Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer: Population screening

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5.1 Colorectal cancer screening benefit

Weak recommendation

1. Evidence-based recommendation

The recommended strategy for population screening in Australia, directed at those at average risk of colorectal cancer and without relevant symptoms, is immunochemical faecal occult blood testing every two years, starting at age 45 years and continuing to age 74 years. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Bretthauer, et al, 2022*[44]*, Juul, et al, 2022*[45]*)

Weak recommendation

2. Evidence-based recommendation

The use of flexible sigmoidoscopy as a primary screening test is not recommended for population screening in the average-risk population. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Juul, et al, 2022*[45]*).

3. Evidence-based recommendation

The recommended age range for organised population screening is 45–74 years.

4. Evidence-based recommendation

Although modelling indicated that it may be cost-effective, starting screening at age 40 is not recommended for population screening because at this age range there is a less favourable benefits to burden balance compared to screening for 45-74 years.

5. Evidence-based recommendation

Extending the upper limit of the age range from 74 to 79 or 84 years is not recommended for population screening, because the likely benefits do not outweigh the burden (number of colonoscopies and associated risk), compared with screening for people aged 45–74 years.

Good practice statement

6. Practice Point

For people aged 75-85 years who are fit, well and healthy, who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#].

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

7. Practice Point

In people aged 40-44 years who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#] every two years during the lead-up to the first routine National Bowel Cancer Screening Program invitation.

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

8. Practice Point

Every effort should be pursued to ensure equitable participation and ongoing quality improvement initiatives in population screening for colorectal cancer in the target age group of 45-74 years and ensure equity of access to culturally safe health care, including access to diagnostic assessment for National Bowel Cancer Screening Program participants with a positive screening test.

5.2 Colorectal cancer screening accuracy

Weak recommendation

9. Evidence-based recommendation

An immunochemical faecal occult blood test is recommended as the screening modality for the detection of colorectal cancer in the average-risk population. (Burón et al, 2019*[72]*, Chang et al, 2017*[73]*, Brenner et al 2018*[70]*, Digby 2016*[76]*, Kim et al, 2017*[78]*, Ribbing et al 2022*[80]*, Shapiro et al, 2017*[83]*, Zorzi et al, 2018*[82]*)

Weak recommendation

10. Evidence-based recommendation

The emerging faecal, blood or serum tests for cancer-specific biomarkers such as DNA are not recommended as population screening modalities for colorectal cancer at this time. (Bosch et al, 2019*[66]*, Bretagne et al, 2021*[71]*, Chiu et al, 2016*[75]*, Imperiale et al, 2021*[68]*, Jin et al 2022*[65]*, Shapiro et al, 2017*[83]*)

Weak recommendation

11. Evidence-based recommendation

Population screening for colorectal cancer using immunochemical faecal occult blood testing every two years is recommended. It is not recommended that the frequency of screening within the National Bowel Cancer Screening Program be increased to yearly. (Bretagne et al, 2021*[71]*, Burón, et al, 2019*[72]*, Digby et al, 2016*[76]*, Jensen et al, 2016*[77]*, Ribbing et al, 2022*[80]*)

Good practice statement

12. Practice Point

Participation in a population screening program is not recommended for people with symptoms such as rectal bleeding or persistent change in bowel habit or with iron-deficiency anaemia, nor for those who should be having regular surveillance or screening based on colonoscopy (e.g., for past colorectal cancer or adenoma, chronic inflammatory bowel disease, a strong family history of colorectal cancer, or a high-risk genetic cancer syndrome). (Chiu et al, 2016*[75]*, Kim et al 2017*[78]*)

Good practice statement

13. Practice Point

It is important that individuals undergo a high-quality diagnostic colonoscopy after a positive immunochemical faecal occult blood test (Aniwan et al, 2017*[69]*, Njor et al, 2022*[79]*, Chiu et al 2016*[75]*, Digby et al 2016*[76]*, Ribbing et al, 2019*[81]*). A colonoscopy which does not meet the clinical care standard warrants a repeat procedure usually initiated by the proceduralist. A high-quality colonoscopy is defined as adequate bowel preparation, complete intubation, as documented and made available in the proceduralist's report. The proceduralist should ensure that the colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care (see ACSQHC).

Good practice statement

14. Practice Point

If a diagnostic colonoscopy after a positive immunochemical faecal occult blood test (iFOBT) is performed and its findings do not require further colonoscopy follow-up, the National Bowel Cancer Screening Program (NBCSP) participant should skip the next round of iFOBT screening through the NBCSP (in line with the Colonoscopy Surveillance Guidelines). Colorectal cancer will rarely occur within that interval.

Good practice statement

15. Practice Point

Participants with positive immunochemical faecal occult blood test (iFOBT) results should have follow-up investigation with the sole exception of cases in which there was a clear breach in sample collection protocol (i.e., menstrual blood contaminating the sample at collection). If there is a clear breach of protocol, repeat iFOBT testing is suggested within six weeks. However, this approach carries the risk of a misleading negative test result because low levels of bleeding from a cancer or adenoma may be intermittent, or unevenly distributed in the stools.

Good practice statement

16. Practice Point

To minimise the risk of psychological harm, colonoscopy should be performed promptly after a positive immunochemical faecal occult blood test. (Kirkøen et al, 2016*[133]*)

Good practice statement

17. Practice Point

There is evidence that colonoscopy should be done within 120 days from the day of the positive immunochemical faecal occult blood test to minimise risk of advancing the severity of disease if cancer is present.

5.3 Participation in population screening for colorectal cancer

Good practice statement

18. Practice Point

Encouragement by health care professionals (including general practitioners (GPs), Aboriginal Health Workers (AHWs), Aboriginal Health Practitioners (AHPs), nurses and other primary health care professionals substantially boosts participation in colorectal cancer screening. Health care professionals play a key role in providing patients with screening advice. GP or clinic endorsement messages in advance of receiving a test kit, the use of GP or clinic reminder systems, leadership of AHWs and AHPs in health promotion activities and practice audits can improve participation rates (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). Increased participation in the National Bowel Cancer Screening Program (NBCSP) through encouragement and access through a variety of NBCSP kit distribution avenues will increase the program's effectiveness and cost-effectiveness.

Good practice statement

19. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a very important role in managing the interface between population screening and personalised care (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). This role includes identifying and advising those who should opt out of the National Bowel Cancer Screening Program (NBCSP) because of the known elevated risk of colorectal cancer, presence of major comorbidities and limited life expectancy, those who should defer participation for several months because of recent surgery or major illness and the most appropriate avenue of NBCSP kit distribution available.

Good practice statement

20. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a key role in advising patients who are at average or slightly above average risk that immunochemical faecal occult blood test is the preferred method of screening. They can advise on the various avenues of kit distribution through the National Bowel Cancer Screening Program. They should also discuss the relative harms and benefits of and discourage inappropriate use of colonoscopy as a screening method.

Good practice statement

21. Practice Point

Ongoing efforts to identify methods to improve colorectal cancer screening participation, access to screening kits through various distribution avenues, modify testing strategies and evaluate existing and new population screening modalities are needed and should be informed by real-world data and other well-designed local and international research, as appropriate.

5.4 Colorectal cancer screening for Aboriginal and Torres Strait Islander peoples

Good practice statement

22. Practice Point

Local access to culturally safe, targeted advice and support for colorectal cancer screening, diagnostic services and treatment should be provided through health care professionals to improve equity for Aboriginal and Torres Strait Islander peoples.

Good practice statement

23. Practice Point

Health care professionals must be adequately supported to provide culturally safe and sensitive information, verbally and in written form, about colorectal cancer screening and local services (including colonoscopies) to promote engagement in the complete colorectal cancer screening pathway.

Good practice statement

24. Practice Point

Ongoing efforts to improve engagement of Aboriginal and Torres Strait Islander peoples in colorectal cancer screening must continue and occur in partnership with Aboriginal and Torres Strait Islander peak health bodies to ensure equitable access to colorectal cancer screening services is achieved, as well as build community awareness of the importance of screening.

6. Colorectal Cancer in Australia

6.1 Population screening of colorectal cancer

6.1.1 Population colorectal cancer screening in Australia

6.1.2 Benefits of organised population colorectal cancer screening

6.1.3 Interventions to improve participation in colorectal cancer screening

7. Colorectal cancer screening benefit

7.1 Clinical question/PICO

7.2 Recommendations and practice points

Weak recommendation

1. Evidence-based recommendation

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8.1 Clinical question/PICO

8.2 Recommendations and practice points

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9. Preferences for colorectal cancer screening modalities

10. Participation in population screening for colorectal cancer

10.1 Factors associated with participation in colorectal cancer screening

10.2 Recommendations and practice points

Good practice statement

18. Practice Point

Encouragement by health care professionals (including general practitioners (GPs), Aboriginal Health Workers (AHWs), Aboriginal Health Practitioners (AHPs), nurses and other primary health care professionals) substantially boosts participation in colorectal cancer screening. Health care professionals play a key role in providing patients with screening advice. GP or clinic endorsement messages in advance of receiving a test kit, the use of GP or clinic reminder systems, leadership of AHWs and AHPs in health promotion activities and practice audits can improve participation rates (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). Increased participation in the National Bowel Cancer Screening Program (NBCSP) through encouragement and access through a variety of NBCSP kit distribution avenues will increase the program's effectiveness and cost-effectiveness.

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11. Colorectal cancer screening for Aboriginal and Torres Strait Islander peoples

11.1 Recommendations and practice points

Good practice statement

22. Practice Point

Local access to culturally safe, targeted advice and support for colorectal cancer screening, diagnostic services and treatment should be provided through health care professionals to improve equity for Aboriginal and Torres Strait Islander peoples.

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23. Practice Point

Health care professionals must be adequately supported to provide culturally safe and sensitive information, verbally and in written form, about colorectal cancer screening and local services (including colonoscopies) to promote engagement in the complete colorectal cancer screening pathway.

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Ongoing efforts to improve engagement of Aboriginal and Torres Strait Islander peoples in colorectal cancer screening must continue and occur in partnership with Aboriginal and Torres Strait Islander peak health bodies to ensure equitable access to colorectal cancer screening services is achieved, as well as build community awareness of the importance of screening.

