EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F – Health and Food (Ispra)
Disease Prevention

European Commission Initiative on Colorectal Cancer (ECICC):

European guidelines on colorectal cancer primary prevention, screening and diagnosis

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QUESTION

Should screening vs. no screening be used for colorectal cancer in asymptomatic adults aged 50 - 69 with an average risk of colorectal cancer?	
POPULATION:	asymptomatic adults aged 50 - 69 with an average risk of colorectal cancer
INTERVENTION:	screening
COMPARISON:	no screening
MAIN OUTCOMES:	Death from colorectal cancer; diagnosis of colorectal cancer; stage of colorectal cancer; harms (major bleeding, colonic perforation, acute severe pain).
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	Colorectal cancer (CRC) is the third most common worldwide cancer, with 1.9 million new cases and, 935 000 cancer death per year (1). Fortunately, with its long screen detectable latent phase and better prognosis of cases detected at early stage, CRC is an ideal candidate for screening. Screening can also reduce the risk of getting the disease as it can lead to the identification of cancer precursor lesions, which can then be excised, interrupting their potential progression to an invasive cancer. However, screening can also result in specific harms and, therefore, the expected net benefit should be assessed before implementing CRC screening at the population level (3). The aim of the current evaluation is to determine the evidence for the harms and benefits of screening and determine whether the benefits outweigh the harms.
CONFLICT OF INTERESTS:	Conflicts of interest (CoI) for ECICC working group (WG) members and subgroup members were assessed and managed by the European Commission's Joint Research Centre (JRC) following an established procedure in line with institutional rules. Participation in the development of the recommendations was restricted, according to CoI disclosure. Consequently, for this particular question, no WG or subgroup members were recused from voting. For more information visit: https://healthcare-quality.jrc.ec.europa.eu/en/ecicc/discover-ecicc/working-groups

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Colorectal cancer (CRC) is the third most common worldwide cancer in men and women, with 1.9 million new cases and a mortality of 10%, 935,000 patients, per year (1). CRC incidence has been increasing in Europe during the past 30 years and mortality rates, although showing a decreasing trend, are still high, with Central, Eastern, and Western European regions showing the highest mortality rates (ranking first, third, and fourth)	The ECICC WG prioritised this question for the ECICC.

○ Don't know	among the 21 regions of the GBD project (2). Early detection of CRC due to screening programs, removal of precancerous polyps with colonoscopy, and advances in treatment management have decreased CRC incidence and mortality rates (3). However, screening could also result in specific harms and, therefore, the expected net benefit should be assessed before implementing CRC screening at the population level (4).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Date of the search:** December 23, 2022	Critical outcomes showing benefits were: death from colorectal cancer, diagnosis of colorectal cancer, and stage of colorectal cancer. Prioritized screening test: • Colonoscopy • Flexible sigmoidoscopy • Faecal immunochemical test • DNA stool-based test For the desirable effects, the WG assessed direct evidence from randomized control trials (RCT) on colonoscopy (5), and flexible sigmoidoscopy (6, 7, 8, 9), and indirect evidence from RCTs on guaiac faecal occult blood test (10, 11, 12, 13, 14) . The participation percentage between RCTs varied from 42 to 84%. For colorectal cancer deaths and diagnoses, the median participation percentage is 65%. In the case of the stage of colorectal cancer, the median participation

