13568. doi:https://dx.doi.org/10.1038/srep13568

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Hybrid Screening Strategy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1					
Dinh et al, 2013, *Clinical Gastroenterology and Hepatology*	To investigate the cost-effectiveness of a hybrid screening strategy that was based on a fecal immunological test (FIT) and colonoscopy	Economic Evaluation; cost-effectiveness analysis using the Archimedes Model to evaluate the effects of different CRC screening strategies on health outcomes and costs related to CRC In simulation model, patients receive annual or biennial FIT, beginning when patients are 50 years old, with a single colonoscopy when they are 66 years old	Population that represents members of Kaiser Permanente Northern California	A hybrid screening strategy led to substantial reductions in CRC incidence and mortality, gains in quality-adjusted life years (QALYs), and reductions in costs, comparable with those of the best single-test strategies. Screening by annual FIT of patients 50–65 years old and then a single colonoscopy when they were 66 years old (FIT/COLOx1) reduced CRC incidence by 72% and gained 110 QALYs for every 1000 people during a period of 30 years, compared with no screening. Compared with annual FIT, FIT/COLOx1 gained 1400 QALYs/100,000 persons at an incremental cost of $9700/QALY gained and required 55% fewer FITs. Compared with FIT/COLOx1, colonoscopy at 10-year intervals gained 500 QALYs/100,000 at an incremental cost of $35,100/QALY gained but required 37% more colonoscopies. Uncertainties associated with estimates of FIT performance within a program setting and sensitivities for flat and right-sided lesions are expected to have significant impacts on the cost-effectiveness results	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Dinh, T., Ladabaum, U., Alperin, P., Caldwell, C., Smith, R., & Levin, T. R. (2013). Health benefits and cost-effectiveness of a hybrid screening strategy for colorectal cancer. *Clinical Gastroenterology & Hepatology*, 11(9), 1158-1166. doi:https://dx.doi.org/10.1016/j.cgh.2013.03.013

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Colonoscopy vs. Sigmoidoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1					
Sharaf et al, 2013, *Am J Gastroenterol*	To explore the comparative effectiveness and cost-effectiveness of colonoscopy vs. sigmoidoscopy and alternative CRC screening strategies	Economic Analysis; performed a contemporary cost-utility analysis using a Markov model validated against data from randomized controlled trials of FOBT and sigmoidoscopy	Persons at average CRC risk within the general US population were modeled. Screening strategies included those recommended by the US Preventive Services Task Force	Compared with FIT, flexible sigmoidoscopy (FS) and colonscopy both cost < $ 50,000 / QALY gained when FIT per-cycle adherence was < 50 % . Colonscopy cost $ 56,800 / QALY gained vs. FS in the base case. Colonoscopy cost < $ 100,000 / QALY gained vs. FS when colonoscopy yielded a relative risk of proximal CRC of < 0.5 vs. no screening. In probabilistic analyses, colonoscopy was cost-effective vs. FS at a willingness-to-pay threshold of $ 100,000 / QALY gained in 84 % of iterations AUTHORS' CONCLUSION: Screening colonoscopy may be cost-effective compared with FIT and sigmoidoscopy, depending on the relative rates of screening uptake and adherence and the protective benefi t of colonoscopy in the proximal colon. Colonoscopy ' s cost-effectiveness compared with sigmoidoscopy is contingent on the ability to deliver ~ 50 % protection against CRC in the proximal colon	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:

☐ High

☐ Moderate

☒ Low

☐ Very Low

References:

1. Sharaf, R. N., & Ladabaum, U. (2013). Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *American Journal of Gastroenterology*, 108(1), 120-132. doi:https://dx.doi.org/10.1038/ajg.2012.

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Colonoscopy vs. Colonography

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 3 # of Systematic Reviews: 1 of RCTs: 0 # of Non-Randomized Studies: 2					
Kriza et al, 2013, *European Journal of Radiology*	To examine cost-effectiveness of CTC versus optical colonoscopy (COL) for CRC screening	Systematic Review of cost effectiveness studies	9 cost-effectiveness studies comparing CTC and COL as a screening tool and providing outcomes in life-years saved, published between January 2006 and November 2012	There was considerable heterogeneity in modelling complexity and methodology. Different model assumptions and inputs had large effects on resulting cost-effectiveness of CTC and COL. CTC was found to be dominant or cost-effective in three studies, assuming the most favourable scenario. COL was found to be not cost effective in one study In the remaining studies where CTC was found to be not cost-effective, it would be possible to transform CTC towards cost-effectiveness when altering assumptions on costs, adherence and for some studies, naturalhistory assumptions and CTC accuracy	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies
Pyenson et al, 2015, *Abdom Imaging*	To compare the Medicare population cost of CRC screening of average risk individuals by CTC vs. optical colonoscopy (OC)	Economic Evaluation; used Medicare claims data, fee schedules, established protocols, and other sources to estimate CTC and OC per-screen costs, including the costs of OC referrals for a subset of CTC patients. They then modeled and compared the Medicare costs of patients who complied with CTC and OC screening recommendations and tested alternative scenarios	Sampling of US Medicare popluation	CTC is 29% less expensive than OC for the Medicare population in the base scenario. Although the CTC cost advantage is increased or reduced under alternative scenarios, it is always positive	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

					☐ The methods for the estimation of quantities and unit costs are not described	
Zafar et al, 2015, *Acad Radiol*	To compare differences in Medicare costs 1 year after initial computed tomographic colonography (CTC) or initial optical colonoscopy (OC)	Retrospective Cohort Study; initial OC patients were matched on county of residence and year of screening	Medicare outpatients aged >/= 66 years who received initial CTC (n = 531) or OC (n = 17,593) between January 2007 and December 2008	**Higher adjusted costs per patient were revealed in the year after initial CTC compared to initial OC for outpatient testing related to potential colonic** ($50; 95% confidence interval [CI], $12–$88; P = .010) **and extracolonic findings** ($64; 95% CI, $23–$106; P = .002). However, **there were no differences in adjusted total costs per patient in the year after either modality ($2065; 95% CI, $1672–$5803; P = .28).** Similarly, adjusted costs did not differ between cohorts for inpatient ($267; 95% CI, $1017–$1550; P = .68) or outpatient care ($2828; 95% CI, $311–$5966; P = .08).	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Kriza, C., Emmert, M., Wahlster, P., Niederlander, C., & Kolominsky-Rabas, P. (2013). An international review of the main cost-effectiveness drivers of virtual colonography versus conventional colonoscopy for colorectal cancer screening: is the tide changing due to adherence? *European Journal of Radiology, 82*(11), e629-636. doi:https://dx.doi.org/10.1016/j.ejrad.2013.07.019
2. Pyenson, B., Pickhardt, P. J., Sawhney, T. G., & Berrios, M. (2015). Medicare cost of colorectal cancer screening: CT colonography vs. optical colonoscopy. *Abdominal Imaging, 40*(8), 2966-2976. doi:https://dx.doi.org/10.1007/s00261-015-0538-1
3. Zafar, H. M., Yang, J., Armstrong, K., & Groeneveld, P. (2015). Cost Differences After Initial CT Colonography Versus Optical Colonoscopy in the Elderly. *Academic Radiology, 22*(7), 807-813. doi:https://dx.doi.org/10.1016/j.acra.2015.03.002

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
☐ Studies are indirect

Modality: Colonoscopy

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*

Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1

Fitch et al, 2015, *Am J Manag Care*	To determine the value of life-years saved due to colorectal cancer (CRC) screening with colonoscopy for the population aged 50 to 64 years	Economic Evaluation; Monte Carlo simulation using a large multi-state cancer registry, a large national administrative claims database, and a model of CRC development based on published clinical literature, estimated the impact of screening with colonoscopy on incidence of CRC, aggregate cost of colonoscopies and CRC, and life-years saved	Model based on US patients	Found that increasing screening adherence from 50% to 100% would cost about $3 per member per month (2013 US$) and reduce CRC treatment costs by about $1 per member per month. The cost per life-year saved is approximately $12,000, an amount that is much lower than for cervical or breast cancer screening and comparable to lung cancer screening	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

References:

1. Fitch, K., Pyenson, B., Blumen, H., Weisman, T., & Small, A. (2015). The value of colonoscopic colorectal cancer screening of adults aged 50 to 64. *American Journal of Managed Care*, 21(7), e430-438.