12. Population screening: implications

12.1 Considerations in making these recommendations

12.2 Applicability to the Australian setting

12.3 Harms and benefits-and-burden balance

12.4 Choice of target age range for population screening

12.5 Choice of testing interval for population screening

12.6 Choice of immunochemical faecal occult blood test as preferred test for population screening

12.6.1 Faecal occult blood tests versus flexible sigmoidoscopy or colonoscopy

12.6.2 Immunochemical versus guaiac occult blood tests

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12.7.3 Barriers to population screening

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13. Population screening: discussion

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13.2.2 Colonoscopy versus iFOBT

13.2.3 Sigmoidoscopy versus iFOBT

13.2.4 iFOBT versus iFOBT

13.2.5 Studies in Australia

13.3 Future research priorities

14. Appendices

1. Abbreviations

Acronym	Description
AA	Advanced adenoma
ACCHOs	Aboriginal and Torres Strait Islander community-controlled health organisations
ACs/LYS	Additional colonoscopies required to save one life-year
AHWs	Aboriginal Health Workers
AHPs	Aboriginal Health Practitioners
AIHW	Australian Institute of Health and Welfare
ASC-FIT	Augmentation of Screening Colonoscopy with Faecal Immunochemical Testing (US clinical trial)
AUD	Australian dollars
BMI	Body mass index
CALD	Culturally and linguistically diverse
CI	Confidence interval
CONFIRM	Colonoscopy versus faecal immunochemical test in reducing mortality from colorectal cancer (US clinical trial)
CRCScreen	Effectiveness of an integrated colorectal cancer screening in Saudi Arabia: A pragmatic randomized trial (clinical trial)
CRC	Colorectal cancer
CSAE	Colonoscopy-related adverse events
CT	Computed tomography
DNA	Deoxyribonucleic acid
EBR	Evidence-based recommendation
FIT	Faecal immunochemical test
FSG	Flexible sigmoidoscopy
g	Grams – unit of measurement
gFOBT	Guaiac faecal occult blood test
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluations (an approach to developing clinical recommendations)
iFOBT	Immunochemical faecal occult blood test

INNC	Incremental number-needed-to-colonoscope
LYS	Life-years saved
MBS	Medicare Benefits Schedule
mSEPT9	methylated septin 9
Mt-sDNA	Multitarget stool DNA
NBCSP	National Bowel Cancer Screening Program
NCSR	National Cancer Screening Register
NHMRC	National Health and Medical Research Council
NORCCAP	Norwegian Colorectal Cancer Prevention Trial
NordICC	Nordic-European Initiative on Colorectal Cancer
NNC	Number-needed-to-colonoscope
NSW	New South Wales
PICO	Population, Intervention, Comparator, Outcome
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer screening trial (clinical trial)
PP	Practice point
RACGP	Royal Australian College of General Practitioners
RCT	Randomised controlled trial (clinical trial)
SCORE	Screening for COlon REctum – Multicentre randomised controlled trial of once-only sigmoidoscopy trial (Italian clinical trial)
SCREESCO	Randomised clinical trial of once-only colonoscopy or two rounds of faecal immunochemical testing 2 years apart for colorectal cancer screening (Swedish clinical trial)
UK	United Kingdom
UKFSST	United Kingdom Flexible Sigmoidoscopy Screening Trial (clinical trial)
US	United States
USPSTF	United States Preventive Services Task Force
µg	Microgram – unit of measurement

2. Glossary

Adenoma	A tumour that is not cancerous
Asymptomatic	Without any symptoms
Average risk	Not known to be at substantially increased risk, such as due to family or comorbidities
Body mass index	A measure of body fat or healthy weight based on a person's height and weight
Biomarkers	A naturally occurring characteristic in the body that helps to identify diseases, etc
Bowel cancer	A cancer of the colon or rectum
Colonoscopy	An examination done by inserting a long flexible tube with a camera into the rectum to look for changes in the colon or to detect cancer
Colorectal cancer	A cancer of the colon or rectum
Comorbidity	1. The simultaneous presence of two or more diseases or medical conditions in one person (also called 'multimorbidity') 2. A disease or medical condition in a person who has more than one condition. For example, if a person with bowel cancer also has heart disease, heart disease is a 'comorbidity' (also called a 'comorbid condition').
Computed tomography	An imaging procedure that uses computerised X-ray images to scan internal areas of the body
Confidence Interval	A statistically estimated range that a calculated value will probably fall within
Cost-effectiveness	A ratio that determines the net cost per change in health outcome
Direct Access Colonoscopy services	An initiative to increase access to colonoscopy services after an individual has been reported with a positive iFOBT
Evidence-based recommendation	Recommendation based on systematic review of medical data (e.g., results of clinical trials) conducted for these guidelines
Family history	A history of disease and/or health conditions found in a person's biological family members
Flexible sigmoidoscopy	An examination procedure done by inserting a long flexible tube with a camera into the rectum to examine the rectum or lower colon
Generalisability	Whether results/findings of a study/report can be applied to other situations or people
Immunochemical faecal occult blood test	A test that checks for unseen blood in a stool sample
Incidence	The occurrence of newly diagnosed cases of a disease
Lesions	Abnormal growth or appearance of a tissue through injury or disease
Mortality	Death (rate); the number of deaths in a group of people
Mutations	A change in the normal structure of a gene or DNA that can be carried through family/inherited
National Bowel Cancer Screening Program	The Australian population screening program for colorectal cancer
Opportunistic screening	Disease screening offered to patients by health professionals as

	an additional examination or test during a healthcare visit, when screening was not the reason for the visit
Plasma	The liquid part of blood
Practice point	Guidance on a topic for which a systematic review was not conducted or was out of scope of the systematic review
Randomised controlled trial	A scientific study in which an intervention or treatment is tested against controlled groups/factors
Risk factors	Characteristics or exposures that can increase the likelihood of developing a disease
Test sensitivity	The ability of a diagnostic test to correctly indicate that an individual has cancer (or whichever disease the test is intended for)
Test specificity	The ability of a diagnostic test to correctly indicate that an individual does not have cancer (or whichever disease the test is intended for)

3. Plain language summary

Population screening for bowel cancer means testing healthy middle-aged people, with no known symptoms of bowel cancer, for early signs of bowel cancer to reduce deaths from this disease. The purpose of this guideline chapter is to help doctors in screening for bowel cancer and those health professionals looking after people before a person may get bowel cancer. It does not cover what happens after the screening process or bowel cancer treatment.

Most people who are eligible for population screening for bowel cancer have a small chance of getting bowel cancer. This includes people who do not have a family history of bowel cancer and people without any obvious signs of bowel cancer. These people can take part in screening, which can find possible signs of bowel cancer as early as possible. When bowel cancer is found early, patients have a higher chance of successful treatment including cure.

Bowel cancer in Australia

Each year in Australia, about 16,000 people are diagnosed with bowel cancer, also known as colorectal cancer and around 5,300 people die from the disease. Bowel cancer is the fourth most common cancer and the second leading cause of cancer death in Australians of all ages. Fewer people are getting bowel cancer than in the past, but people now tend to be younger when the cancer is first found. It is important to diagnose bowel cancer as early as possible. If diagnosed early, people with bowel cancer have a higher chance of survival.

Who gets bowel cancer?

Getting bowel cancer is linked to several risk factors. These include smoking, eating large amounts of processed meats (such as smoked, cured, salted or preserved meats) and red meat, drinking alcohol, and being overweight or obese. Bowel cancer is also linked to lack of physical activity, low milk intake, and low fibre intake. In some cases, bowel cancer runs in families due to family history of genetic changes. Bowel cancer can affect both men and women.

Who should have regular screening for bowel cancer?

Bowel cancer risk depends on a person's age, which in turn determines when an individual should be screened. Bowel cancer screening is for people who do not already have bowel cancer, symptoms of bowel cancer, or any reason to have a high risk of bowel cancer. Individuals experiencing symptoms of bowel cancer (including blood in stool, blood in toilet bowl, changes in appearance or consistency of stool, abdominal pain, unexpected weight loss, fatigue, etc.,) should consult their general practitioner for appropriate investigation.

The Australian National Bowel Cancer Screening Program (NBCSP) provides population screening for bowel cancer free of charge to all eligible people every 2 years.

In Australia, screening people aged 45–74 years who do not have symptoms of bowel cancer every 2 years offers the best balance of effectiveness, acceptable levels of safety, and value for money while avoiding unnecessary screening.

The best population screening test for the Australian population is the 'poo test'. The technical name for this test is immunochemical faecal occult blood test (iFOBT). This is the test used by the NBCSP. The NBCSP mails a 'poo test' to be completed at home. The person collects tiny samples of their poo using the kit and sends them to the program's pathology provider through the post. The pathology lab examines the samples for invisible traces of blood. If the lab test finds some blood (i.e., a positive screening result), the person's health care provider (e.g., general practitioner) advises them to have more tests, which may include a colonoscopy. A positive screening test does not always mean that a person has bowel cancer.

For a colonoscopy to be successful, the bowel must be adequately cleaned of any faecal matter (poo). Preparation

for the colonoscopy often involves not eating fibre for 2-3 days leading up to the procedure, drinking clear fluids and taking strong laxatives (usually liquid formula) in the 24 hours before the procedure. During the colonoscopy, the person is positioned on their side and given sedative medicine to help them relax. The doctor then inserts a flexible tube through the anus and into the colon to check for any abnormalities. A colonoscopy is generally performed as a day procedure and is painless, with full recovery usual within 1-2 hours of the procedure.

Population screening for bowel cancer is recommended only for people aged 45-74 years because overall, population screening must offer more benefit than harm. Screening aims to find cancer early but, in some people, screening can result in unnecessary colonoscopies or unnecessary worry for people with a positive test result who don't have bowel cancer. In the target age range, studies have shown that population screening offers more benefit than harm. People outside the recommended target age range should talk to their doctor if they are worried about getting bowel cancer. For someone without symptoms and younger than 45, a decision to screen should be made with their doctor, after considering if they have a family history of bowel cancer or any other factors that affect their risk. For someone older than 74 without symptoms, a decision to screen should be made with their doctor to determine if they are fit and healthy and that they understand the benefits and potential harms associated with having a follow-up colonoscopy if they have a positive screening result.