Outcomes	№ of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Non-screening	Risk difference with Screening
Death from Colorectal Cancer assessed with: Intention to treat follow-up: range 5 years to 30 years	10 RCTs[1,10,2,3,4,5,6,7,8,9,a]	⨁⨁⨁◯ Moderate[b,c,d]	**Rate ratio 0.82** (0.75 to 0.89)	Estimated at 20 years timeframe	
				674 per 100,000[e,f]	**109 fewer per 100,000** (150 fewer to 66 fewer)
Diagnosis of Colorectal Cancer assessed with: Intention to treat follow-up: range 5 years to 30 years	10 RCTs[1,10,11,2,4,5,6,7,8,9,a]	⨁⨁⨁◯ Moderate[g,h,i]	**Rate ratio 0.88** (0.81 to 0.96)	Estimated at 20 years timeframe	
				2,172 per 100,000[e,f]	**240 fewer per 100,000** (381 fewer to 80 fewer)
Stage of Colorectal Cancer assessed with: stage III/IV or Duke's C/D - Intention to treat follow-up: range 11 years to 19 years	7 RCTs[1,12,13,14,15,4,6]	⨁⨁⨁◯ Moderate[i,j]	**RR 0.84** (0.78 to 0.92)	887 per 100,000[k]	**142 fewer per 100,000** (195 fewer to 71 fewer)

Major Bleeding	106 observational studies[16,l]	⊕⊕⊕◯ Moderate[m]	-	The overall incidence of major bleeding after screening was approximately 73 cases (95% CI 45.78 – 117.77) per 100,000 procedures. **Colonoscopy:** 104 cases (95% CI 67.79 – 160.81) per 100,000 procedures when colonoscopy **Colonoscopy was performed after abnormal results in other screening modalities:** 194 cases (95% CI 112.93 – 333.37) per 100,000 procedures. **Flexible sigmoidoscopy alone:** 4 cases (95% CI 0.65 - 22.13) per 100,000 procedures.
Colonic Perforation	106 observational studies[16,l]	⊕⊕⊕◯ Moderate[m]	-	The overall incidence of perforation after screening was approximately 27 cases (95% CI 18.26 - 41.02) per 100,000 procedures. **Colonoscopy:** 34 cases (95% CI 23.13 – 49.38) per 100,000 procedures. **Colonoscopy was performed after abnormal results in other screening modalities:** 79 cases (95% CI 55.10 – 112.32) per 100,000 procedures. **Flexible sigmoidoscopy alone:** 3 cases (95% CI 1.11 – 9.87) per 100,000 procedures.

1. Miller, E.A.,et al.. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. Lancet Gastroenterol Hepatol; 2019.
2. Pitkäniemi, J.,et al.. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterology; 2015.
3. Shaukat, A.,et al.. Long-Term Mortality after Screening for Colorectal Cancer. New England Journal of Medicine; 2013.
4. Lindholm, E.,H. Brevinge,and E. Haglind. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg; 2008.
5. Kronborg, O.,et al.. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol; 2004.
6. Scholefield, J.H.,et al.. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut; 2012.
7. Bretthauer, M.,et al.. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. New England Journal of Medicine; 2022.
8. Atkin, W.,et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised

percentage is 63%.

Only four RCTs (6, 5, 9, 11) reported per-protocol estimations adjusted for non-compliance for the outcome of death from colorectal cancer, indicating that screening may result in 216 fewer deaths (ranging from 252 fewer to 174 fewer) per 100,000 patients over 20 years compared with non-screening. Also, three RCTs (15, 9, 5) reported per-protocol estimations for the diagnosis of colorectal cancer, suggesting that screening may lead to 680 fewer cases of colorectal cancer (ranging from 780 fewer to 580 fewer) per 100,000 patients over 20 years compared with non-screening.

The assumption is that the outcomes substantially overlap and are not additive.

Decision thresholds

<u>CRC Mortality</u>

- Trivial/Small: 35 per 100000
- Small/Moderate: 95 per 100000
- Moderate/Large: 175 per 100000