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Colonography

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0					
Hanley et al, 2012, *International Journal of Technology Assessment in Health Care*	To review evidence on, and identify key factors influencing, cost-effectiveness of CTC screening	Systematic Review of cost-effectiveness and cost-utility analyses	16 cost-effectiveness or cost-utility analyses of CTC-based screening (11 from the US)	CTC appeared cost-effective versus no screening and, in general, compared to flexible sigmoidoscopy and fecal occult blood testing. Results were mixed comparing CTC to colonoscopy. Parameters most influencing cost-effectiveness included: CTC costs, screening uptake, threshold for polyp referral, and extra-colonic findings	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Hanly, P., Skally, M., Fenlon, H., & Sharp, L. (2012). Cost-effectiveness of computed tomography colonography in colorectal cancer screening: a systematic review. *International Journal of Technology Assessment in Health Care*, 28(4), 415-423. doi:https://dx.doi.org/10.1017/S0266462312000542

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: FIT

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0					
Guy et al, 2014, *International Journal of Technology Assessment in Health Care*	To estimate the initial investment required and the cost per person screened of a nationwide FIT-based colorectal cancer screening program among adults aged 50 years to 75 years	Economic Evaluation; using estimates from the literature, examined the total initial (first 2 years) annual cost and the cost per person screened under each intervention design	The target population included all adults aged 50 years to 75 years in the United States regardless of insurance status and CRC screening status	The initial additional investment required was estimated at $277.9 to $318.2 million annually, with an estimated 8.7 to 9.4 million individuals screened at a cost of $32 to $39 per person screened. The program was estimated to prevent 2900 to 3100 deaths annually	Study Limitations = ☐ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☒ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

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☐ Publication Bias
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Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Guy, G. P., Jr., Richardson, L. C., Pignone, M. P., & Plescia, M. (2014). Costs and benefits of an organized fecal immunochemical test-based colorectal cancer screening program in the United States. *Cancer*, 120(15), 2308-2315. doi:https://dx.doi.org/10.1002/cncr.28724

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: SEPT9 vs other modalitites

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 0 # of RCTs: 0 # of Non-Randomized Studies: 1					
Ladabaum et al, 2013, *American Association for Caner Research Journal*	To estimate the comparative effectiveness and cost effectiveness of colorectal cancer screening with emerging biomarkers, illustrated by a methylated Septin 9 DNA plasma assay (mSEPT9), versus established strategies	Economic Evaluation; cost-utility analysis using a validated decision analytic model comparing mSEPT9, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), sigmoidoscopy, and colonoscopy, projecting lifetime benefits and costs	Modeled the contemporary population in the United States at average risk for colorectal cancer, with age specific all-cause mortality based on U.S. Life Tables from 2003	SEPT9 decreased colorectal cancer incidence by 35% to 41% and colorectal cancer mortality by 53% to 61% at costs of $8,400 to $11,500/quality-adjusted life year gained versus no screening. **All established screening strategies were more effective than mSEPT9. FIT was cost saving, dominated mSEPT9, and was preferred among all the alternatives.** Screening uptake and longitudinal adherence rates over time strongly influenced the comparisons between strategies. At the population level, mSEPT9 yielded incremental benefit at acceptable costs when it increased the fraction of the population screened more than it was substituted for other strategies	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Ladabaum, U., Allen, J., Wandell, M., & Ramsey, S. (2013). Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. *Cancer Epidemiology, Biomarkers & Prevention*, 22(9), 1567-1576. doi:https://dx.doi.org/10.1158/1055-9965.EPI-13-0204

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Fecal DNA

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0					
Skally et al, 2013, *Appl Health Econ Health Policy*	To identiy key variables that impinge cost effectiveness of fDNA as a CRC screening tool	Systematic Review of cost-effectiveness studies	7 studies (4 from US) that undertook an economic evaluation of fDNA, using either a cost-effectiveness or cost-utility analysis, compared with other relevant screening modalities and/or no screening	fDNA was cost-effective when compared with no screening in six studies. **Compared with other screening modalities, fDNA was not considered cost-effective in any of the base-case analyses: in five studies it was dominated by all alternatives considered.** Sensitivity analyses identified cost, compliance, and test parameters as key influential parameters	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect
(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias
(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

References:

1. Skally, M., Hanly, P., & Sharp, L. (2013). Cost effectiveness of fecal DNA screening for colorectal cancer: a systematic review and quality appraisal of the literature. *Applied Health Economics & Health Policy*, 11(3), 181-192. doi:https://dx.doi.org/10.1007/s40258-013-0010-8

PICO Question: What is the comparative cost-effectiveness of the following screening programs: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA?

Modality: Various

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Systematic Reviews: 1 # of RCTs: 0 # of Non-Randomized Studies: 0					
Barzi et al, 2017, *Cancer*	To compare the outcomes of various screening strategies on CRC outcomes	Economic Evaluation; Markov model representing the natural history of CRC was built and validated against empiric data from screening trials as well as the Microstimulation Screening Analysis (MISCAN) model. Thirteen screening strategies based on colonoscopy, sigmoidoscopy, computed tomographic colonography, as well as fecal immunochemical, occult blood, and stool DNA testing were compared with no screening – societal perspective	A simulated sample of the US general population ages 50 to 75 years with an average risk of CRC was followed for up to 35 years or until death	Colonoscopy emerged as the most effective strategy under the base and alternate cases. CT colonography and flexible sigmoidoscopy were the next 2 most effective strategies, respectively. DNA testing was more effective than FOBT and FIT by a small margin. Screening was associated with a 5% to 23%relative-risk reduction and a 12% to 34% cancer-specific mortality risk reduction compared with no screening. The highest risk-reduction levels were associated with the colonoscopy strategy. Colonoscopy emerged as the most effective screening strategy with the highest life years gained (0.022 life years) and CRCs prevented (n = 1068) and the lowest total costs ($2861). These values were 0.012 life years gained, 574 CRCs prevented, and a total cost of $3164, respectively, for FOBT; and 0.011 life years gained, 647 CRCs prevented, and a total cost of $4296, respectively, for DNA testing. Authors noted that improved sensitivity or specificity of a screening test for CRC detection was not sufficient to close the outcomes gap compared with colonoscopy	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

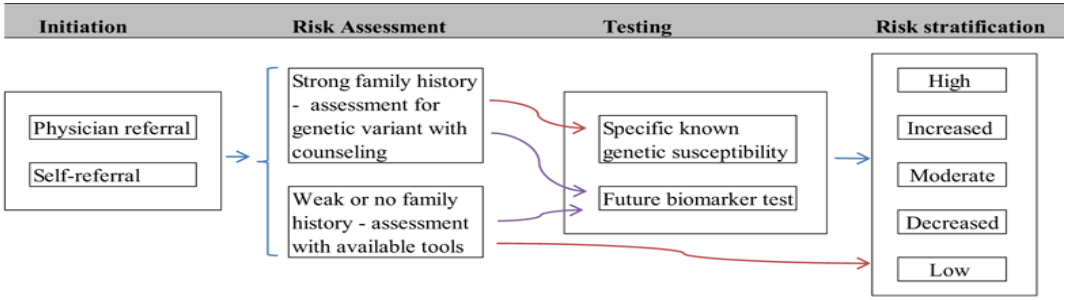
Quality (certainty) of evidence for studies as a whole:
☐ High

Subramanian et al, 2017, *Cancer Causes and Control*	To develop an innovative model to assess the effectiveness, cost, and harms of risk stratified colorectal cancer screening	Economic Evaluation; updated a previously validated microsimulation model consisting of three interlinked components: risk assessment, natural history, and screening/treatment modules. Used data from representative national surveys and the literature to create a synthetic population that mimics the family history and genetic profile of the US population. Applied risk stratification based on published risk assessment tools to triage individuals into five risk categories: high, increased, medium, decreased, and low See table 1 below	US population	On average, the incremental cost of risk stratified screening for colorectal cancer compared to the current approach at 60% and 80% compliance rates is $18,342 and $23,961 per life year gained. The harms in terms of false positives and perforations are consistently lower for personalized scenarios across all compliance rates. False positives are reduced by more than 47.0% and perforations by at least 9.9%. There is considerable uncertainty in the life years gained, but the reduction in harms remains stable under all scenarios	Study Limitations = ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described	☐ Moderate ☒ Low ☐ Very Low

References:

1. Barzi, A., Lenz, H. J., Quinn, D. I., & Sadeghi, S. (2017). Comparative effectiveness of screening strategies for colorectal cancer. *Cancer*, 123(9), 1516-1527. doi:10.1002/cncr.30518
2. Subramanian, S., Bobashev, G., Morris, R. J., & Hoover, S. (2017). Personalized medicine for prevention: can risk stratified screening decrease colorectal cancer mortality at an acceptable cost? *Cancer Causes & Control*, 28(4), 299-308. doi:10.1007/s10552-017-0864-4

Table 1. Framework for Risk Stratification, Screening Schedules and Scenarios --- from Subramanian study



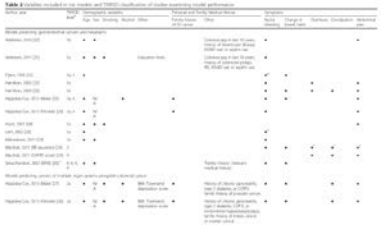
Risk Category	% Pop	Screening Schedule
High*	<0.01%	Colonoscopy every 2 years starting at age 20
Increased	~10%	Colonoscopy every 5 years starting at age 40
Medium	~30%	Colonoscopy every 10 years or fecal test annually starting at age 50**
Decreased	~30%	Colonoscopy at age 50 only, or fecal test every 2 years starting at age 50**
Low	~30%	Colonoscopy at age 50 only
Scenarios	**Description**	
Present	Majority of individuals are considered average risk and begin screening at age 50 using either colonoscopy or fecal tests. Individuals only undergo risk assessment when family history is present; they are then assigned to high or increased risk and begin screening colonoscopies at an earlier age	
Personalized	Individuals undergo risk assessment when family history is known and at ages 40 and 50. Individuals are assigned to the five risk categories described above and screening schedule is based on assigned risk category	
Future	Individuals undergo risk assessment and biomarker testing when family history is known and at ages 40 and 50. Individuals are assigned to the five risk categories described above and screening schedule is based on assigned risk category	