Where to find information about bowel cancer, bowel cancer screening, and bowel cancer treatment

Cancer Council

131120

www.cancer.org.au

Understanding bowel cancer. A guide for people with cancer, their families and friends – Booklet available from: https://www.cancer.org.au/cancer-information/downloadable-resources

A Guide for Health Professionals. Frequently asked questions about bowel cancer screening from: https://www.naccho.org.au/programs-projects/bowel-cancer-screening/

National Bowel Cancer Screening Program – Clinical resources: https://www.health.gov.au/resources/collections/national-bowel-cancer-screening-program-clinical-resources

A Guide for Community Members. Frequently asked questions about bowel cancer screening from: https://www.naccho.org.au/programs-projects/bowel-cancer-screening/

Information for GPs. Bowel screening and Aboriginal and Torres Strait Islander peoples from: https://www.health.gov.au/resources/publications/indigenous-people-and-bowel-screening-information-for-doctors?language=en

Resources for families and communities – Indigenous bowel screening: https://www.health.gov.au/resources/collections/resources-for-families-and-communities-indigenous-bowel-screening?language=en

Information for Aboriginal and Torres Strait Islander peoples on free bowel cancer screening: www.indigenousbowelscreen.com.au

Understanding the bowel cancer screening test in your language: https://www.cancer.org.au/bowelscreening/multilingual-resources

4. Introduction

4.1 Background

In 2022, colorectal cancer (CRC), also known as bowel cancer, was estimated to be the fourth most commonly diagnosed cancer and the second leading cause of cancer death in Australians of all ages *[1]*. According to the Australian Institute of Health and Welfare (AIHW), in 2022 there were an estimated 15,713 new CRC cases and 5,326 CRC deaths *[1]*. Key risk factors for CRC include tobacco consumption, excess alcohol consumption, excess body fatness, and dietary factors, including excess red and processed meat consumption, and insufficient intake dietary fibre *[2]*. Consumption of milk and dairy products, and physical activity, can reduce CRC risk *[2]*. CRC screening aims to facilitate the early detection and prevention of CRC, with survival rates highest for those detected through screening *[3]*.

This guideline chapter on Population screening for CRC has been updated from that developed in 2017 *[4]* in response to emerging evidence relevant to the target age range for population screening in Australia.

4.2 Intended users

This guideline chapter is intended for health professionals caring for people without symptoms or signs of CRC to whom screening applies.

It may also be of use to policy makers and people with training in medicine or other health sciences and healthcare teams, including Aboriginal Health Practitioners and Aboriginal Health Workers.

They are not intended as health information for the general public.

4.3 Target populations

This guideline chapter covers all people without symptoms or signs of CRC to whom screening applies, and/or people with a positive faecal occult blood test including Aboriginal and Torres Strait Islander peoples.

Clinicians should consider the specific needs of priority/underrepresented groups nationally, as defined in annual AIHW National Bowel Cancer Screening Program (NBCSP) monitoring reports *[5]*, including Aboriginal and Torres Strait Islander peoples, people living with disabilities, and culturally and linguistically diverse people. For each systematic review undertaken to inform this chapter, search strategies specifically included terms to capture priority groups, including Aboriginal and Torres Strait Islander peoples.

4.4 Health care settings in which the guidelines will be applied

This guideline chapter applies to the range of public and private healthcare settings in which services are provided for the target screening populations. These include, but are not limited to:

- screening services
- hospitals
- specialist clinics
- pathology services
- primary healthcare services, including general practice, community health, and Aboriginal and Torres Strait Islander community-controlled health organisations (ACCHOs).

4.5 Purpose and scope

This guideline chapter (*Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer: population screening*) provides information and recommendations to guide practice in CRC screening and the assessment pathway. These guidelines also provide an evidence base for the NBCSP.

The first *Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer* were developed in 1999 *[6]* and, since then, have been widely used as a reference by health practitioners, including general practitioners (GPs), Aboriginal Health Workers, Aboriginal health practitioners, and other primary health care workers, to guide clinical practice.

4.6 Publication Approval

Australian Government

National Health and Medical Research Council

The guideline recommendations in this chapter, (Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer: Population screening), were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 28 September 2023 under section 14A of the National Health and Medical Research Council Act 1992. In approving the guideline recommendations NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years. NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting. This publication reflects the views of the authors and not necessarily the views of the Australian Government

4.7 Funding

Cancer Council Australia was funded by the Department of Health and Aged Care to update two of the 16 chapters from the 2017 *Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer* (the 2017 guidelines) *[4]*. Cancer Council Australia sub-contracted The Daffodil Centre, a joint venture between the University of Sydney and Cancer Council NSW, to perform the systematic reviews and predictive modelling, and provide project coordination to support guideline development. Cancer Council Australia and the Daffodil Centre formed the Guideline development team. The funding body did not influence the content of these guidelines.

4.8 Guideline development process

4.8.1 Contributors

A working party of key experts in colorectal cancer (the Working Party) was established to support and oversee the update (see **Appendix A** for full guideline development process and **Appendix B** for the clinical questions). Key experts involved in the development of the 2017 guidelines for the prevention, early detection, and management of colorectal cancer were included and the group was broadened to cover the majority of jurisdictions across Australia. Professor Tim Price, co-chair of the 2017 guidelines, retained his

position as chair of the Working Party for the current guideline chapter updates. Additionally, the Working Party included three consumer representatives.

A complete list of contributors can be found in **Appendix C** and a register of competing interests in **Appendix D**.

4.8.2 Clinical questions

The update was guided by the following clinical question (see **Appendix B** for a full list of clinical questions):

Is population screening based on testing with (a) immunochemical faecal occult blood test (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) computed tomography (CT) colonography, (e) faecal biomarkers such as DNA, (f) plasma biomarkers such as DNA, (g) any combination of the above screening tests, effective in reducing colorectal cancer mortality, colorectal cancer incidence or the incidence of metastases at diagnosis, feasible, acceptable, and a cost-effective method of screening for the target population?

> a) Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 years? [with 2-yearly iFOBT screening]
>
> b) In population screening, do the harms outweigh the benefits if routine screening, by any method, is continued beyond the age of 75 years?

The development and update of this question was guided by current evidence and practice and agreed upon by the Working Party. From this clinical question, specific PICO (population, intervention, comparator, and outcome) questions were formulated by the Guideline development team in consultation with the Working Party, and systematic reviews were conducted.

4.8.3 Systematic reviews

The recommendations were informed by two systematic reviews (PSC1a and PSC1b) and two modelling reports (PSC1c and PSC1d) outlined in **Appendix E**. The Working Party also considered an additional modelled evaluation based on a published analysis of age extension modelling for Aboriginal and Torres Strait Islander peoples *[7]*. A summary of the systematic review questions is shown in Table 1 and a summary of the modelling evaluation aims is shown in Table 2.

Table 1. Summary of systematic review questions

PICO	Systematic review question
PSC1a	In persons without a CRC diagnosis or symptoms that might indicate colorectal cancer, which screening modalities (iFOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combination) compared with no screening, reduce colorectal cancer mortality, colorectal cancer incidence, or the incidence of metastases at diagnosis?
PSC1b	For persons without a (CRC) diagnosis or symptoms that might indicate CRC, which screening modality (iFOBT, faecal or blood biomarkers, or any combination) performs best in detecting colorectal cancer, and how does the diagnostic performance change with family history, age, or sex?

Table 2. Summary of modelled evaluation aims

	Modelled evaluation aims
PSC1c	**Alternative screening age range:** To evaluate the health benefits (i.e. CRC incidence and mortality reduction and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the NBCSP age range from age 40 years to 84 years using a modelling approach
PSC1d	**Alternative test technologies:** To evaluate the health benefits (as measure by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e., the number of colonoscopy-related adverse events), and cost-effectiveness of yearly iFOBT or 5-yearly faecal biomarker screening, compared with 2-yearly iFOBT screening
Published evaluation *[7]*	**Age extension modelling for Aboriginal and Torres Strait Islander:** To evaluate the health outcomes and cost-effectiveness of the NBCSP and evaluate the potential health benefits and cost-effectiveness of extending the NBCSP to include Aboriginal and Torres Strait Islander peoples from age 40 years

4.8.4 Evidence appraisal and synthesis

The Working Party appraised the evidence from the systematic reviews and predictive modelling studies using a hybrid approach reflecting the guideline's transition from the former evidence appraisal approach to Grading of Recommendations Assessment, Development and Evaluations (GRADE) methodology.

4.8.5 Development of recommendations and practice points

The Working Party formulated recommendations and practice points based on the updated evidence and in line with the NHMRC process (outlined in **Appendix F**, **Appendix G** and **Appendix H**). Evidence-based recommendations (EBR) were developed through a structured process, considering the body of evidence and its relevance to Australian clinical practice. Each EBR was assigned a grade (either strong or weak) by the expert Working Party, taking into account the certainty of the body of evidence for the 2023 update, and the evidence base and consistency for the 2005 guidelines and 2017 update evidence, as well as the generalisability, applicability, acceptability, feasibility and clinical impact of the body of evidence using the National Health and Medical Research Centre (NHMRC) evidence statement form.

Practice points were also developed or adapted to support the recommendations and provide guidance on areas not examined by a systematic review. Practice points were developed where there were issues out of scope of a systematic review. This may be differentiated from a consensus-based recommendation (not included in this chapter), which are developed in cases where a systematic review is conducted but no evidence or low-quality evidence is identified. The wording used in the practice points reflects the urgency of the issue. In some cases, the practice points indicate the likelihood of a benefit, rather than its urgency.

Table 3. Types of recommendations included in these guidelines

Type	**Process**
Evidence-based recommendation (EBR)	Recommendation based on a systematic review conducted for these guidelines
Practice point	Guidance on a topic for which a systematic review was not conducted, or for which issues were out of scope of the systematic

	review undertaken.