<u>CRC incidence</u>

- Trivial/Small: 75 per 100000
- Small/Moderate: 200 per 100000

	controlled trial. Lancet; 2017. 9. Senore, C.,et al.. Long-Term Follow-up of the Italian Flexible Sigmoidoscopy Screening Trial. Ann Intern Med; 2022. 10. Holme, Ø.,et al.. Long-Term Effectiveness of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality in Women and Men: A Randomized Trial. Ann Intern Med; 2018. 11. Mandel, J.S.,et al.. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med; 2000. 12. Kronborg, O.,et al.. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet; 1996. 13. Mandel, J.S.,et al.. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst; 1999. 14. Segnan, N.,et al.. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst; 2011. 15. Holme, Ø.,et al.. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA; 2014. 16. Lin JS, Perdue LA,Henrikson NB,Bean SI,Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA; 2021. a. The RCTs informing this outcome assessed colonoscopy, flexible sigmoidoscopy, and guaiac fecal occult blood test as screening tests. b. The inspection of the forest plot identified heterogeneity (I2=64%), but it was not considered relevant. c. The ECICC WG defined the threshold for going from trivial to small effect as 35 CRC deaths per 100,000 participants on screening. d. Most of the studies had concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about measuring the outcome, as the definition of mortality was based on the specific cause reported; however, we do not consider this to be a differential bias between the arms. Additionally, six studies have some concerns about the potential impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis. e. The absolute risk was obtained as follows, considering a standardization for 20 years: 1) We converted the annual basal risk (RB) into a rate (r) per unit time (20 years) r= basal risk*20; 2) We calculated the absolute rate (AR) using the formula: AR= (RB*IRR) – RB, where IRR is the incidence risk ratio; Finally 3) We converted the absolute rate into a probability: 1 - exp(-AR) f. The baseline risk was obtained from the rates of colorectal cancer in the 50-69 age group reported by the European Cancer Information System for European Union	• Moderate/Large: 375 per 100000 <u>Late stage of colorectal cancer</u> • Trivial/Small: 58 per 100000 • Small/Moderate: 135 per 100000 • Moderate/Large: 225 per 100000 The WG agreed that, according to the decision thresholds, for the ITT analysis the desirable effects are moderate, but they will be larger in a truly screened population.

countries (EU-27) and converted for 20 years time frame

g. The inspection of the forest plot identified heterogeneity (I2=87%), but it was not considered relevant.
h. The ECICC WG defined the threshold for going from trivial to small effect as 75 CRC incident cases per 100,000 participants on screening.
i. Most of the studies had some concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about the measurement of the outcome, as they relied on public databases, which may not have captured all the cases; however, we do not consider this to introduce a significant differential bias, and its impact is expected to be minimal. Three studies were considered at a high risk of bias because of the impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis. However, their impact on the overall findings is minimal due to their weight being less than 30%.
j. The ECICC WG defined the threshold for going from trivial to small effect as 58 CRC incident cases at a late stage per 100,000 participants on screening.
k. Median basal risk reported in the included studies
l. We identified one systematic review including 106 observational studies assessing flexible sigmoidoscopy and colonoscopy.
m. Most of the studies did not disclose their follow-up and there are some concerns about the possibility of reporting bias regarding the outcome.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Date of the search:** December 23, 2022	Critical outcomes showing harms were: major bleeding and colonic perforation. Prioritized screening test: • Colonoscopy • Flexible sigmoidoscopy • Faecal immunochemical test • DNA stool-based test For the undesirable effects, the included studies assessed colonoscopy (including colonoscopies

Outcomes	№ of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Non-screening	Risk difference with Screening
Death from Colorectal Cancer assessed with: Intention to treat follow-up: range 5	10 RCTs[1,10,2,3,4,5,6,7,8,9,a]	⨁⨁⨁◯ Moderate[b,c,d]	**Rate ratio 0.82** (0.75 to	Estimated at 20 years timeframe	
				674 per 100,000[e,f]	**109 fewer per 100,000** (150 fewer to 66