Question #7: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Primary Literature:

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Modality: Clinical Scoring System; **Outcome:** CRC

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 3 # of Systematic Reviews: 1 # of Non-Randomized Studies: 2					
Usher-Smith, J.A., et al., 2016, *Cancer Prevention Research*	To systematically review and compare the performance of models that predict the risk of undiagnosed prevalent primary CRC for symptomatic individuals	Systematic Review	18 papers describing 15 risk models were included	Nine models were developed in primary care populations and six in secondary care. **Four had good discrimination (AUROC > 0.8) in external validation studies, and sensitivity and specificity ranged from 0.25 and 0.99 to 0.99 and 0.46 depending on the cut-off chosen.** Seventeen variables were included in three or more models: four demographic variables (age, sex, smoking, alcohol); family history of CRC; eight symptoms (rectal bleeding, change in bowel habit, diarrhoea, constipation, abdominal pain, weight loss, loss of appetite, mucous in the stool); abnormal rectal examination; and three investigations (haemoglobin, mean cell volume, faecal occult blood testing). All models included symptoms, four included only symptoms, and most also included age (n = 11) and sex (n = 9). 	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies

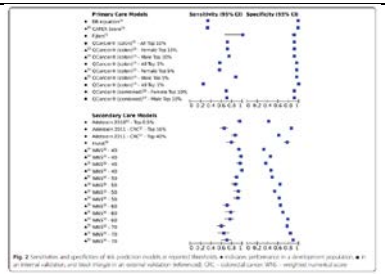
Lower Quality Rating if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

						Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Hsu, L., et al., 2015, *Gastroenterology*	To refine models designed to determine risk of CRC by incorporating information from common genetic susceptibility loci	Retrospective Study; Developed risk determination models based on sex, age, family history, genetic risk score (number of risk alleles carried at 27 validated common CRC susceptibility loci), and history of endoscopic examinations from data collected in six studies performed from 1990 through 2011 in the United States and Germany. The model was validated using data collected from approximately 1800 participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, conducted from 1993 through 2001 in the United States.	120,000 participants	A CRC genetic risk score that independently predicted which patients in the training set would develop CRC was identified. **Compared with determination of risk based only on family history, adding the genetic risk score increased discriminatory accuracy from 0.51 to 0.59 (P=.0028) for men and from 0.52 to 0.56 (P=.14) for women**. The age- and sex-specific 10 y CRC absolute risk was calculated and estimates were based on the number of risk alleles, family history, and history of endoscopic examinations. A model that included a genetic risk score better determined the recommended starting age for screening in subjects with and without family histories of CRC. The starting age for high-risk men (family history of CRC and genetic risk score=90%) was 42 y, and for low-risk men (no family history of CRC and genetic risk score=10%) was 52 years. For men with no family history and a high genetic risk score (90%), the starting age would be 47 years; this is an intermediate value that is 5 years earlier than it would be for men with a genetic risk score of 10%. Similar trends were observed in women.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Hsu, L., et al. (2015). "A model to determine colorectal cancer risk using common genetic susceptibility loci." Gastroenterology 148(7): 1330-1339.e1314.
2. Usher-Smith, J. A., et al. (2016). "Risk Prediction Models for Colorectal Cancer: A Systematic Review." Cancer Prevention Research 9(1): 13-26.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Modality: Clinical Scoring System; **Outcome:** Adenoma Risk						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Non-Randomized Studies: 2						
Shaukat, A., et al., 2015, *Biomarkers & Prevention*	To develop and validate a clinical score for predicting risk of adenoma from screening colonoscopy	Cohort Study; Baseline data from men and women who underwent screening colonoscopy from the RCT National Colonoscopy Study (NCS) was used to develop and validate an adenoma risk model. The study asked all participants to complete baseline questionnaires on clinical risk factors and family history. The risk score developed on phase I participants was applied to phase II participants. Risk score was estimated from logistic regression yielded an area under the receiver operating characteristics curve (AUROCC).	451 subjects were included in the development model and 1,334 subjects were included in the validation of the risk score	Variables in the prediction of adenoma risk for colonoscopy screening were age (likelihood ratio test for overall contribution to model, P < 0.001), male sex (P < 0.001), body mass index (P < 0.001), family history of at least one first-degree relative with colorectal cancer (P = 0.036), and smoking history (P < 0.001). **The adjusted AUROCC of 0.67 [95% confidence interval (CI), 0.61-0.74] for the derivation cohort was not statistically significantly different from that in the validation cohort.** The adjusted AUROCC for the entire cohort was 0.64 (95% CI, 0.60-0.67).	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Cao, Y., et al., 2015, *International Journal of Cancer*	To develop a risk assessment tool for high-risk colorectal adenoma (advanced adenoma or >/= 3 adenomas) that can be implemented in clinical/general settings through evaluating a comprehensive list of risk factors	Prospective cohort study; Utilized the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) participant data. Participants were asked in questionnaire whether polyps had been diagnosed in the past two years. When a diagnosis was reported, investigators acquired medical records and pathology reports. A risk assessment was conducting including age, personal history of diabetes, family history of colorectal cancer in first-degree relative, regular use of aspirin, multivitamin use, body mass index, height, calcium intake from supplement and food, supplemental vitamin D, red meat intake, smoking	4,881 asymptomatic white men and 17,970 women who underwent colonoscopy as first time screening for CRC	A total of 330 (6.7%) men and 678 (3.8%) women were diagnosed with high-risk adenoma at first-time screening colonoscopy. The model for men included age, family history of colorectal cancer, BMI, smoking, sitting watching TV/VCR, regular aspirin/NSAID use, physical activity, and a joint term of multivitamin and alcohol. For women, the model included age, family history of colorectal cancer, BMI, smoking, alcohol, beef/pork/lamb as main dish, regular aspirin/NSAID, calcium, and oral contraceptive use. The C-statistic of the model for men was 0.67 and 0.60 for women (0.64 and 0.57 in cross-validation). Both models calibrated well. **The predicted risk of high-risk adenoma for men in the top decile was 15.4% vs 1.8% for men in the bottom decile (Odds**	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☒ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

		status, alcohol intake, and sedentary behavior. Additional, oral contraceptive use, menopausal status, and postmenopausal hormone use was evaluated in women.		**Ratio [OR]=9.41), and 6.6% vs 2.1% for women (OR=3.48).**		

References:

1. Cao, Y., et al. (2015). "Assessing individual risk for high-risk colorectal adenoma at first-time screening colonoscopy." International Journal of Cancer 137(7): 1719-1728.
2. Shaukat, A., et al. (2015). "Development and validation of a clinical score for predicting risk of adenoma at screening colonoscopy." Cancer Epidemiology, Biomarkers & Prevention 24(6): 913-920.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Modality: Clinical Scoring System; **Outcome:** Colorectal Neoplasia

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 6 # of Non-Randomized Studies: 6					
Wong, M.C., et al., 2014, *Gut*	To develop and validate a clinical scoring system to predict the risks of colorectal neoplasia to better inform screening participants and facilitate their screening test choice	Prospective Cohort Study; Random sampling of Chinese participants undergoing colonoscopy in Hong Kong. Independent risk factors were evaluated from first cohort for colorectal neoplasia, defined as adenoma, advanced neoplasia, colorectal cancer or any combination therefore using binary regression analysis. The ORs from cohort for significant risk factors were used to develop a scoring system ranging from 0 to 6: 0 – 2 "average risk" (AR) and 3 – 6 "high risk" (HR). The risk factors examined included age, gender, family history of CRC, smoking, drinking (current drinkers of alcohol for more than two times per week vs those drinking less or non-drinkers), Body Mass index (BMI), self-reported	5,220 asymptomatic screening participants; 2,000 participants evaluated for independent risk factors	The prevalence of colorectal neoplasia in the derivation and validation cohorts was 31.4% and 30.8%, respectively. Using the scoring system developed, 78.9% and 21.1% in the validation cohort were classified as AR and HR, respectively. The prevalence of colorectal neoplasia in the AR and HR groups was 27.1% and 44.6%, respectively. **The subjects in the HR group had 1.65-fold (95% CI 1.49 to 1.83) increased prevalence of colorectal neoplasia than the AR group.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