The Working Party followed a structured process and consensus was reached through formal meetings and offline correspondence, where required. To reach consensus, the recommendations and practice points were circulated to the Working Party for comments and a voting process was used, both in meetings and through offline correspondence. In this way, Working Party members were able to comment on each recommendation and practice point. Any uncertainties were raised and discussed with the Working Party Chair. Comments and suggested changes were circulated to the Working Party. All subsequent changes were raised, discussed, and voted on in Working Party meetings and offline correspondence until consensus was reached. The recommendations and practices from 2017 guidelines are reported alongside the updated statements in **Appendix I.**

4.8.6 Consideration of priority groups

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander populations. Although no evidence for priority groups was identified for inclusion, it is important to acknowledge related issues including the impact of cultural determinants of health, ongoing effects of colonisation, systemic racism, stigma and social marginalisation on the provision of health care.

Successful implementation of CRC prevention and screening in Australia requires the provision of culturally sensitive and safe health care. Culturally sensitive and safe health services can be provided through an understanding, consideration and respectful accommodation of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected. In Australia, frameworks, manuals and guidelines have been developed to support health care professionals in providing culturally sensitive and safe services, specific to Aboriginal and Torres Strait Islanders *[8][9]*, people living in remote communities *[10]* refugees to Australia *[11][12][13]*, people impacted by the justice system *[14]* and to support inclusiveness of gender identities *[15]*. Guidance in this area outlines the principles of respect for patients and their families' cultural and religious beliefs, taking time to understand a patient's knowledge, values and cultural needs throughout the decision-making process *[16][17]*. Health care professionals are encouraged to use plain language in communications and to ensure information is accessible and in culturally appropriate formats.

4.8.7 Consultation

The guideline chapter was released for targeted expert consultation and public consultation in April 2023. The Working Party considered all submissions and agreed on appropriate amendments in response to comments and proposed changes (see **Appendix J**). The 2023 guideline chapter was endorsed by NHMRC in September 2023.

4.9 Scheduled review of these guidelines

Newly published evidence relevant to each systematic review question will continue to be monitored. If there is strong evidence emerging in CRC screening, the Working Party will be reconvened to assess if this warrants a guideline update (full or partial), and determine the resources required to conduct this revision. It is recommended that the 2023 guideline chapter be updated within 5 years.

4.10 Acknowledgements

We thank the chair of the Working Party, Professor Timothy Price, members of the Working Party, the guideline development team, systematic reviewers, the modelling team, and all others who contributed to the development of these guidelines. We would like to acknowledge and thank Ms Jenni Harman for her editorial assistance.

A complete list of contributors can be found in **Appendix C** and a register of competing interests in **Appendix D**.

4.11 Citation

Cancer Council Australia Colorectal Cancer Screening Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer: Population screening. September 2023. Sydney: Cancer Council Australia. Available from Magicapp

5. Summary of recommendations for population screening

To download a summary of recommendations click here

Population screening for colorectal cancer (CRC) is primarily directed at middle-aged people in good general health, with no symptoms that might indicate CRC, so that preventative measures or early treatment may be offered to improve health outcomes. Risk assessment methods to determine targeted screening strategies are addressed in the chapter on Risk and screening based on family history (found here).

These recommendations are intended to guide decision-making in determining who should take part in population screening for colorectal cancer. All recommendations and practice points included should be considered for implementation in practice.

Principles of clinical judgement and shared decision-making, using a culturally sensitive and safe approach, apply when implementing these guidelines.

These guidelines include evidence-based recommendations (EBR) and practice points. For each EBR except those based on modelling evaluation, the Working Party assigned a strength (weak or strong) in support of the EBR, after considering the volume, consistency, generalisability, applicability and clinical impact of the body of evidence using the NHMRC evidence statement form.

A strength was not assigned (N/A) to recommendations based on mathematical modelling evaluation because GRADE methodology does not cover this type of evidence. Recommendations and practice points were developed by Working Party members. The choice of recommendation and wording reflects the certainty of evidence (Refer to development of recommendations and practice points, **Appendix A**).

5.1 Colorectal cancer screening benefit

Weak recommendation

1. Evidence-based recommendation

The recommended strategy for population screening in Australia, directed at those at average risk of colorectal cancer and without relevant symptoms, is immunochemical faecal occult blood testing every two years, starting at age 45 years and continuing to age 74 years. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Bretthauer, et al, 2022*[44]*, Juul, et al, 2022*[45]*)

Practical info

Several RCTs evaluating gFOBT-based screening demonstrated a reduction in colorectal cancer-specific mortality, compared with no screening *[49][50][51][52][53][54][55]*.

A large study evaluating the combination of once-only iFOBT-based screening, with flexible sigmoidoscopy (but not colonoscopy) for those with a positive test, showed a 32% reduction in rectal cancer mortality but no statistically significant reduction in CRC-specific or colon cancer-specific mortality at 8-year follow-up*[40]*.

Four RCTs assessing flexible sigmoidoscopy as a screening modality, compared with usual care, reported a combined 26% (20–32%) reduction in CRC-specific mortality and a 22% (17–27%) reduction in CRC incidence in those randomised to screening, after median follow-up of at least 14.8 years, with greater benefits in males*[45]*. This benefit in CRC-specific mortality was attributed entirely to a reduction in distal CRC-specific

mortality and not proximal CRC-specific mortality. Three out of four of the trials provided a once-only flexible sigmoidoscopy as the screening test *[40][41][42]*, the trial conducted in the US provided flexible sigmoidoscopy at baseline and at 3 or 5 years *[43]*.

One RCT assessed colonoscopy screening, compared with no screening *[43]*. This study had only 10 years' follow-up and a screening participation rate of 42% in the screening arm. It reported a numerical reduction in CRC-specific mortality (although the 95% confidence interval [CI] crossed 1.0), and a reduction in CRC incidence with a risk ratio of 0.82 (95% CI 0.70–0.93) *[43]*.

Only one RCT evaluated the combination of two screening modalities (flexible sigmoidoscopy and iFOBT) and reported a reduction in CRC-specific mortality of 27% after a median follow-up of 14.8 years *[41]*.

No RCTs were found that assessed screening with CT colonography, faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA, compared with no screening.

No studies were found that evaluated screening in participants aged younger than 50 years or older than 74 years.

Evidence to decision

Benefits and harms

Screening benefits have been assessed in terms of reductions in CRC incidence, mortality, and the incidence of metastases at diagnosis. These benefits should be weighed against the burden of screening procedures which, in the case of colonoscopy, can include the risk of perforation and bleeding. Data on screening-related harms were not extracted in the systematic review but have been assessed in the modelled evaluations (see section 4.4.2 Findings of modelling evaluation).

The age range of population screening also affects the balance of benefits versus harms. For those younger than 45 years, the risk of CRC is lower, so population screening would result in unnecessary testing for the average-risk population.

For those over age 74 years, there is little empirical evidence to support screening. The United States Preventive Services Task Force (USPSTF) maintained its recommendation for to stop screening at age 75 years *[56]*. Given that the balance of benefits and harms of CRC screening becomes less favourable in those aged 76–85 years due to the higher prevalence of colonoscopy-related serious adverse events *[57]*, the USPSTF recommended screening on a case-by-case basis in this age-group, and recommended against screening for people with significant comorbidity *[56]*. Modelling studies undertaken for the USPSTF estimated few additional life-years gained by extending screening beyond the 75 years among adults at average risk who had previously participated in screening *[58][59]*.

While the Australian population may have different comorbidity patterns, the US findings are likely relevant.

Certainty of the Evidence

CRC-specific mortality: The systematic review found that available studies reporting CRC-specific mortality provided a high certainty of evidence for flexible sigmoidoscopy overall and in male subgroups, and a moderate certainty of evidence in female subgroups. Studies reporting this outcome provided a moderate certainty of evidence for colonoscopy.

CRC incidence: Studies reporting CRC incidence provided a high certainty of evidence for colonoscopy.

Proportion of metastatic colorectal cancer at diagnosis: Studies reporting this outcome provided a

low certainty of evidence for flexible sigmoidoscopy, and a moderate certainty of evidence for colonoscopy.

Values and preferences

Many countries, including Australia, New Zealand, Canada, and several European countries, have established national population-based CRC screening programs that use either gFOBT or iFOBT as a primary screening modality. The advantage of iFOBTs is that they specifically detect haemoglobin with no need to change diet or medication prior to testing *[60]*. Many iFOBT methods use automated analysis, and several allow quantitative analysis of haemoglobin. In contrast, flexible sigmoidoscopy and colonoscopy are invasive procedures, requiring a highly trained workforce and special facilities. There are particular concerns about the acceptability and feasibility of flexible sigmoidoscopy and colonoscopy as population screening modalities in the Australian setting, as well as their cost-effectiveness.

Resources and other considerations

Population screening based on colonoscopy and flexible sigmoidoscopy is not feasible in the Australian context, as the current healthcare system capacity could not meet the estimated demand on resources. Colonoscopy services in the public health system are already at capacity, and there are difficulties meeting the demand for diagnostic colonoscopy following a positive screening test result. However, the NBCSP with 2-year iFOBT offered to eligible participants from 50-74 years is predicted to contribute 10–14% of all MBS-funded colonoscopies by 2030 *[61]*.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen *[40][41][42]* and one reported on two screens *[43]*. The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial *[44]* reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up *[45]*. No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and

proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 *[40]*.

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years *[41]*.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence *[43]*.

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years *[42]*.

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.74 (CI 95% 0.68 — 0.8) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	7.81 per 1000 Difference:	5.78 per 1000 **2.03 fewer per 1000** (CI 95% 2.5 fewer — 1.56 fewer)	High [1]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 50-74years
CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.8 (CI 95% 0.72 — 0.88) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	6.02 per 1000 Difference:	4.82 per 1000 **1.2 fewer per 1000** (CI 95% 1.69 fewer — 0.72 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 55-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC incidence (Age range 50-74) [measured as CRC incidence per 1000]	Hazard ratio 0.78 (CI 95% 0.73 — 0.83) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	25.3 per 1000 Difference:	19.7 per 1000 **5.6 fewer per 1000** (CI 95% 6.8 fewer — 4.3 fewer)	High [3]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 50-74years.
CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.79 (CI 95% 0.75 — 0.83) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	21.7 per 1000 Difference:	17.1 per 1000 **4.6 fewer per 1000** (CI 95% 5.4 fewer — 3.7 fewer)	High [4]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 55-64years.
% CRC metastatic at diagnosis (Age range 55-74) [measured as metastatic disease at diagnosis per 100 CRC diagnoses] [5]	Relative risk 0.9 (CI 95% 0.76 — 1.07) Based on data from 154,887 participants in 1 studies. Follow up: N/A.	15.9 per 1000 Difference:	14.4 per 1000 **1.6 fewer per 1000** (CI 95% 3.8 fewer — 1.1 more)	Low High risk of bias due to deviations from intended interventions and missing outcome data; imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [6]	CRC screening with flexible sigmoidoscopy may reduce proportion of CRC metastatic at diagnosis for those in the age group 55-74years.