years to 30 years			0.89)		fewer)
Diagnosis of Colorectal Cancer assessed with: Intention to treat follow-up: range 5 years to 30 years	10 RCTs[1,10,11,2,4,5,6,7,8,9,a]	⨁⨁⨁◯ Moderate[g,h,i]	**Rate ratio 0.88** (0.81 to 0.96)	Estimated at 20 years timeframe	
				2,172 per 100,000[e,f]	**240 fewer per 100,000** (381 fewer to 80 fewer)
Stage of Colorectal Cancer assessed with: stage III/IV or Duke's C/D - Intention to treat follow-up: range 11 years to 19 years	7 RCTs[1,12,13,14,15,4,6]	⨁⨁⨁◯ Moderate[i,j]	**RR 0.84** (0.78 to 0.92)	Estimated at 20 years timeframe	
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Major Bleeding	106 observational studies[16,l]	⨁⨁⨁◯ Moderate[m]	-	The overall incidence of major bleeding after screening was approximately 73 cases (95% CI 45.78 – 117.77) per 100,000 procedures. **Colonoscopy:** 104 cases (95% CI 67.79 – 160.81) per 100,000 procedures when colonoscopy **Colonoscopy was performed after abnormal results in other screening modalities:** 194 cases (95% CI 112.93 – 333.37) per 100,000 procedures. **Flexible sigmoidoscopy alone:** 4 cases (95% CI 0.65 - 22.13) per 100,000 procedures.	
Colonic Perforation	106 observational studies[16,l]	⨁⨁⨁◯ Moderate[m]	-	The overall incidence of perforation after screening was approximately 27 cases (95% CI 18.26 - 41.02) per 100,000 procedures. **Colonoscopy:** 34 cases (95% CI 23.13 – 49.38) per 100,000 procedures. **Colonoscopy was performed after abnormal results in other screening modalities:** 79 cases (95% CI 55.10 – 112.32) per 100,000 procedures.	

performed after abnormal result in faecal occult blood tests) and flexible sigmoidoscopy as screening tests.

Two publications (16, 13) of one RCT provided data on the number of false positive results obtained from the faecal occult blood test for colorectal cancer screening across multiple rounds. The RCT with more screening rounds (13) revealed 1691 false positive cases out of the 1888 positive results obtained using the screening modality.

Moreover, two RCTs (17, 15) reported estimations for severe pain after the screening was performed. Both studies evaluated endoscopy procedures. After the screening procedure, severe pain ranged from approximately 2001 to 2712 cases per 100,000 procedures.

The WG considered that the outcomes are to some degree independent. Individually the outcomes were judged as trivial for bleeding and perforation and pain was moderate (but transient), but taking bleeding, perforation, and pain together may be considered small.

To judge the undesirable effects, the WG decided to vote separately for different screening strategies (11 voting members):

<u>Voting results for colonoscopy alone</u>

- trivial 3
- small 6

				Flexible sigmoidoscopy alone: 3 cases (95% CI 1.11 – 9.87) per 100,000 procedures.

1. Miller, E.A.,et al.. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. Lancet Gastroenterol Hepatol; 2019.
2. Pitkäniemi, J.,et al.. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterology; 2015.
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16. Lin JS, Perdue LA,Henrikson NB,Bean SI,Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA; 2021.

- abstain 2

Voting results for flexible sigmoidoscopy plus colonoscopy

- trivial 7
- small 1
- moderate 1
- abstain 2

Voting results for fit plus colonoscopy

- trivial 8
- small 1
- abstain 2

Decision thresholds

Major Bleed

- Trivial/Small: 175 per 100000
- Small/Moderate: 550 per 100000
- Moderate/Large: 950 per 100000