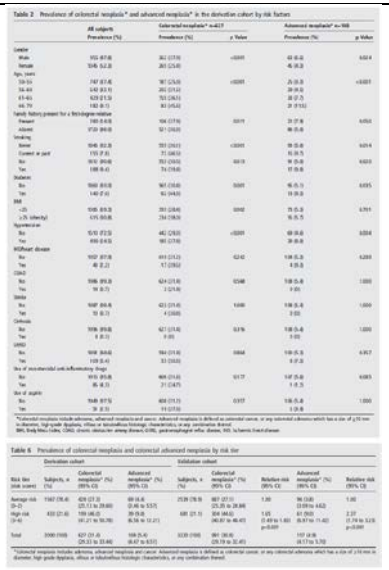
☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

		medical conditions, use of non-steroidal anti-inflammatory agents (NSAIDS) and aspirin.				☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Ruco, A., et al., 2015, *BMC Gastroenterology*	To conduct an external evaluation of a previously published risk index for advanced neoplasia (AN)	Cohort Study; One cohort consisted of patients completing baseline questionnaire that covered demographic information, history of prior colon examinations, medical history, prior surgeries, smoking history, alcohol consumption, physical activity, non-steroidal anti-inflammatory drug (NSAID) use, and family history of cancer. The external validation cohort assessed the strength of the association between the predictors of AN. The analysis used the risk score developed by Kaminski et al. with updated definitions to include	5,137 asymptomatic participants	The prevalence of AN in the study cohort was 6.8 %. The likelihood of detecting AN increased from 3.6 to 13.1 % for those with a risk score of 1 to 6 respectively. **The c-statistic for the multivariable logistic model in our cohort was 0.64 (95 % CI = 0.61–067) indicating modest overlap between risk scores.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

		participants as old as 74 years of age. **Table 1** Risk index adapted from Kaminski et al. [6] with updated definitions to include participants older than 66 years Risk factor / Category / Score Age, years: 40–49 (0); 50–54 (1); 55–59 (2); 60–66 (3); >66 (3) Sex: Female (0); Male (2) Family history: None (0); 1 first-degree relative ≥ 60 years old (1); 1 first-degree relative < 60 years old (2); 2 first-degree relatives (2) Smoking, pack years: None (0); <10 (0); 10–19 (1); ≥20 (1) BMI, kg/m²: <25 (0); 25–29 (0); ≥30 (1 – Female, 0 – Male)				
Kim, D.H., et al., 2015, *Journal of Clinical Gastroenterology*	To develop and validate a risk stratification-based screening model for predicting colorectal advance neoplasia in Korea	Prospective Cohort Study; Developed Korean Colorectal Screening (KCS) score by optimizing and adjusting Asia-Pacific Colorectal Screening (APCS) score to predict advanced neoplasia in asymptotic Korean population who received screening colonoscopy. The KCS score was divided into 3 risk tiers: score 0 to 1, "average risk (AR)"; 2 to 3, "moderate risk (MR)"; and 4 to 8, "high risk (HR)." Score validities were assessed by receiver operating characteristics (ROC) analysis, and the predicted risks of advanced neoplasia were assessed by comparing risk tier groups. Each subject in the validation group was assigned a personal risk score, as	3,561 subjects in derivation cohort and 1,316 subjects in the validation cohort	4.7% in the derivation cohort and 4.3% in the validation cohort had a prevalence of advanced neoplasia. After a multivariate analysis, KCS was developed as 0 to 8 points comprising of age, sex, body mass index, smoking, and family history of CRC. Using KCS scores to stratify the validation cohort, the prevalence of advanced neoplasia in the 3 risk tiers (average, moderate, and high) were 2.0%, 3.7%, and 10.9%, respectively. Moderate-risk and high-risk tiers showed 2.1- and 6.5-fold increased prevalence, respectively, of advanced neoplasia compared with average risk tier. In addition, **KCS score showed relatively good discriminative power (ROC=0.681) and higher sensitivity compared with APCS score for the high-risk tier.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

		calculated by the KCS scoring method. The performance of the KCS score to predict the risk of advanced neoplasia was evaluated by determining the ORs for each risk tier, and the validity of the KCS score was assessed by ROC analysis.		**TABLE 4.** Prevalence of Advanced Neoplasia by Risk Tier in the Validation Cohort According to KCS and APCS Score Risk Tier | No. Subjects (%) | Advanced Neoplasia Number (%) (95% CI) | RR (95% CI) KCS score Average (0-1) 429 (32.6) 8 (1.9) (0.55-3.17) Reference Moderate (2-3) 686 (52.1) 26 (3.8) (2.33-5.25) 2.1 (0.9-4.6) High (4-8) 201 (15.3) 22 (10.9) (6.53-15.37) 6.5 (2.8-14.8) Total 1316 (100) 56 (4.3) (3.15-5.36) APCS score Average (0-1) 495 (37.6) 12 (2.4) (1.04-3.80) Reference Moderate (2-3) 704 (53.5) 28 (4.0) (2.51-5.45) 1.7 (0.8-3.3) High (4-7) 117 (8.9) 16 (13.7) (7.30-20.06) 6.4 (2.9-13.9) Total 1316 (100) 56 (4.3) (3.15-5.36) APCS indicates Asia-Pacific Colorectal Screening; CI, confidence interval; KCS, Korean Colorectal Screening.		
Ladabaum, U., et al., 2016, *Cancer*	To explore whether the National Cancer Institute (NCI) CRC risk-assessment tool, which was developed to predict future CRC risk, could predict current AN prevalence in a diverse population, thereby allowing its use in risk stratification for screening.	Prospective Study; Individuals who underwent colonoscopy were invited to complete a risk factor questionnaire that included the NCI tool questions before their colonoscopy. The 10-year NCI risk score was calculated for each participant using the appropriate algorithm for women and men, and the association between AN at colonoscopy and predicted CRC risk was analyzed. The predictors included in the NCI CRC risk-assessment tool for women are an age indicator, body mass index, estrogen status within the last 2 years, servings of vegetables per day, aspirin and nonsteroidal anti-inflammatory drug use, prior negative sigmoidoscopy and/or colonoscopy, polyp history, number of relatives with CRC, and current vigorous leisure time activity (with different individual factors used to	509 screenees; 256 women and 253 men	58 had AN**. The prevalence of AN increased progressively from 6% in the lowest risk-score quintile to 17% in the highest risk-score quintile (P = .002).** Risk-score distributions in individuals with versus without AN differed significantly (median, 1.38 [0.90–1.87] vs 1.02 [0.62–1.57], respectively; P = .003), with substantial overlap. **The discriminatory accuracy of the tool was modest, with areas under the curve of 0.61 (95% confidence interval [CI], 0.54–0.69) overall, 0.59 (95% CI, 0.49–0.70) for women, and 0.63 (95% CI, 0.53–0.73) for men.** The results did not change substantively when the analysis was restricted to adenomatous lesions or to screening procedures without any additional incidental indication.	Study Limitations = ☐ None Non-Randomized Studies ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	

		predict proximal CRC, distal CRC, or rectal cancer). The predictors included in the NCI CRC risk-assessment tool for men are body mass index, servings of vegetables per day, aspirin and nonsteroidal anti-inflammatory drug use, usual number of cigarettes smoked per day and years of smoking in current and former smokers, prior negative sigmoidoscopy and/or colonoscopy, polyp history, number of relatives with CRC, and current vigorous leisure time activity (with different individual factors used to predict proximal CRC, distal CRC, or rectal cancer).				
Park, Y.M., et al., 2017, *BMC Gastroenterology*	To identify risk factors and develop a simple prediction model for advanced colorectal neoplasm in asymptomatic individuals aged 40-49	Cross-sectional Study; Clinical data were collected on asymptomatic subjects aged 40–49 years who underwent colonoscopy for routine health examination. Subjects were randomly allocated to a development or validation set. Logistic regression analysis was used to determine predictors of advanced colorectal neoplasm. A simple scoring model for advanced colorectal neoplasm = Age [0: 40–44, 1: 45–49 years] × 1 + Sex [0: female, 1: male] × 2 + Serology of H. pylori [0: negative, 1: positive] × 2 + High triglyceride level [0: normal range, 1: high] × 2 + Low HDL level [0: normal range, 1: low] × 2 The range of the total score for this risk model was 0–9. This	2,781 subjects	The prevalence of overall and advanced colorectal neoplasm was 20.2% in development cohort and 2.5% in validation cohort. Older age (45–49 years), male sex, positive serology of Helicobacter pylori, and high triglyceride and low high-density lipoprotein (HDL) levels were independently associated with an increased risk of advanced colorectal neoplasm. BMI (body mass index) was not significant in multivariable analysis. We developed a simple scoring model for advanced colorectal neoplasm (range 0–9). **A cutoff of ≥4 defined 43% of subjects as high risk for advanced colorectal neoplasm (sensitivity, 79%; specificity, 58%; area under the receiver operating curve = 0.72) in the validation datasets.**	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