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with a median follow-up of at least 14.8 years show a reduced risk of CRC-specific mortality following FSG overall. Confidence intervals of individual trials overlapped, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR=0.74 (0.68-0.80) overall and HR = 0.69 (0.60-0.80). Power is unlikely to be an issue with > 400,000 participants and 3,188 events overall.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions

resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with over 15 years follow-up show a reduced risk of CRC-specific mortality following FSG. Confidence intervals of individual trials overlapped and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs limited to participants aged 55-64 years at 15 years follow-up was RR=0.80(0.72-0.88_ with narrow 95% C that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.

3. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected (I2 = 36.1%) but this is not statistically significant and point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.78 (0.73-0.83) for CRC incidence with a narrow 95% CI that did not include the null effect. The FSG meta-analysis results are likely to be adequately powered with > 400,000 participants and 10,495 events.

4. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. The point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to participants aged 55-64 years at 15 years follow-up was RR=0.79 (0.75-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.

5. undefined

6. **Risk of Bias: serious.** Single trial at high risk of bias due to deviations from intended interventions and missing outcome data. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome for this trial were relevant. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.76-1.07). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-64) [measured by CRC deaths per 1000]	Hazard ratio 0.75 (CI 95% 0.57 — 0.99) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	6.78 per 1000 Difference:	5.09 per 1000 **1.69 fewer per 1000** (CI 95% 2.91 fewer — 0.07 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for those in the age group 50-64years
CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.81 (CI 95% 0.7 — 0.93) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	22.4 per 1000 Difference:	18.1 per 1000 **4.3 fewer per 1000** (CI 95% 6.7 fewer — 1.6 fewer)	High [2]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for those in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.75 (0.57-0.99) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). . **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant.. **Imprecision: no serious.** The HR is 0.81 (0.70-0.93) with a 95% CI that does not cross the null effect..

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with colonoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Nordic-European Initiative on Colorectal Cancer (NordICC): This population-based RCT (N=84,585) conducted in Poland, Norway and Sweden assessed single colonoscopy compared with usual care. Median follow-up was 10 years for CRC incidence and specific mortality. The study also reported on the percentage of metastatic CRC at diagnosis (44).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 55-64) [measured by CRC deaths per 1000]	Relative risk 0.9 (CI 95% 0.64 — 1.16) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	2.79 per 1000 Difference:	2.51 per 1000 **0.28 fewer per 1000** (CI 95% 1 fewer — 0.45 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [1]	CRC screening with colonoscopy may reduce CRC-specific mortality for those in the age group 55-64years
CRC incidence (Age range 55-64) [measured by CRC incidence per 1000]	Relative risk 0.82 (CI 95% 0.7 — 0.93) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 3.3 fewer — 0.76 fewer)	High [2]	CRC screening with colonoscopy probably reduces CRC incidence for those in the age group 55-64years
% CRC metastatic at diagnosis (Age range 55-64) [measured by metastatic	Relative risk 1.06 (CI 95% 0.77 — 1.44) Based on data from 84,585 participants in 1 studies. Follow up: NA.	17.2 per 100 Difference:	18.2 per 100 **1 more per 100** (CI 95% 4 fewer	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e.	CRC screening with colonoscopy may or may not reduce proportion of CRC metastatic at diagnosis for those in the age group

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
disease at diagnosis per 100 CRC diagnosis]			— 7.6 more)	includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [3]	55-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that only 42% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.64-1.16) at 10 years follow-up. 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in CRC mortality so unsure as to the effect i.e. imprecise. The results were interim not mature results. The study was powered to detect 25% difference in CRC mortality at 15 years; it was not powered to detect difference of 25% or more at 10 years follow-up. The study was not powered to detect differences <25%.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: no serious.** Single study with risk ratio (95% CI) = 0.82 (0.70-0.93). The risk of CRC was 11.0/1000 in the control group and the upper limit of estimated absolute risk (upper limit of the 95% confidence interval) in the intervention arm was 10.3/1000. With 84,585 participants and 881 events power is unlikely to be an issue..
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 1.06 (0.77-1.44). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to the effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 (40).

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence (43).

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years (42).

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality (45).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.73 (CI 95% 0.64 — 0.83) Based on data from 135,452 participants in 4 studies. Follow up: 15yrs.	7.71 per 1000 Difference:	5.63 per 1000 **2.08 fewer per 1000** (CI 95% 2.78 fewer — 1.31 fewer)	High [1]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for males in the age group 55-64years
Male CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.69 (CI 95% 0.6 — 0.79) Based on data from 137,905 participants in studies. Follow up: >14.8yrs (median).	8.82 per 1000 Difference:	6.09 per 1000 **2.73 fewer per 1000** (CI 95% 3.52 fewer — 1.85 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for males in the age group 50-74years
Female CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.92 (CI 95% 0.78 — 1.08) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	5.51 per 1000 Difference:	5.07 per 1000 **0.44 fewer per 1000** (CI 95% 1.21 fewer — 0.44 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [3]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for females in the age group 50-74years
Female CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.91 (CI 95% 0.77 — 1.17) Based on data from 139,449 participants in 4 studies. Follow up: 15yrs.	4.37 per 1000 Difference:	3.98 per 1000 **0.39 fewer per 1000** (CI 95% 1.01 fewer — 0.74 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy may reduce CRC-specific mortality for females in the age group 55-64years
Male CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [5]	Hazard ratio 0.74 (CI 95% 0.64 — 0.86) Based on data from 137,905 participants in 3 studies. Follow up: >14.8yrs (median).	26.6 per 1000 Difference:	19.7 per 1000 **6.9 fewer per 1000** (CI 95% 9.6 fewer — 3.7 fewer)	High [6]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for males in the age group 50-74years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.75 (CI 95% 0.7 — 0.81) Based on data from 135,453 participants in 4 studies. Follow up: 15yrs.	26.3 per 1000 Difference:	19.7 per 1000 **6.6 fewer per 1000** (CI 95% 7.9 fewer — 5 fewer)	High [7]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for males in the age group 55-64years
Female CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [8]	Hazard ratio 0.88 (CI 95% 0.81 — 0.96) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	19.5 per 1000 Difference:	17.2 per 1000 **2.3 fewer per 1000** (CI 95% 3.7 fewer — 0.8 fewer)	High [9]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for females in the age group 50-74years
Female CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.84 (CI 95% 0.77 — 0.91) Based on data from 139,499 participants in 4 studies. Follow up: 15yrs.	17.3 per 1000 Difference:	14.5 per 1000 **2.8 fewer per 1000** (CI 95% 4 fewer — 1.6 fewer)	High [10]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for females in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. Inconsistency could not be assessed for FSG + FIT as only a single trial, however, results appeared consistent with those for FSG alone. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analysis of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to male participants aged 55-64 years at 15 years follow-up was RR=0.73 (0.64-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with > 100,000 participants.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions

resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials included in the meta-analysis were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** The point estimates for 3 trials with a median follow-up of at least 14.8 years included in the meta-analysis for males show a reduced risk of CRC-specific mortality following FSG Confidence intervals of individual trials overlapped including the female subgroup, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR = 0.69 (0.60-0.80) for males with narrow 95% CIs that did not include the null effect. Power is unlikely to be an issue with >100,000 participants and 1,100 events in the male subgroup analysis.

3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** In the subgroup meta-analysis for females, the point estimate for 2 trials was consistent with a decrease whereas the point estimate for the third trial was consistent with an increased risk of CRC-specific mortality following FSG. However, confidence intervals of individual trials overlapped , no variability due to heterogeneity was detected and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled HR = 0.92 (0.78-1.08) for FSG alone crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled RR = 0.91 (0.77-1.17) crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.
5. undefined
6. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was

detected in the male subgroup analysis (I2 = 63.3%) but did not reach statistical significance with confidence intervals overlapping and none of the upper CIs crossing 1.0. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.74 (0.64-0.86) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 3,412 events in the male subgroup analysis.

7. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate for males for FSG interventions was RR=0.75 (0.70-0.81) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.
8. undefined
9. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of the 3 FSG trials included in this subgroup analysis were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 3 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens in the female subgroup analysis no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect do not vary widely. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.88 (0.81-0.96) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 2,600 events in the female subgroup analysis.
10. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was RR=0.84 (0.77-0.91) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex

Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

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Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.62 (CI 95% 0.42 — 0.91) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	7.85 per 1000 Difference:	4.87 per 1000 **2.98 fewer per 1000** (CI 95% 4.55 fewer — 0.71 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for males in the age group 50-64years
Female CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.94 (CI 95% 0.64 — 1.37) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	5.73 per 1000 Difference:	5.39 per 1000 **0.34 fewer per 1000** (CI 95% 2.06 fewer — 2.12 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [2]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC-specific mortality for females in the age group 50-64years
Male CRC	Hazard ratio 0.72	24.7	17.85	High	CRC screening with

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
incidence (Age range 50-64) [measured by CRC incidence per 1000]	(CI 95% 0.59 — 0.89) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	per 1000 Difference:	per 1000 **6.85 fewer per 1000** (CI 95% 10.05 fewer — 2.69 fewer)	[3]	flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for males in the age group 50-64years
Female CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.91 (CI 95% 0.74 — 1.11) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	20.1 per 1000 Difference:	18.31 per 1000 **1.79 fewer per 1000** (CI 95% 5.19 fewer — 2.19 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC incidence for females in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.72 (0.59-0.89) with a 95% CI that does not cross the null effect.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The population, intervention, comparator and outcome were relevant.

Weak recommendation

2. Evidence-based recommendation

The use of flexible sigmoidoscopy as a primary screening test is not recommended for population screening in the average-risk population. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Juul, et al, 2022*[45]*).