Perforation

- Trivial/Small: 125 per 100000
- Small/Moderate: 450 per 100000
- Moderate/Large: 775 per 100000

	a. The RCTs informing this outcome assessed colonoscopy, flexible sigmoidoscopy, and guaiac fecal occult blood test as screening tests. b. The inspection of the forest plot identified heterogeneity (I2=64%), but it was not considered relevant. c. The ECICC WG defined the threshold for going from trivial to small effect as 35 CRC deaths per 100,000 participants on screening. d. Most of the studies had concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about measuring the outcome, as the definition of mortality was based on the specific cause reported; however, we do not consider this to be a differential bias between the arms. Additionally, six studies have some concerns about the potential impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis. e. The absolute risk was obtained as follows, considering a standardization for 20 years: 1) We converted the annual basal risk (RB) into a rate (r) per unit time (20 years) r= basal risk*20; 2) We calculated the absolute rate (AR) using the formula: AR= (RB*IRR) – RB, where IRR is the incidence risk ratio; Finally 3) We converted the absolute rate into a probability: 1 - exp(-AR) f. The baseline risk was obtained from the rates of colorectal cancer in the 50-69 age group reported by the European Cancer Information System for European Union countries (EU-27) and converted for 20 years time frame g. The inspection of the forest plot identified heterogeneity (I2=87%), but it was not considered relevant. h. The ECICC WG defined the threshold for going from trivial to small effect as 75 CRC incident cases per 100,000 participants on screening. i. Most of the studies had some concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about the measurement of the outcome, as they relied on public databases, which may not have captured all the cases; however, we do not consider this to introduce a significant differential bias, and its impact is expected to be minimal. Three studies were considered at a high risk of bias because of the impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis. However, their impact on the overall findings is minimal due to their weight being less than 30%. j. The ECICC WG defined the threshold for going from trivial to small effect as 58 CRC incident cases at a late stage per 100,000 participants on screening. k. Median basal risk reported in the included studies l. We identified one systematic review including 106 observational studies assessing	

	flexible sigmoidoscopy and colonoscopy. m. Most of the studies did not disclose their follow-up duration and there are some concerns about the possibility of reporting bias regarding the outcome.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		The overall certainty of evidence was judged as moderate.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Date of the search:** February 15, 2023	We performed a systematic review aiming at evaluating patients´ values and preferences regarding outcomes derived from CRC screening. Besides the prioritized outcomes presented, we have also found information on the following outcomes, which can be made available upon request:

Outcome	Finding	Certainty
Death from Colorectal Cancer 16 studies (8,692 participants) [1-16]	People place a high value in reducing the risk of death while participating in CRC screening. In accordance with these findings individuals report that not believing that the programme is effective and would improve the chance of survival are reasons for not undergoing the test. Reduction in risk of death (as well as a reduction in CRC incidence) are perceived by the participants as the most important attributes of tests.	⊕⊕⊕⊕ **HIGH**
Detection of Non-Advanced Adenoma 13 studies (5.031 participants) [11-23]	People place a high value on detecting a lesion as soon as possible, and prefer tests with higher sensitivity levels.	⊕⊕⊕⊕ **HIGH**

Outcome	Finding	Certainty
Acute Severe Pain 2 studies (126 participants) [15, 24]	Fear of pain probably deters some patients from complying with CRC screening.	⊕⊕⊕◯ **MODERATE**[b]
Colonic Perforation 2 studies (56 participants) [25, 26]	The risk of bowel perforation may be a significant concern for patients considering CRC screening.	⊕⊕◯◯ **LOW**[c]
Major Bleeding 1 study (30 participants) [25]	People may worry about major bleeding, but it may not affect their decisions to undergo CRC screening.	⊕⊕◯◯ **LOW**[c]
Complications 11 studies (5,140 participants) [3, 4, 8, 10, 12, 14, 15, 17, 23, 25, 27]	Most people probably place a high value on the risk of complications, and for some individuals this is probably a barrier for participation in screening.	⊕⊕⊕◯ **MODERATE**[a]

a We downgraded the certainty of the overall evidence due to serious indirectness (most individuals did not actually experience a CRC diagnosis).

b We downgraded the certainty of the overall evidence due to very serious indirectness (participants did not actually mention specific complications or did not actually experience

- False negative Screening Result
- Moderate Stress and Anxiety; Severe stress and anxiety
- Death from Colorectal Cancer
- Recall for assessment.