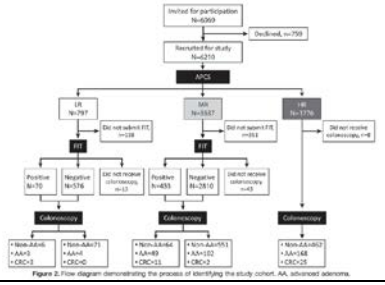
		model yielded an AUROC of 0.74 for predicting advanced neoplasm in the development set.		**Table 3** Comparison of variables based on the presence of advanced neoplasm in the training set Advanced neoplasm | Development set ($n = 1,844$) | *P*-value No ($n = 1,798$) | Yes ($n = 46$) Sex | | | <0.001 Male | 1,044 (96.4) | 39 (3.6) Female | 754 (99.1) | 7 (0.9) Age group | | | 0.053 40–44 | 805 (98.3) | 14 (1.7) 45–49 | 993 (96.9) | 32 (3.1) Blood pressure (mmHg) | | | 0.151 Normal | 809 (98.2) | 15 (1.8) Pre-HTN | 741 (97.2) | 21 (2.8) HTN | 248 (96.1) | 10 (3.9) BMI (kg/m^2) | | | 0.016 < 23.0 | 845 (98.6) | 12 (1.4) < 25.0 | 458 (96.8) | 15 (3.2) 25.0 | 495 (96.3) | 19 (3.7) Anti-*H. pylori* IgG | | | 0.009 Positive | 1,062 (96.7) | 36 (3.3) Negative | 736 (98.7) | 10 (1.3) Total cholesterol | | | 0.755 Normal | 1,529 (97.8) | 40 (2.2) Elevation (≥240 mg/dL) | 222 (97.5) | 5 (2.5) LDL-c | | | 0.237 Normal | 140 (100) | 0 Elevation (≥100 mg/dL) | 998 (99.0) | 10 (1.0) HDL-c (<40 mg/dL) | | | <0.001 Normal | 1,554 (98.1) | 30 (1.9) Low (<40 mg/dL) | 244 (93.8) | 16 (6.2) Triglyceride | | | <0.001 Normal | 1,588 (98.0) | 32 (2.0) Elevation (≥200 mg/dL) | 210 (93.8) | 14 (6.3) *HTN* hypertension, *BMI* body mass index, *LDL-c* low-density lipoprotein, *HDL-c* high-density lipoprotein, *H. pylori*, *Helicobacter pylori*		
Schroy, P.C., et al., 2015, *American Journal of Gastroenterology*	To develop and validate a clinical index for estimating the probability of ACN at screening colonoscopy	Cross-sectional Study; Conducted analysis of patients undergoing screening colonoscopy at two urban safety net hospitals. Final index consisted of 5 independent predictors of risk (age, smoking, alcohol, intake, height and a combined sex/race/ethnicity variable).	3,543 asymptomatic, mostly average-risk patients 50- 79 years of age undergoing screening colonoscopy	Smoking was the strongest predictor (net reclassification improvement [NRI], 8.4% and height the weakest (NRI, 1.5%). **Using a simplified weighted scored system based on 0.5 increments of the adjusted odds ratio, the risk of ACN ranged from 3.2% (95% CI, 2.6 to 3.9) for the low-risk group (score </=2) to 8.6% (95% CI, 7.4-9.7) for the intermediate/high-risk group (score 3-11).** The model had moderate to good over discrimination (C-statistic, 0.69; 95% CI, 0.66-0.72) and good calibration (*P* = 0.73 to 0.93).	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	

References:

1. Kim, D. H., et al. (2015). "Development and validation of a risk stratification-based screening model for predicting colorectal advanced neoplasia in Korea." Journal of Clinical Gastroenterology 49(1): 41-49.
2. Ladabaum, U., et al. (2016). "Predicting advanced neoplasia at colonoscopy in a diverse population with the National Cancer Institute colorectal cancer risk-assessment tool." Cancer 122(17): 2663-2670.
3. Park, Y. M., et al. (2017). "A simple scoring model for advanced colorectal neoplasm in asymptomatic subjects aged 40-49 years." BMC Gastroenterology 17(1): 7.
4. Ruco, A., et al. (2015). "Evaluation of a clinical risk index for advanced colorectal neoplasia among a North American population of screening age." BMC Gastroenterology 15: 162.
5. Schroy, P. C., 3rd, et al. (2015). "A Risk Prediction Index for Advanced Colorectal Neoplasia at Screening Colonoscopy." American Journal of Gastroenterology 110(7): 1062-1071.
6. Wong, M. C., et al. (2014). "A validated tool to predict colorectal neoplasia and inform screening choice for asymptomatic subjects." Gut 63(7): 1130-1136.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Modality: Combining Clinical Scoring System and FIT; **Outcome:** Identification of High-Risk Patients

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 2 # of Non-Randomized Studies: 2					
Chiu, H.M., et al., 2016, *Gastroenterology*	To test an algorithm that combined Asia-Pacific Colorectal Screening (APCS) scores with fecal immunochemical test (FIT) in colorectal cancer screening	Prospective Study; Asymptomatic individuals visiting bowel cancer screening centers or general medical outpatient clinics older than 40 years old in 12 Asia-Pacific regions were included. APCS scores were calculated for each individual (0-1 = low risk [LR], 2 – 3 = medium risk [MR], and 4 – 7 = high risk [HR] for advanced neoplasm [AN]. LR and MR subjects were offered FIT and referred for early colonoscopies.	5,657 subjects	646 subjects (11.4%) were considered LR, 3,243 subjects (57.3%) were considered MR, and 1,768 subjects (31.3%) were considered HR for AN. The proportions of individuals with an AN in these groups were 1.5%, 5.1%, and 10.9% respectively. Compared with LR group, MR and HR subjects had a 3.4-fold increase and a 7.8-fold increase in risk for AN, respectively**. A total of 70.6% of subjects with AN (95% CI: 65.6% - 75.1%) and 95.1% subjects with invasive cancers (95% CI: 82.2% - 99.2%) were correctly instructed to undergo early colonoscopy examination.** 	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

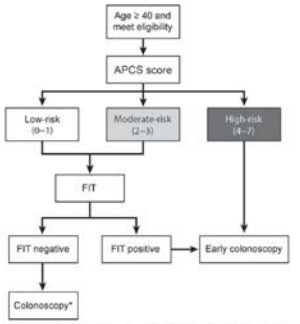
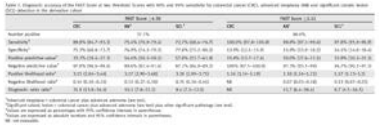
☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

		 **Figure 1.** Conceptual framework of the Asia-Pacific Colorectal Screening (APCS) score-based screening algorithm. *Only for this study.				☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low
Cubiella, J., et al., 2017, *International Journal of Cancer*	To develop and asses the diagnostic accuracy of the FAST (Fecal hemoglobin concentration, Age, and Sex Test) Score, an easy to calculate prediction tool based not only on f-Hb, but also on age and sex	Retrospective Cohort Study; Using data collected from 5 studies, the FAST Score (Validation Cohort) was compared with the COLONPREDICT Score (Derivation) Derivation cohort – Included consecutive symptomatic patients referred to colonoscopy from the COLONPREDICT study. Patients collected one fecal sample from a single bowel movement during the week before the colonoscopy. Validation cohort – FAST Score studies included symptomatic patients recruited in five studies evaluating the diagnostic accuracy of different FIT analytical systems for CRC, advanced neoplasia (AN), and significant colonic lesion (SCL) detection or exclusion in symptomatic patients. Patients were rapidly allocated to one of three risk groups: high risk, medium risk and low risk.	1,572 patients in derivation cohort and 3,976 patients in validation cohort	**For CRC, the odds ratio (OR) of the variables included in the Score were: age (years): 1.03 (95% confidence intervals (CI): 1.02–1.05), male sex: 1.6 (95% CI: 1.1–2.3) and f-Hb (0–<20 mg Hb/g feces): 2.0 (95% CI: 0.7–5.5), (20-<200 mg Hb/g): 16.8 (95% CI: 6.6–42.0), _200 mg Hb/g: 65.7 (95% CI: 26.3–164.1).** The AUC for CRC detection was 0.88 (95% CI: 0.85–0.90) in the derivation and 0.91 (95% CI: 0.90–093; p50.005) in the validation cohort. At the two Score thresholds with 90% (4.50) and 99% (2.12) sensitivity for CRC, the Score had equivalent sensitivity, although the specificity was higher in the validation cohort ($p < 0.001$). Accordingly, the validation cohort was divided into three groups: high (21.4% of the cohort, positive predictive value—PPV: 21.7%), intermediate (59.8%, PPV: 0.9%) and low (18.8%, PPV: 0.0%) risk for CRC. 	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

1. Chiu, H. M., et al. (2016). "A Risk-Scoring System Combined With a Fecal Immunochemical Test Is Effective in Screening High-Risk Subjects for Early Colonoscopy to Detect Advanced Colorectal Neoplasms." Gastroenterology 150(3): 617-625.e613.
2. Cubiella, J., et al. (2017). "The fecal hemoglobin concentration, age and sex test score: Development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients." International Journal of Cancer 140(10): 2201-2211.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?

Modality: Patient Characteristics; **Outcome:** CRC

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*
Total # of Studies: 1 # of Non-Randomized Studies: 1					
Carroll, J.C., et al., 2017, *Canadian Family Physician*	To assess the proportion of primary care patients who report a family history (FH) of type 2 diabetes, coronary artery disease, breast cancer, or colorectal cancer, assess concordance of FH information derived from the electronic medical record (EMR) compared with patient-completed health questionnaires; and assess whether appropriate screening was informed by risk based solely on FH.	Data from the BETTER (Building on Existing Tools to Improve Chronic Disease Prevention and Screening in Primary Care) trial were used. Patients were mailed questionnaires. Baseline FH and screening data were obtained for enrolled patients from the EMR and health questionnaires.	775 participants	The mean age of participants was 52.5 years and 72% were female. A minimum of 12% of patients (range 12% to 36%) had a reported FH of 1 of 4 chronic diseases. **Among patients with positive FH, the following proportions of patients had that FH recorded in the EMR compared with the questionnaire: CRC, 12% in the EMR versus 14% on the questionnaire, kappa = 0.510**. There was moderate agreement for CRC. The presence of FH was a significant predictor of CRC screening (odds ratio 1.9, 95% CI 1.1 to 3.1).	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline

Lower Quality Rating if:

☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:

☐ Large Effect

☐ Dose-response gradient

☐ Plausible confounders or other biases increase certainty of effect

						Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

References:

1. Carroll, J. C., et al. (2017). "Assessing family history of chronic disease in primary care: Prevalence, documentation, and appropriate screening." Canadian Family Physician 63(1): e58-e67.