Practical info

A large study evaluating the combination of once-only iFOBT-based screening, with flexible sigmoidoscopy (but not colonoscopy) for those with a positive test, showed a 32% reduction in rectal cancer mortality but no statistically significant reduction in CRC-specific or colon cancer-specific mortality at 8-year follow-up *[40]*.

Four RCTs assessing flexible sigmoidoscopy as a screening modality, compared with usual care, reported a combined 26% (20–32%) reduction in CRC-specific mortality and a 22% (17–27%) reduction in CRC incidence in those randomised to screening, after median follow-up of at least 14.8 years, with greater benefits in males *[45]*. This benefit in CRC-specific mortality was attributed entirely to a reduction in distal CRC-specific mortality and not proximal CRC-specific mortality. Three out of four of the trials provided a once-only flexible sigmoidoscopy as the screening test *[40][41][42]*, the trial conducted in the US provided flexible sigmoidoscopy at baseline and at 3 or 5 years *[43]*.

Only one RCT evaluated the combination of two screening modalities (flexible sigmoidoscopy and iFOBT) and reported a reduction in CRC-specific mortality of 27% after a median follow-up of 14.8 years *[41]*.

No studies were found that evaluated screening in participants aged younger than 50 years or older than 74 years.

Evidence to decision

Benefits and harms

Screening benefits have been assessed in terms of reductions in CRC incidence, mortality, and the incidence of metastases at diagnosis. These benefits should be weighed against the burden of screening procedures which can include the risk of perforation and bleeding.

Certainty of the Evidence

CRC-specific mortality: The systematic review found that available studies reporting CRC-specific mortality provided a high certainty of evidence for flexible sigmoidoscopy overall and in male subgroups, and a moderate certainty of evidence in female subgroups.

Proportion of metastatic colorectal cancer at diagnosis: Studies reporting this outcome provided a low certainty of evidence for flexible sigmoidoscopy.

Values and preferences

Flexible sigmoidoscopy, along with colonoscopy, is an invasive procedure, requiring a highly trained workforce and special facilities. There are particular concerns about the acceptability and feasibility of flexible sigmoidoscopy as population screening modalities in the Australian setting, as well as their cost-effectiveness.

Resources and other considerations

Population screening based flexible sigmoidoscopy is not feasible in the Australian context, as the current healthcare system capacity could not meet the estimated demand on resources.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen *[40][41][42]* and one reported on two screens *[43]*. The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial *[44]* reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up *[45]*. No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 *[40]*.

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years *[41]*.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence *[43]*.

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years *[42]*.

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from

four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.74 (CI 95% 0.68 — 0.8) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	7.81 per 1000 Difference:	5.78 per 1000 **2.03 fewer per 1000** (CI 95% 2.5 fewer — 1.56 fewer)	High [1]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 50-74years
CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.8 (CI 95% 0.72 — 0.88) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	6.02 per 1000 Difference:	4.82 per 1000 **1.2 fewer per 1000** (CI 95% 1.69 fewer — 0.72 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 55-64years
CRC incidence (Age range 50-74) [measured as CRC incidence per 1000]	Hazard ratio 0.78 (CI 95% 0.73 — 0.83) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	25.3 per 1000 Difference:	19.7 per 1000 **5.6 fewer per 1000** (CI 95% 6.8 fewer — 4.3 fewer)	High [3]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 50-74years.
CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.79 (CI 95% 0.75 — 0.83) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	21.7 per 1000 Difference:	17.1 per 1000 **4.6 fewer per 1000** (CI 95% 5.4 fewer — 3.7 fewer)	High [4]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 55-64years.
% CRC metastatic at	Relative risk 0.9 (CI 95% 0.76 — 1.07)	15.9	14.4	Low High risk of bias	CRC screening with flexible sigmoidoscopy

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
diagnosis (Age range 55-74) [measured as metastatic disease at diagnosis per 100 CRC diagnoses] [5]	Based on data from 154,887 participants in 1 studies. Follow up: N/A.	per 1000 Difference:	per 1000 **1.6 fewer per 1000** (CI 95% 3.8 fewer — 1.1 more)	due to deviations from intended interventions and missing outcome data; imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [6]	may reduce proportion of CRC metastatic at diagnosis for those in the age group 55-74years.

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with a median follow-up of at least 14.8 years show a reduced risk of CRC-specific mortality following FSG overall. Confidence intervals of individual trials overlapped, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR=0.74 (0.68-0.80) overall and HR = 0.69 (0.60-0.80). Power is unlikely to be an issue with > 400,000 participants and 3,188 events overall.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with over 15 years follow-up show a reduced risk of CRC-specific mortality following FSG. Confidence intervals of individual trials overlapped and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs limited to participants aged 55-64 years at 15 years follow-up was RR=0.80(0.72-0.88_ with narrow 95% C that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.
3. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence

following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected (I2 = 36.1%) but this is not statistically significant and point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.78 (0.73-0.83) for CRC incidence with a narrow 95% CI that did not include the null effect. The FSG meta-analysis results are likely to be adequately powered with > 400,000 participants and 10,495 events.

4. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. The point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to participants aged 55-64 years at 15 years follow-up was RR=0.79 (0.75-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.
5. undefined
6. **Risk of Bias: serious.** Single trial at high risk of bias due to deviations from intended interventions and missing outcome data. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome for this trial were relevant. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.76-1.07). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible

sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-64) [measured by CRC deaths per 1000]	Hazard ratio 0.75 (CI 95% 0.57 — 0.99) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	6.78 per 1000 Difference:	5.09 per 1000 **1.69 fewer per 1000** (CI 95% 2.91 fewer — 0.07 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for those in the age group 50-64years
CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.81 (CI 95% 0.7 — 0.93) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	22.4 per 1000 Difference:	18.1 per 1000 **4.3 fewer per 1000** (CI 95% 6.7 fewer — 1.6 fewer)	High [2]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for those in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.75 (0.57-0.99) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). . **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant.. **Imprecision: no serious.** The HR is 0.81 (0.70-0.93) with a 95% CI that does not cross the null effect..

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC

Intervention: CRC screening with colonoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Nordic-European Initiative on Colorectal Cancer (NordICC): This population-based RCT (N=84,585) conducted in Poland, Norway and Sweden assessed single colonoscopy compared with usual care. Median follow-up was 10 years for CRC incidence and specific mortality. The study also reported on the percentage of metastatic CRC at diagnosis (44).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 55-64) [measured by CRC deaths per 1000]	Relative risk 0.9 (CI 95% 0.64 — 1.16) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	2.79 per 1000 Difference:	2.51 per 1000 **0.28 fewer per 1000** (CI 95% 1 fewer — 0.45 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [1]	CRC screening with colonoscopy may reduce CRC-specific mortality for those in the age group 55-64years
CRC incidence (Age range 55-64) [measured by CRC incidence per 1000]	Relative risk 0.82 (CI 95% 0.7 — 0.93) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 3.3 fewer — 0.76 fewer)	High [2]	CRC screening with colonoscopy probably reduces CRC incidence for those in the age group 55-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
% CRC metastatic at diagnosis (Age range 55-64) [measured by metastatic disease at diagnosis per 100 CRC diagnosis]	Relative risk 1.06 (CI 95% 0.77 — 1.44) Based on data from 84,585 participants in 1 studies. Follow up: NA.	17.2 per 100 Difference:	18.2 per 100 **1 more per 100** (CI 95% 4 fewer — 7.6 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [3]	CRC screening with colonoscopy may or may not reduce proportion of CRC metastatic at diagnosis for those in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that only 42% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.64-1.16) at 10 years follow-up. 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in CRC mortality so unsure as to the effect i.e. imprecise. The results were interim not mature results. The study was powered to detect 25% difference in CRC mortality at 15 years; it was not powered to detect difference of 25% or more at 10 years follow-up. The study was not powered to detect differences <25%.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: no serious.** Single study with risk ratio (95% CI) = 0.82 (0.70-0.93). The risk of CRC was 11.0/1000 in the control group and the upper limit of estimated absolute risk (upper limit of the 95% confidence interval) in the intervention arm was 10.3/1000. With 84,585 participants and 881 events power is unlikely to be an issue..
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to

deviations from intended interventions for the single trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 1.06 (0.77-1.44). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to the effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 (40).

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence (43).

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more

than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years (42).

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality (45).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.73 (CI 95% 0.64 — 0.83) Based on data from 135,452 participants in 4 studies. Follow up: 15yrs.	7.71 per 1000 Difference:	5.63 per 1000 **2.08 fewer per 1000** (CI 95% 2.78 fewer — 1.31 fewer)	High [1]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for males in the age group 55-64years
Male CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.69 (CI 95% 0.6 — 0.79) Based on data from 137,905 participants in studies. Follow up: >14.8yrs (median).	8.82 per 1000 Difference:	6.09 per 1000 **2.73 fewer per 1000** (CI 95% 3.52 fewer — 1.85 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for males in the age group 50-74years
Female CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.92 (CI 95% 0.78 — 1.08) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	5.51 per 1000 Difference:	5.07 per 1000 **0.44 fewer per 1000** (CI 95% 1.21 fewer — 0.44 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [3]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for females in the age group 50-74years
Female CRC - specific mortality (Age range 55-64)	Relative risk 0.91 (CI 95% 0.77 — 1.17) Based on data from 139,449 participants in 4 studies.	4.37 per 1000 Difference:	3.98 per 1000 **0.39 fewer per**	Moderate Imprecision as effect estimate 95% confidence interval crosses	CRC screening with flexible sigmoidoscopy may reduce CRC-specific mortality for females in the age group

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
[measured as CRC deaths per 1000]	Follow up: 15yrs.		**1000** (CI 95% 1.01 fewer — 0.74 more)	the null i.e. includes increases as well as decreases [4]	55-64years
Male CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [5]	Hazard ratio 0.74 (CI 95% 0.64 — 0.86) Based on data from 137,905 participants in 3 studies. Follow up: >14.8yrs (median).	26.6 per 1000 Difference:	19.7 per 1000 **6.9 fewer per 1000** (CI 95% 9.6 fewer — 3.7 fewer)	High [6]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for males in the age group 50-74years
Male CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.75 (CI 95% 0.7 — 0.81) Based on data from 135,453 participants in 4 studies. Follow up: 15yrs.	26.3 per 1000 Difference:	19.7 per 1000 **6.6 fewer per 1000** (CI 95% 7.9 fewer — 5 fewer)	High [7]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for males in the age group 55-64years
Female CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [8]	Hazard ratio 0.88 (CI 95% 0.81 — 0.96) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	19.5 per 1000 Difference:	17.2 per 1000 **2.3 fewer per 1000** (CI 95% 3.7 fewer — 0.8 fewer)	High [9]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for females in the age group 50-74years
Female CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.84 (CI 95% 0.77 — 0.91) Based on data from 139,499 participants in 4 studies. Follow up: 15yrs.	17.3 per 1000 Difference:	14.5 per 1000 **2.8 fewer per 1000** (CI 95% 4 fewer — 1.6 fewer)	High [10]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for females in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study

to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. Inconsistency could not be assessed for FSG + FIT as only a single trial, however, results appeared consistent with those for FSG alone. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analysis of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to male participants aged 55-64 years at 15 years follow-up was RR=0.73 (0.64-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with > 100,000 participants.