The WG judged that there is no important uncertainty or variability on how people value the CRITICAL outcomes

<u>Specific considerations discussed by the ECICC WG</u>:

- False positive screening result: this outcome was prioritised as an IMPORTANT one (not CRITICAL). A clear description of the outcome is provided through the specific marker state [REF] and it refers to the effects associated with having a screening test that caused a recall for further assessment and therefore may cause anxiety.
- Overdiagnosis: the WG discussed that overdiagnosis is not an issue in CRC screening and issues related to its definition and measurement.

them).

c We downgraded the certainty of the overall evidence due to serious indirectness (most people did not actually experience false positive results).

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Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The WG considered that the desirable effects are MODERATE, the undesirable effects VARIES (for colonoscopy alone they are SMALL, and for flexible sigmoidoscopy or FIT both plus colonoscopy are TRIVIAL), and there is no important uncertainty or variability for values.

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No systematic review was conducted.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**Date of the search:** December 23, 2022 **Microsimulation** (table below) 1. Arrospide, Arantzazu. Cost-effectiveness and budget impact analyses of a colorectal cancer screening programme in a high adenoma prevalence scenario using MISCAN-Colon microsimulation model. BMC Cancer; 2018. 2. Barre, Stéphanie. Cost-effectiveness analysis of alternative colon cancer screening strategies in the context of the French national screening program. Ther Adv Gastroenterol; 2020. 3. Babela, Robert. Cost-effectiveness of colorectal cancer screening in Slovakia. European Journal of Cancer Prevention; 2022. 4. Coldman, A. Projected effect of fecal immunochemical test threshold for colorectal cancer screening on outcomes and costs for Canada using the OncoSim microsimulationmodel; 2017. 5. Lew, Jie-Bin. Benefits, harms and cost-effectiveness of potential age-extensions to the National Bowel Cancer Screening Program in Australia. Cancer Epidemiology, Biomarkers & Prevention; 2018. 6. Lew, Jie-Bin. Evaluation of the benefits, harms and cost-effectiveness of potential alternatives to iFOBT testing for colorectal cancer screeningin Australia. Int J Cancer; 2018. 7. Lew, Jie-Bin. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. Lancet Public Health; 2017.	Prioritized screening test: • Colonoscopy • Flexible sigmoidoscopy • Faecal immunochemical test • DNA stool-based test The studies evaluated different types of screening modalities, including colonoscopy, flexible sigmoidoscopy, fecal immunochemical test, guaiac fecal occult blood test, and DNA stool-based test. The WG judged that all of the different screening strategies are cost-effective but that this approach does not differentiate between the individual approaches. That was assumed for the published studies (that include different tests and populations). We prioritized cost-effectiveness analysis that reported any attempt at the validation of the model, such as face validation, calibration, structure validation, or external validation. Analysis failing to report this are not included in the evidence profile, but are available in the technical report.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	ICER	Incremental cost per patient	Incremental effect per patient
ICER per QALY (microsimulation)	4 studies[1,2,3,4]	⨁⨁⨁◯ Moderate[a,b]	Median €3,171 (from dominant to €5,697)	Range	
				form €28.2 to €58.5	from 0.007 to 0.0185
ICER per LYG (microsimulation)	7 studies[10,11,5,6,7,8,9]	⨁⨁◯◯ Low	Median €3,598 (from dominant to €24,121)	Range	
				from €317 to €1675	from 0.005 to 0.1057

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11. Goede, Lucas. Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. Gut; 2013.

a. Modelling studies (cost-effectiveness studies)
b. Downgraded one level due to the risk of bias of the bodies of evidence that informed the input parameters. Most models rely on estimates of the accuracy of each test, incidence/prevalence of CRC and adenomas at different age groups, and assumptions about the rate of progression of adenomas

All models included (microsimulations and Markov models reporting any validation procedure)