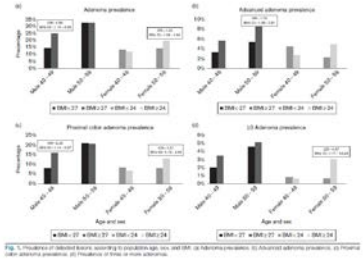
PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?						Lower Quality Rating if: ☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient
Modality: Patient Characteristics; **Outcome:** Colorectal Adenoma						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Non-Randomized Studies: 2						
Lee, S.E., et al., 2016, *World Journal of Gastroenterology*	To investigate prevalence and risk factors for colorectal neoplasms in adults aged < 50 years, for whom screening is not recommended.	Cross-Sectional Study; Compared prevalence and characteristics of colorectal and advanced adenomas in patients aged < 50 years who underwent colonoscopy screening with subjects aged >= 50 years. To evaluate risk factors for colorectal and advanced adenoma in young adults, we used multivariable logistic regression models. Colorectal neoplasm characteristics were evaluated and compared with those in older patients.	2,819 patients	Prevalence of colorectal adenoma and advanced adenoma were 19.7% and 1.5%, respectively. As patient age increased, so did the prevalence of colorectal neoplasm. However, **prevalence of advanced adenoma did not differ between age-groups 45-49 years and >= 50 years (OR = 0.43, 95%CI: 0.17-1.07, P = 0.070).** In younger age-group (< 50 years), **colorectal adenoma was significantly associated with older age, waist circumference (OR = 1.72, 95%CI: 1.15-2.55, P = 0.008), and current smoking (OR = 1.60, 95%CI: 1.07-2.41, P = 0.023). Alcohol consumption was an independent risk factor for colorectal advanced adenoma (OR = 3.69, 95%CI: 1.08-12.54, P = 0.037).** Multiple neoplasms and large neoplasms (>= 1 cm) were more prevalent in subjects >= 50 years.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Lieberman, D.A., et al., 2014, *Gastroenterology*	To measure the prevalence of significant colorectal polyps in average-risk	Prospective study; Data were derived from the Clinical Outcomes Research Initiative (CORI), established in 1995 to study endoscopy utilization and	327,785 average-risk adults who underwent colorectal cancer screening	**Risk of large polyps progressively increases with advancing age beyond age 75 years in both men (z = 23.5, P < 0.001) and women (z = 17.8, P < 0.001).** Women had lower risks than men in every age	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria	

	individuals and to determine differences based on age, sex, race, or ethnicity	outcomes in diverse practice settings throughout the United States. The colonoscopy reports came from 84 practices, including community practice and endoscopy centers (78.5%), academic centers (8.3%) and VA medical centers (13.2%). Colonoscopy indications and findings were analyzed for patient groups based on age, sex, and race/ethnicity.		group, regardless of race**. Blacks had higher risk than whites from ages 50 through 65 years** (50-54 years (7.1% vs. 6.2%; OR: 1.17; 95% CI: 1.02-1.35), 55-59 years (8.5% vs. 7.4%; OR: 1.16; 95% CI: 0.996-1.36), 60-64 years (11.5% vs. 8.6%; OR: 1.38; 95% CI:1.18-1.61), and **Hispanics had lower risk than whites from ages 50 through 80 years** (5.1% vs. 6.7%; OR: 0.75; 95% CI 0.70 - 0.79). The prevalence of large polyps was 6.2% in white men 50-54 years old. The risk was similar among the groups of white women 65-69 years old, black women 55-59 years old, black men 50-54 years old, Hispanic women 70-74 years old, and Hispanic men 55-59 years old. The risk of proximal large polyps increased with age, female sex, and black race. The proportion with one or more large polyps steadily increased with age.	☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

References:

1. Lee, S. E., et al. (2016). "Characteristics of and risk factors for colorectal neoplasms in young adults in a screening population." World Journal of Gastroenterology 22(10): 2981-2992.
2. Lieberman, D. A., et al. (2014). "Race, ethnicity, and sex affect risk for polyps >9 mm in average-risk individuals." Gastroenterology 147(2): 351-358; quiz e314-355.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?						Lower Quality Rating if:
Modality: Patient Characteristics; **Outcome:** Colonic Neoplasia						☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Non-Randomized Studies: 1						☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*
Zapatier, J., et al., 2015, *European Journal of Gastroenterology & Hepatology*	To evaluate the influence of BMI on colonic neoplasia in average-risk patients aged between 40 and	Retrospective Study; Patients undergoing a first-time screening or average-risk colonoscopy were included in the analysis. Data on demographics, smoking, and BMI were collected and correlated to the presence of adenomas and advanced adenomas.	4,443 patients; 1,197 colonoscopies in patients aged between 40 and 49 years and 3,246 in those aged between 50 and 59 years	**Among men between 40 and 49 years, increasing BMI** [**odds ratio (OR) = 1.05**, 95% confidence interval (CI): 1.00-1.09] **and BMI of at least 27** (OR=1.95, 95% CI: 1.15-3.29) **were predictors of adenomas. Younger men with a BMI of at least 27 were more likely to have proximal adenomas** (**OR=2.23**, 95% CI: 1.14-4.37) **but not advanced adenomas**. There was	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding	

	59 years, analyzed by sex			no relation between BMI and adenomas in younger women. **Among women aged between 50 and 59 years, increasing BMI (OR=1.03**, 95% CI: 1.01-1.05) **and a BMI of at least 24 (OR=1.43**, 95% CI: 1.06-2.94) **was found to be correlated with adenomas, and increasing BMI was also found to be associated with proximal adenomas (OR=1.67**, 95% CI: 1.13-2.45). **Among men aged between 50 and 59 years, there was no relation between BMI and adenomas, but there was a positive correlation for advanced adenomas (OR=1.05**, 95% CI: 1.002-1.09). **Among women aged between 50 and 59 years, BMI was not predictive of advanced adenomas.** 	☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

References:

1. Zapatier, J., et al. (2015). "Can adjusting BMI for age and sex provide for a better predictor of colonic neoplasia?" European Journal of Gastroenterology & Hepatology 27(8): 974-980.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?						Lower Quality Rating if:
Modality: Predictive Model; **Outcome:** Lynch Syndrome Identification						☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in*
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Non-Randomized Studies: 1						
Khan, O., et al., 2011, *American Journal of Gastroenterology*	To evaluate the test characteristics of Lynch syndrome predictive	Retrospective Study; Collected data on individuals undergoing genetic testing for MMR gene mutations. Each individual's risk of mutation was examined using	230 individuals	**113 (49%) probands were MMR mutation carriers. Areas under the receiver operator curves were 0.76, 0.78, and 0.82 for MMRPredict, PREMM(1,2,6), and MMRPro respectively**. While similar in	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria	

	models in a tertiary referral group at two US academic centers	MMRPredict, PREMM(1,2,6), and MMRPro. Amsterdam and Bethesda criteria were also determined. Testing characteristics were calculated for each of the models. Testing characteristics was calculated for each of the models.		overall performance, study highlights unique test characteristics of these three quantitative models including comparisons of sensitivity and specificity. Moreover, characteristics were identified of mutation carriers who were missed by each model.	☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☒ Differences in important prognostic factors at baseline	*regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

References:

1. Khan, O., et al. (2011). "Performance of Lynch syndrome predictive models in a multi-center US referral population." American Journal of Gastroenterology 106(10): 1822-1827; quiz 1828.