2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials included in the meta-analysis were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** The point estimates for 3 trials with a median follow-up of at least 14.8 years included in the meta-analysis for males show a reduced risk of CRC-specific mortality following FSG Confidence intervals of individual trials overlapped including the female subgroup, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR = 0.69 (0.60-0.80) for males with narrow 95% CIs that did not include the null effect. Power is unlikely to be an issue with >100,000 participants and 1,100 events in the male subgroup analysis.

3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** In the subgroup meta-analysis for females, the point estimate for 2 trials was consistent with a decrease whereas the point estimate for the third trial was consistent with an increased risk of CRC-specific mortality following FSG. However, confidence intervals of individual trials overlapped , no variability due to heterogeneity was detected and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled HR = 0.92 (0.78-1.08) for FSG alone crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.

4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For

females the pooled RR = 0.91 (0.77-1.17) crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.

5. undefined
6. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected in the male subgroup analysis (I2 = 63.3%) but did not reach statistical significance with confidence intervals overlapping and none of the upper CIs crossing 1.0. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.74 (0.64-0.86) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 3,412 events in the male subgroup analysis.
7. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate for males for FSG interventions was RR=0.75 (0.70-0.81) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.
8. undefined
9. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of the 3 FSG trials included in this subgroup analysis were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 3 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens in the female subgroup analysis no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect do not vary widely. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.88 (0.81-0.96) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 2,600 events in the female subgroup analysis.
10. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important

source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was RR=0.84 (0.77-0.91) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.62 (CI 95% 0.42 — 0.91) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	7.85 per 1000 Difference:	4.87 per 1000 **2.98 fewer per 1000** (CI 95% 4.55 fewer — 0.71 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for males in the age group 50-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Female CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.94 (CI 95% 0.64 — 1.37) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	5.73 per 1000 Difference:	5.39 per 1000 **0.34 fewer per 1000** (CI 95% 2.06 fewer — 2.12 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [2]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC-specific mortality for females in the age group 50-64years
Male CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.72 (CI 95% 0.59 — 0.89) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	24.7 per 1000 Difference:	17.85 per 1000 **6.85 fewer per 1000** (CI 95% 10.05 fewer — 2.69 fewer)	High [3]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for males in the age group 50-64years
Female CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.91 (CI 95% 0.74 — 1.11) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	20.1 per 1000 Difference:	18.31 per 1000 **1.79 fewer per 1000** (CI 95% 5.19 fewer — 2.19 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC incidence for females in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.72 (0.59-0.89) with a 95% CI that does not cross the null effect.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this

trial (Holme 2018). **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The population, intervention, comparator and outcome were relevant.

3. Evidence-based recommendation

The recommended age range for organised population screening is 45–74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality

reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges, expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

4. Evidence-based recommendation

Although modelling indicated that it may be cost-effective, starting screening at age 40 is not recommended for population screening because at this age range there is a less favourable benefits to burden balance compared to screening for 45-74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges,

expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

5. Evidence-based recommendation

Extending the upper limit of the age range from 74 to 79 or 84 years is not recommended for population screening, because the likely benefits do not outweigh the burden (number of colonoscopies and associated risk), compared with screening for people aged 45–74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges, expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

Good practice statement

6. Practice Point

For people aged 75-85 years who are fit, well and healthy, who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#].

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

7. Practice Point

In people aged 40-44 years who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#] every two years during the lead-up to the first routine National Bowel Cancer Screening Program invitation.

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

8. Practice Point

Every effort should be pursued to ensure equitable participation and ongoing quality improvement initiatives in population screening for colorectal cancer in the target age group of 45-74 years and ensure equity of access to culturally safe health care, including access to diagnostic assessment for National Bowel Cancer Screening Program participants with a positive screening test.

5.2 Colorectal cancer screening accuracy

Weak recommendation

9. Evidence-based recommendation

An immunochemical faecal occult blood test is recommended as the screening modality for the detection of colorectal cancer in the average-risk population. (Burón et al, 2019*[72]*, Chang et al, 2017*[73]*, Brenner et al 2018*[70]*, Digby 2016*[76]*, Kim et al, 2017*[78]*, Ribbing et al 2022*[80]*, Shapiro et al, 2017*[83]*, Zorzi et al, 2018*[82]*)

Practical info

Evidence statement

The iFOBT performed best at detection of colorectal cancer and was also able to detect a proportion of advanced adenomas. The iFOBT was better at detecting colorectal cancer compared with advanced adenomas.

In a meta-analysis of four studies assessing iFOBT with a threshold of 10 µg haemoglobin per gram faeces (3/4 single sample only) the sensitivity for colorectal cancer was 92 (95% confidence interval [CI] 74–98)% and the specificity was 88 (95% CI 86–90)% *[69]*.

In a meta-analysis of 11 studies assessing iFOBT with a threshold of 20 µg haemoglobin per gram faeces (11/11 single sample only) the sensitivity for colorectal cancer was 84 (95% CI 82–86) % and the specificity was 95 (95% CI 94–96)% *[70]*.

At either threshold, iFOBT detected less than 50% of advanced adenomas, serrated lesions, advanced serrated lesions and advanced precancerous lesions.

Only one study identified in the systematic review directly compared the iFOBT performance of using 2-sample vs 1-sample within the same test technology. The study found that 2-sample has a higher mean test sensitivity in detecting advanced neoplasia than 1-sample. However, the study results were not statistically significant given the wide and overlapping confidence interval resulted from the small sample size *[81]*.

There is evidence from a single study that the sensitivity of iFOBT is higher for males *[79]*.

There is insufficient evidence to determine how the diagnostic performance of iFOBT assays may alter with participant age or risk of colorectal cancer.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For iFOBT, the sensitivity and specificity vary by the haemoglobin per gram of faeces threshold. The NBCSP uses a two-sample iFOBT with a 20 µg/g threshold which, based on current evidence, has a sensitivity of 84% and specificity of 95% for detection of CRC, with lower sensitivity (24%) for detection of advanced adenoma.

Certainty of the Evidence

The systematic review found that studies reporting CRC detection using an iFOBT threshold of 20 µg haemoglobin per grams of faeces provided evidence of moderate certainty overall and for data analysed by participant sex, but a low

certainty of evidence for data analysed by age. Studies reporting CRC detection using an iFOBT threshold of 10 µg haemoglobin per gram of faeces provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

The NBCSP uses an iFOBT containing 2 sample (with a 20µg/g threshold) every 2 years. There has been consideration of both providing iFOBT with only one sample and modification of the threshold to account for one sample specificity and sensitivity. Exploratory analysis on the iFOBT threshold change has been conducted *[85]* but no change to the threshold has been recommended at this point. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Resources and other considerations

As of 2023, CRC population screening in Australia is offered via 2-yearly iFOBT screening through the NBCSP. The NBCSP is estimated to contribute 10-14% of MBS-recorded colonoscopies as of 2023, and is projected to continue contributing 10-14% of MBS-recorded colonoscopies every year to 2030 *[61]*. The health system is under strain to meet the demands of colonoscopy services. Increasing the frequency of iFOBT screening and/or modifying the threshold is not feasible at this time.

Colonoscopies performed following a positive iFOBT should be of high quality. A high-quality colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care *[86]*. This is defined as adequate bowel preparation, complete intubation, and preferably done by a proceduralist with current certification by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. On completion of the colonoscopy, a proceduralist's report is produced with an indication of its quality based on the standards. Based on this information, a proceduralist identifies whether the standard has been met and, if not met, the proceduralist would request a repeat procedure. Using the report, health care practitioners can confirm that the colonoscopy has met the appropriate standards.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Internationally, population screening for CRC is typically offered using 2-yearly iFOBT screening, as is the case in Australia; however, a small number of countries instead offer yearly iFOBT screening.(84) In the analysis undertaken for the 2017 guidelines, yearly iFOBT screening was found to be potentially cost-effective at a 40–60% participation level, but with a less favourable benefits-and-burden balance compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of yearly iFOBT compared to 2-yearly iFOBT screening.

A modelled evaluation of yearly iFOBT and 2-yearly iFOBT screening was conducted using an extensively

calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of yearly iFOBT , compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03 times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that yearly iFOBT would reduce CRC incidence by 9–10% and mortality by 15% at 40% screening participation; these were further reduced to 21–22% and 26–29%, respectively, with a participation level of 100% (see **Appendix E**5 table 3). However, yearly iFOBT would lead to significant increase in colonoscopy demand (54–63%) and related adverse events (47–57%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS. Yearly iFOBT screening had a much higher INNC of 4.1–14.8 ACs/LYS across all participation rates and cohorts analysed.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Yearly iFOBT (40%, 60%, and 100%)	4.1–14.8

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Yearly iFOBT had an incremental cost-effectiveness ratio (ICER) under $20,000 per life-year saved at a 40% participation rate but was not cost-effective at 100% participation with an ICER above $50,000 per life-year saved.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. Yearly iFOBT was found to be incrementally cost-effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*, and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Weak recommendation

10. Evidence-based recommendation

The emerging faecal, blood or serum tests for cancer-specific biomarkers such as DNA are not recommended as population screening modalities for colorectal cancer at this time. (Bosch et al, 2019*[66]*, Bretagne et al, 2021*[71]*, Chiu et al, 2016*[75]*, Imperiale et al, 2021*[68]*, Jin et al 2022*[65]*, Shapiro et al, 2017*[83]*)

Practical info

With only one or two studies reporting on the diagnostic accuracy of the different biomarker assays there is insufficient evidence to fully assess the diagnostic performance of the various non-FOBT faecal or blood-based cancer-specific biomarker assays.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For multitarget stool DNA tests, the sensitivity and specificity vary with sensitivity ranging from 85.7%-92.9% and specificity of 84.9%-88.5% for detection of CRC, with lower sensitivity (47.8%) for detection of advanced adenoma.