Outcomes	№ of studies	Certainty of the evidence (GRADE)	ICER, range	Incremental cost per patient	Incremental effect per patient
ICER per QALY	9 observational studies[1,2,3,4,5,6,7,8,9,a]	⨁⨁⨁◯ Moderate[b,c,d]	Median: € 3,291 (from dominant to €22,482 per QALY)e	Range and median	
				Median: € 78 (from €1675 to €317)	Median: 0.0228 (from 0.005 to 0.1057)
ICER per LYG	11 observational studies[10,11,12,13,14,15,16,17,18,19,a]	⨁⨁◯ Low[c,d]	Median: € 3,504 (from dominant to €24,121 per LYG)	Range	
				Median: € 196 (from €404 to €1238)	Median: 0.0477 (from 0.0001 to 0.1600)

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Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No systematic review was conducted	The utilization of cancer screening services may largely depend on the availability of national public screening programs; although European findings highlight that inequalities are larger in countries without population-based screening programs (18). Coverage distribution with screening programs appears to increase and there does not seem be a differential based on education and other factors (19, 20, 21)

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No systematic review conducted. Most (8 out of 9) of the randomized clinical trials (RCT) identified in our review and performed in European countries show that the participation in the screening for CRC was higher than 50%. Only two RCTs reported an participation lower than 50%.	**People**: there may be differences based on the type of test used due to the differences in possible undesirable effects. Access may also have an effect on acceptability. Language barriers and understanding of information may have an effect. **Health care providers**: there may be differences based on the test accuracy of the test. **Policy-makers**: there may be barriers related investments that need to be made. **Other stakeholders of interest**: cultural factors, costs and the way the screening programme is organised may have impact on acceptability. The considerations above are based on the evidence reported under research evidence. Additional evidence may come from existing EU screening programmes (18)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies	No systematic review conducted	Some countries do not have organized screening programs and may be unable to implement them mainly due to a lack of resources and/or infrastructure.

○ Don't know		Since there countries providing CRC screening programmes, this suggests that they are feasible, but barriers exist for their implementation: • organisational barriers, e.g. provision of sedation routinely; kit distribution and return of the samples; organization of the endoscopy units; • resources needed for offering the screening programme for free; • cultural barriers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
OF REQUIRED RESOURCES							
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For asymptomatic adults aged 50-69 with an average risk of colorectal cancer, the ECICC working group (WG) **recommends screening** for colorectal cancer in the context of an organised population-based screening programme (strong recommendation, moderate certainty of the evidence).

Justification

The ECICC working group agreed on this recommendation by consensus.

The WG judged that the balance between desirable and undesirable effects favours screening, that there is no important uncertainty or variability in how much people value the main outcomes and that the intervention is probably cost-effective and acceptable. These judgments applied to all screening tests considered (Faecal Immunochemical Test (FIT), colonoscopy, flexible sigmoidoscopy), although the balance between desirable and undesirable effects, cost/effectiveness, and acceptability considerations may vary

according to the different strategy. The WG also considered that organised screening will probably increase equity, and it is feasible to implement.

Subgroup considerations

This recommendation is for screening in general. Specific considerations should be made depending on the screening test used and their implications.

The ECICC working group is currently working on the development of recommendations for colorectal cancer screening covering other age-ranges and different types of tests that may be used. These recommendations will be published on the ECICC website once finalised.

Implementation considerations

Possible barriers for implementation:

- organisational barriers, e.g. provision of sedation routinely;
- resources needed for offering the screening programme for free;
- cultural barriers;
- language barriers and undestandability.

Monitoring and evaluation

Within the ECICC, the quality indicators for this recommendation are being developed.

Research priorities

- Interplay between adherence and cost-effectiveness should be explored;
- Characteristics and factors that may have an impact on participation to CRC screening programmes (e.g. in people with low socio-economic status);
- Collect data from screening programs in Europe to review findings here and find optimal screening approaches;
- Research data on equity.

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