PICO Question: In screening for CRC, what tools and/or strategies are most effective in identifying high-risk patients?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Modality: Serrated Polyps; **Outcome:** CRC						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Non-Randomized Studies: 1						

Erichsen, R., et al., 2016, *Gastroenterology*	To study CRC risks associated with serrated polyps	Case-control study; Conducted a nationwide population-based study in Denmark with individuals who had received a colonoscopy. For each case and control, investigators identified the first colorectal polyp(s) that underwent a biopsy or were excised during or after the initial colonoscopy, and obtained tissue blocks for hyperplastic lesions. Four expert pathologists reviewed these lesions using current terminology for serrated polyps. Logistic regression was used to compute odds ratios (ORs) to associate the risk of CRC with polyp type and estimated the absolute risks by multiplying the risk in patients with no polyps by these ORs.	272,342 colonoscopies; 2,045 CRC cases and 8,105 CRC-free individuals (control)	Seventy-nine cases and 142 controls had SSA/Ps (OR, 3.07; 95% confidence interval [CI], 2.30-4.10). **SSA/Ps with cytology markers of dysplasia were associated with a particularly high OR** (*4.76*; 95% CI, 2.59-8.73). **Women with SSA/P had a higher risk for CRC than men with SSA/P** (**OR for women, 5.05**; 95% CI, 3.05-8.37 vs **OR for men, 2.18**; 95% CI, 1.24-3.82); **patients with SSA/P proximal to the splenic flexure had the highest risk for CRC** (**OR, 12.42**; 95% CI, 4.88-31.58). **The OR for CRC was 4.84 in the 14 cases vs 17 controls with TSAs** (95% CI, 2.36-9.93), **2.51 in the 757 cases vs 1698 controls with conventional adenomas** (95% CI, 2.25-2.80), **and 1.30 in the 55 cases vs 235 controls with hyperplastic polyps** (95% CI, 0.96-1.77). The 10-year risk for CRC was 4.4% for patients with SSA/P with dysplasia, 4.5% for patients with TSAs, and 2.3% for patients with conventional adenomas.	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

				Table 1. Characteristics of Colorectal Cancer Cases and Matched Population Controls With a Documented Colonoscopy		

	Colorectal cancer cases, n (%)	Population controls, n (%)
Total	2045	8105
Men	938 (45.9)	3712 (45.8)
Women	1107 (54.1)	4393 (54.2)
Age at diagnosis/index date, *y*		
<40	44 (2.2)	152 (1.9)
40–59	430 (21.0)	1521 (18.8)
60–69	625 (30.6)	2369 (29.2)
70–79	706 (34.5)	2824 (34.8)
≥80	240 (11.7)	1239 (15.3)
Period of initial colonoscopy		
1977–1996	1172 (57.3)	4233 (52.2)
1997–2009	873 (42.7)	3872 (47.8)
Colorectal cancer stage		
Localized	942 (46.1)	N/A
Regional/metastatic	816 (39.9)	N/A
Unknown	287 (14.0)	N/A
Colorectal cancer anatomic region		
Proximal colon	898 (43.9)	N/A
Distal colorectum	988 (48.3)	N/A
Unknown or more than one region	159 (7.8)	N/A
Lesions from the first endoscopy that yielded polyps[a]		
No polyps	1155 (56.5)	6014 (74.2)
Sessile serrated adenomas/polyp	79 (3.9)	142 (1.8)
Traditional serrated adenoma	14 (0.7)	17 (0.2)
Conventional adenoma	757 (37.0)	1698 (21.0)
Hyperplastic polyp	105 (5.1)	356 (4.4)
Uncertain diagnosis	73 (3.6)	145 (1.8)
Subjects with subsequent colonoscopy by type of polyp[b]		
Sessile serrated adenomas/polyp (n = 221)	4 (0.2)	13 (0.2)
Traditional serrated adenoma (n = 31)	0 (0.0)	0 (0.0)
Conventional adenoma (2455)	78 (3.8)	174 (2.1)
Hyperplastic polyp (n = 461)	10 (0.5)	45 (0.6)
Uncertain diagnosis (n = 218)	5 (0.2)	12 (0.1)

References:

1. Erichsen, R., et al. (2016). "Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps." Gastroenterology 150(4): 895-902.e895.

Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high
Observational study–low
Any other evidence–very low

Criteria for increasing or decreasing level

Reductions
Study quality has serious (–1) or very serious (–2) problems
Important inconsistency in evidence (–1)
Directness is somewhat (–1) or seriously (–2) uncertain
Sparse or imprecise data (–1)
Reporting bias highly probable (–1)
Increases
Evidence of association† strong (+1) or very strong (+2)
Dose-response gradient evident (+1)
All plausible confounders would reduce the effect (+1)
†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders
Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.

C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.

Appendix C. Search Strategies

PICO 1-3:

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	*Ovid MEDLINE Search Strategy* 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 exp feces/ or ((feces or faeces or faecal or fecal or stool*) adj3 sampl*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (48539) 5 exp Mass Screening/ (80519) 6 exp "Early Detection of Cancer"/ (14867) 7 5 or 6 (92250) 8 3 and 4 and 7 (503) 9 limit 8 to yr="2015 -Current" (97) 10 exp Colorectal Neoplasms/di, dg (21577) 11 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 12 10 or 11 (25572) 13 exp feces/ or ((feces or faeces or faecal or fecal or stool*) adj3 sampl*).mp. (48539) 14 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 15 12 and 13 and 14 (720) 16 limit 15 to yr="2015 -Current" (121) 17 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 ((feces or faeces or faecal or fecal or stool*) adj3 sampl*)).mp. (602)

	18 3 and 17 (77) 19 limit 18 to yr="2015 -Current" (10) 20 9 or 16 or 19 (127) 21 limit 20 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (18) 22 exp Epidemiologic Studies/ (1633944) 23 20 and 22 (39) 24 21 or 23 (53) 25 limit 24 to english language (53) 26 limit 24 to abstracts (53) 27 25 or 26 (53) 28 20 not 27 (74) AND 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 exp sigmoidoscopy/ (2180) 5 exp Mass Screening/ (80519) 6 exp "Early Detection of Cancer"/ (14867) 7 5 or 6 (92250) 8 3 and 4 and 7 (895) 9 limit 8 to yr="2015 -Current" (68) 10 exp Colorectal Neoplasms/di (17939) 11 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 12 10 or 11 (22212) 13 (sigmoidoscop* or (sigmoid* adj7 (endoscop* or scope or scoping or scoped))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3597)

	14 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 15 12 and 13 and 14 (1540) 16 limit 15 to yr="2015 -Current" (106) 17 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 (sigmoidoscop* or (sigmoid* adj7 (endoscop* or scope or scoping or scoped)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (826) 18 3 and 17 (787) 19 limit 18 to yr="2015 -Current" (60) 20 9 or 16 or 19 (109) 21 limit 20 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (31) 22 exp Epidemiologic Studies/ (1633944) 23 20 and 22 (26) 24 21 or 23 (51) 25 limit 24 to english language (50) 26 limit 24 to abstracts (49) 27 25 or 26 (51) 28 20 not 27 (58) AND 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 (blood adj5 (occult or feces or faeces or faecal or fecal or stool*)).mp. (7255) 5 exp Mass Screening/ (80519) 6 exp "Early Detection of Cancer"/ (14867) 7 5 or 6 (92250) 8 3 and 4 and 7 (2463) 9 limit 8 to yr="2015 -Current" (284) 10 exp Colorectal Neoplasms/di, dg (21577)

	11 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 12 10 or 11 (25572) 13 (blood adj5 (occult or feces or faeces or faecal or fecal or stool*)).mp. (7255) 14 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 15 12 and 13 and 14 (2859) 16 limit 15 to yr="2015 -Current" (302) 17 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 (blood adj5 (occult or feces or faeces or faecal or fecal or stool*))).mp. (1867) 18 3 and 17 (1752) 19 limit 18 to yr="2015 -Current" (147) 20 9 or 16 or 19 (306) 21 limit 20 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (73) 22 exp Epidemiologic Studies/ (1633944) 23 20 and 22 (88) 24 21 or 23 (147) 25 limit 24 to english language (143) 26 limit 24 to abstracts (143) 27 25 or 26 (146) 28 20 not 27 (160) AND 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 exp feces/ and exp immunochemistry/ (343) 5 ((feces or faeces or faecal or fecal or stool*) adj7 immunochem*).mp. (617)

	6 4 or 5 (861) 7 exp Mass Screening/ (80519) 8 exp "Early Detection of Cancer"/ (14867) 9 7 or 8 (92250) 10 3 and 6 and 9 (507) 11 limit 10 to yr="2015 -Current" (131) 12 exp Colorectal Neoplasms/di, dg (21577) 13 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 14 12 or 13 (25572) 15 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 16 6 and 14 and 15 (584) 17 limit 16 to yr="2015 -Current" (149) 18 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 ((feces or faeces or faecal or fecal or stool*) adj7 immunochem*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (324) 19 3 and 18 (320) 20 limit 19 to yr="2015 -Current" (89) 21 11 or 17 or 20 (152) 22 limit 21 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (30) 23 exp Epidemiologic Studies/ (1633944) 24 21 and 23 (46) 25 22 or 24 (67) 26 limit 25 to english language (66) 27 limit 25 to abstracts (67) 28 26 or 27 (67) 29 21 not 28 (85) AND

	1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 exp Tomography, X-Ray Computed/ (273244) 5 exp Mass Screening/ (80519) 6 exp "Early Detection of Cancer"/ (14867) 7 5 or 6 (92250) 8 3 and 4 and 7 (495) 9 limit 8 to yr="2015 -Current" (54) 10 exp Colorectal Neoplasms/di, dg (21577) 11 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 12 10 or 11 (25572) 13 ((comput* adj3 tomogra*) or ct scan* or cat scan* or (virtual* adj2 (colonogra* or colonoscop*))).mp. (370260) 14 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 15 12 and 13 and 14 (1062) 16 limit 15 to yr="2015 -Current" (104) 17 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 ((comput* adj3 tomogra*) or ct scan* or cat scan* or (virtual* adj2 (colonogra* or colonoscop*)))).mp. (3674) 18 3 and 17 (331) 19 limit 18 to yr="2015 -Current" (22) 20 9 or 16 or 19 (110) 21 limit 20 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (22) 22 exp Epidemiologic Studies/ (1633944) 23 20 and 22 (29) 24 21 or 23 (45) 25 limit 24 to english language (43)

	26 limit 24 to abstracts (42) 27 25 or 26 (45) 28 20 not 27 (65) AND 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 exp Colonoscopy/ (19740) 5 exp Mass Screening/ (80519) 6 exp "Early Detection of Cancer"/ (14867) 7 5 or 6 (92250) 8 3 and 4 and 7 (3392) 9 limit 8 to yr="2015 -Current" (528) 10 exp Colorectal Neoplasms/di, dg (21577) 11 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 12 10 or 11 (25572) 13 colonoscop*.mp. (25076) 14 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 15 12 and 13 and 14 (5203) 16 limit 15 to yr="2015 -Current" (753) 17 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 colonoscop*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3397) 18 3 and 17 (2951) 19 limit 18 to yr="2015 -Current" (492)

	20 9 or 16 or 19 (865) 21 limit 20 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (162) 22 exp Epidemiologic Studies/ (1633944) 23 20 and 22 (325) 24 21 or 23 (429) 25 limit 24 to english language (417) 26 limit 24 to abstracts (423) 27 25 or 26 (428) 28 20 not 27 (437) AND 1 exp Colorectal Neoplasms/ (120015) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144610) 3 1 or 2 (149646) 4 ((hematolog* or blood or plasma or serum) adj3 (test or tests or testing or tested or assay* or sampl* or draw or drawing or drawn or drew or draws)).mp. (200978) 5 exp Blood Specimen Collection/ or exp Hematologic Tests/ or bl.fs. (939407) 6 4 or 5 (1012330) 7 exp Mass Screening/ (80519) 8 exp "Early Detection of Cancer"/ (14867) 9 7 or 8 (92250) 10 3 and 4 and 9 (1816) 11 limit 10 to yr="2015 -Current" (212) 12 exp Colorectal Neoplasms/di, dg (21577) 13 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9618) 14 12 or 13 (25572) 15 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

	supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (584716) 16 6 and 14 and 15 (2702) 17 limit 16 to yr="2015 -Current" (319) 18 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj10 ((hematolog* or blood or plasma or serum) adj3 (test or tests or testing or tested or assay* or sampl* or draw or drawing or drawn or drew or draws))).mp. (5841) 19 3 and 18 (1362) 20 limit 19 to yr="2015 -Current" (138) 21 11 or 17 or 20 (329) 22 limit 21 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (72) 23 exp Epidemiologic Studies/ (1633944) 24 21 and 23 (120) 25 22 or 24 (175) 26 limit 25 to english language (170) 27 limit 25 to abstracts (174) 28 26 or 27 (175)
Database Searched	Ovid MEDLINE, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse
Years Searched - All Questions	January 2015 – May 2017
Language	English
Age of Subjects	Adults, >/= 18 years

PICO 4-5:

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	*Ovid MEDLINE Search Strategy* 1 exp Colorectal Neoplasms/ (120268) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144939) 3 1 or 2 (149981) 4 exp Mass Screening/ (80658)

	5 exp "Early Detection of Cancer"/ (14954) 6 4 or 5 (92445) 7 3 and 6 (8061) 8 exp Colorectal Neoplasms/di, dg (21629) 9 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9639) 10 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (586400) 11 8 and 10 (8551) 12 9 or 11 (12557) 13 7 or 12 (13490) 14 exp attitude to health/ (287414) 15 exp health behavior/ (118920) 16 exp sociologic factors/ or exp socioeconomic factors/ (254082) 17 14 or 15 or 16 (548046) 18 exp decision making/ (125680) 19 13 and 17 and 18 (139) 20 ((share or shared or sharing or shares or joint* or collaborat* or confer* or consult* or participat* or interact* or conversation* or discuss*) adj7 (patient* or decision* or decid* or choice* or choos*)).mp. (148137) 21 13 and 20 (511) 22 (patient* adj7 (decision* or decid* or choice* or choos* or counsel* or ((inform* or educat*) adj5 (opt or opts or opting or opted or option*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (65144) 23 13 and 22 (318) 24 (patient* adj7 (prefer* or input* or suggest* or thought* or think* or consider* or feedback) adj5 (decision* or decid* or choice* or choos* or opt or opts or opting or opted or option)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5096) 25 13 and 24 (34) 26 exp Physician-Patient Relations/ (41349)

	27 13 and 26 (163) 28 19 or 21 or 23 or 25 or 27 (890) 29 limit 28 to yr="2002 -Current" (808)
Database Searched	Ovid MEDLINE, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse
Years Searched - All Questions	2002 – May 2017
Language	English
Age of Subjects	Adults, >/= 18 years

PICO 6:

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	*Ovid MEDLINE Search Strategy* 1 exp Colorectal Neoplasms/ (120268) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (144939) 3 1 or 2 (149981) 4 exp Mass Screening/ (80658) 5 exp "Early Detection of Cancer"/ (14954) 6 4 or 5 (92445) 7 3 and 6 (8061) 8 exp Colorectal Neoplasms/di, dg (21629) 9 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9639) 10 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (586400) 11 8 and 10 (8551) 12 9 or 11 (12557) 13 7 or 12 (13490) 14 exp cost benefit analysis/ (53627) 15 13 and 14 (586)

	16 ((compar* or effectiv* or relativ* or total or overall* or benefi* or valu* or evaluat* or estimat*) adj5 (cost or costs or financ* or expens* or econom* or reimburs* or insur* or dollar* or fiscal*) adj7 (screen* or test* or procedur*)).mp. (12902) 17 13 and 16 (573) 18 ((compar* or effectiv* or relativ* or total or overall* or benefi* or valu* or evaluat* or estimat*) adj5 (cost or costs or financ* or expens* or econom* or reimburs* or insur* or dollar* or fiscal*) adj7 (((feces or faeces or faecal or fecal or stool*) adj3 sampl*) or (sigmoidoscop* or (sigmoid* adj7 (endoscop* or scope or scoping or scoped))) or (blood adj5 (occult or feces or faeces or faecal or fecal or stool*)) or ((feces or faeces or faecal or fecal or stool*) adj7 immunochem*) or ((comput* adj3 tomogra*) or ct scan* or cat scan* or (virtual* adj2 (colonogra* or colonoscop*))) or (colonoscop* or ((colon* or bowel*) adj3 (endoscop* or scope* or scoping))))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (643) 19 13 and 18 (214) 20 17 or 19 (628) 21 15 or 20 (875) 22 limit 21 to yr="2002 -Current" (662) 23 limit 22 to english language (619) 24 limit 22 to abstracts (586) 25 23 or 24 (656)
Database Searched	Ovid MEDLINE, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse
Years Searched - All Questions	2002 – May 2017
Language	English
Age of Subjects	Adults, >/= 18 years

PICO 7:

Search Strategies	Document Strategies Used
Search Terms/Strategies Used:	*Ovid MEDLINE Search Strategy* 1 exp Colorectal Neoplasms/ (121384) 2 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (146418) 3 1 or 2 (151492) 4 exp Mass Screening/ (81391) 5 exp "Early Detection of Cancer"/ (15331)

	6 4 or 5 (93462) 7 exp Risk/ (845308) 8 exp mortality/ (257936) 9 exp life tables/ (12955) 10 exp epidemiologic studies/ (1662464) 11 7 or 8 or 9 or 10 (2288842) 12 exp "sensitivity and specificity"/ (457054) 13 exp reproducibility of results/ (312603) 14 12 or 13 (650587) 15 3 and 6 and 7 and 12 (342) 16 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))).mp. (594407) 17 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*)))).mp. (9740) 18 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj7 (accura* or predict*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (16078) 19 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj7 (accura* or predict* or (success* adj3 rate*))).mp. (16214) 20 19 not 18 (136) 21 ((screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))) adj7 (accura* or predict* or (success* adj3 (rate* or locat* or identif*)))).mp. (16396) 22 21 not 19 (182) 23 3 and 21 (754) 24 ((accura* or predict* or (success* adj3 (rate* or locat* or identif*))) adj10 ((colorect$ or colon or colonic$ or bowel$ or rectum or rectal) adj3 (cancer$ or neoplas$ or tumor$ or tumour$ or adenocarcin$ or carcin$ or malig$) adj7 (screen* or ((earl* or routin*) adj5 (diagnos* or detect* or discover*))))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (310) 25 7 and 23 (190) 26 3 and 6 and 11 and 14 (670) 27 11 and 14 and 17 (682) 28 3 and 11 and 21 (349) 29 25 or 26 or 27 or 28 (1139) 30 limit 29 to english language (1068) 31 limit 29 to abstracts (1062)

	32 30 or 31 (1126) 33 limit 32 to yr="2002 -Current" (1001) 34 limit 33 to (comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or randomized controlled trial or systematic reviews or validation studies) (382) 35 33 not 34 (619)
Database Searched	Ovid MEDLINE, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse
Years Searched - All Questions	2002 – May 2017
Language	English
Age of Subjects	Adults, >/= 18 years