Certainty of the Evidence

Studies reporting CRC detection using multitarget stool DNA provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

In the Australian context, multitarget stool DNA tests are not commonly used or available. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Stool biomarker screening (also known as faecal DNA screening or multitarget stool DNA testing) is an alternative stool testing modality available for CRC screening. In the analysis undertaken for the 2017 guidelines, 5-yearly stool biomarker testing was found not to be cost-effective compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of 5-yearly stool biomarker screening, compared to 2-yearly iFOBT screening.

A modelled evaluation of 2-yearly iFOBT and 5-yearly stool biomarker screening was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of 5-yearly stool biomarker screening, compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03 times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that five-yearly stool biomarker screening resulted in modest different in CRC incidence and mortality compared with 2-yearly iFOBT (see **Appendix E**5 table 1). However, 5-yearly stool biomarker would lead to a slight reduction in colonoscopy demand (0–3%) but a small increase in colonoscopy-related serious adverse events (6–9%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT and five-yearly stool biomarker screening had very similar colonoscopy burden and life-years saved (Table 11). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS; five-yearly stool biomarker testing had a favourable benefits-and-burden balance at 100% participation, with an INNC of 2.2–2.5 ACs/LYS.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Five-yearly stool biomarker (100%)	2.2–2.5

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Five-yearly stool biomarker testing was more expensive and less cost-effective compared with 2-yearly and/or yearly iFOBT at all participation rates and in both cohorts.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels, whereas 5-yearly stool biomarker was found to have most favourable benefits-and-burden balance at a participation level of 100%. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. 5-yearly stool biomarker was more expensive and less effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*, and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Weak recommendation

11. Evidence-based recommendation

Population screening for colorectal cancer using immunochemical faecal occult blood testing every two years is recommended. It is not recommended that the frequency of screening within the National Bowel Cancer Screening Program be increased to yearly. (Bretagne et al, 2021*[71]*, Burón, et al, 2019*[72]*, Digby et al, 2016*[76]*, Jensen et al, 2016*[77]*, Ribbing et al, 2022*[80]*)

Practical info

Evidence statement

The iFOBT performed best at detection of colorectal cancer and was also able to detect a proportion of advanced adenomas. The iFOBT was better at detecting colorectal cancer compared with advanced adenomas.

In a meta-analysis of four studies assessing iFOBT with a threshold of 10 µg haemoglobin per gram faeces (3/4 single sample only) the sensitivity for colorectal cancer was 92 (95% confidence interval [CI] 74–98)% and the specificity was 88 (95% CI 86–90)% *[69]*.

In a meta-analysis of 11 studies assessing iFOBT with a threshold of 20 µg haemoglobin per gram faeces (11/11 single sample only) the sensitivity for colorectal cancer was 84 (95% CI 82–86) % and the specificity was 95 (95% CI 94–96)% *[70]*.

At either threshold, iFOBT detected less than 50% of advanced adenomas, serrated lesions, advanced serrated lesions and advanced precancerous lesions.

Only one study identified in the systematic review directly compared the iFOBT performance of using 2-sample vs 1-sample within the same test technology. The study found that 2-sample has a higher mean test sensitivity in detecting advanced neoplasia than 1-sample. However, the study results were not statistically significant given the wide and overlapping confidence interval resulted from the small sample size *[81]*.

There is evidence from a single study that the sensitivity of iFOBT is higher for males *[79]*.

There is insufficient evidence to determine how the diagnostic performance of iFOBT assays may alter with participant age or risk of colorectal cancer.

With only one or two studies reporting on the diagnostic accuracy of the different biomarker assays there is insufficient evidence to fully assess the diagnostic performance of the various non-FOBT faecal or blood-based cancer-specific biomarker assays.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For iFOBT, the sensitivity and specificity vary by the haemoglobin per gram of faeces threshold. The NBCSP uses a two-sample iFOBT with a 20 µg/g threshold which, based on current evidence, has a sensitivity of 84% and specificity of 95% for detection of CRC, with lower sensitivity (24%) for detection of advanced adenoma.

Certainty of the Evidence

The systematic review found that studies reporting CRC detection using an iFOBT threshold of 20 µg haemoglobin per grams of faeces provided evidence of moderate certainty overall and for data analysed by participant sex, but a low certainty of evidence for data analysed by age. Studies reporting CRC detection using an iFOBT threshold of 10 µg haemoglobin per gram of faeces provided evidence of very low certainty. Studies reporting CRC detection using multitarget stool DNA provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

The NBCSP uses an iFOBT containing 2 sample (with a 20µg/g threshold) every 2 years. There has been consideration of both providing iFOBT with only one sample and modification of the threshold to account for one sample specificity and sensitivity. Exploratory analysis on the iFOBT threshold change has been conducted *[85]* but no change to the threshold has been recommended at this point. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Resources and other considerations

As of 2023, CRC population screening in Australia is offered via 2-yearly iFOBT screening through the NBCSP. The NBCSP is estimated to contribute 10-14% of MBS-recorded colonoscopies as of 2023, and is projected to continue contributing 10-14% of MBS-recorded colonoscopies every year to 2030 *[61]*. The health system is under strain to meet the demands of colonoscopy services. Increasing the frequency of iFOBT screening and/or modifying the threshold is not feasible at this time.

Colonoscopies performed following a positive iFOBT should be of high quality. A high-quality colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care *[86]*. This is defined as adequate bowel preparation, complete intubation, and preferably done by a proceduralist with current certification by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. On completion of the colonoscopy, a proceduralist's report is produced with an indication of its quality based on the standards. Based on this information, a proceduralist identifies whether the standard has been met and, if not met, the proceduralist would request a repeat procedure. Using the report, health care practitioners can confirm that the colonoscopy has met the appropriate standards.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Internationally, population screening for CRC is typically offered using 2-yearly iFOBT screening, as is the case in Australia; however, a small number of countries instead offer yearly iFOBT screening.(84) Stool biomarker screening (also known as faecal DNA screening or multitarget stool DNA testing) is an alternative stool testing modality available for CRC screening. In the analysis undertaken for the 2017 guidelines, 5-yearly stool biomarker testing was found not to be cost-effective, and yearly iFOBT screening was found to be potentially cost-effective at a 40–60% participation level, but with a less favourable benefits-and-burden balance compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of yearly iFOBT or 5-yearly stool biomarker screening, compared to 2-yearly iFOBT screening.

A modelled evaluation of yearly iFOBT, 2-yearly iFOBT and 5-yearly stool biomarker screening was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of yearly iFOBT or 5-yearly stool biomarker screening, compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03 times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that yearly iFOBT would reduce CRC incidence by 9–10% and mortality by 15% at 40% screening participation; these were further reduced to 21–22% and 26–29%, respectively, with a participation level of 100% (see **Appendix E**5 table 3). However, yearly iFOBT would lead to significant increase in colonoscopy demand (54–63%) and related adverse events (47–57%) (see **Appendix E**5 table 2). Five-yearly stool biomarker resulted in modest different in CRC incidence and mortality compared with 2-yearly iFOBT (see **Appendix E**5 table 1). However, 5-yearly stool biomarker would lead to a slight reduction in colonoscopy demand (0–3%) but a small increase in colonoscopy-related serious adverse events (6–9%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT and five-yearly stool biomarker screening had very similar colonoscopy burden and life-years saved (Table 11). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS; five-yearly stool biomarker testing had a favourable benefits-and-burden balance at 100% participation, with an INNC of 2.2–2.5 ACs/LYS. Yearly iFOBT screening had a much higher INNC of 4.1–14.8 ACs/LYS across all participation rates and cohorts analysed.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Five-yearly stool biomarker (100%)	2.2–2.5
Yearly iFOBT (40%, 60%, and 100%)	4.1–14.8

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Yearly iFOBT had an incremental cost-effectiveness ratio (ICER) under $20,000 per life-year saved at a 40% participation rate but was not cost-effective at 100% participation with an ICER above $50,000 per life-year saved. Five-yearly stool biomarker testing was more expensive and less cost-effective compared with 2-yearly and/or yearly iFOBT at all participation rates and in both cohorts.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels, whereas 5-yearly stool biomarker was found to have most favourable benefits-and-burden balance at a participation level of 100%. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. Yearly iFOBT was found to be incrementally cost-effective, and 5-yearly stool biomarker was more expensive and less effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*, and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Good practice statement

12. Practice Point

Participation in a population screening program is not recommended for people with symptoms such as rectal bleeding or persistent change in bowel habit or with iron-deficiency anaemia, nor for those who should be having regular surveillance or screening based on colonoscopy (e.g., for past colorectal cancer or adenoma, chronic inflammatory bowel disease, a strong family history of colorectal cancer, or a high-risk genetic cancer syndrome). (Chiu et al, 2016*[75]*, Kim et al 2017*[78]*)

Good practice statement

13. Practice Point

It is important that individuals undergo a high-quality diagnostic colonoscopy after a positive immunochemical faecal occult blood test (Aniwan et al, 2017*[69]*, Njor et al, 2022*[79]*, Chiu et al 2016*[75]*, Digby et al 2016*[76]*, Ribbing et al, 2019*[81]*). A colonoscopy which does not meet the clinical care standard warrants a repeat procedure usually initiated by the proceduralist. A high-quality colonoscopy is defined as adequate bowel preparation, complete intubation, as documented and made available in the proceduralist's report. The proceduralist should ensure that the colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care (see ACSQHC).

Good practice statement

14. Practice Point

If a diagnostic colonoscopy after a positive immunochemical faecal occult blood test (iFOBT) is performed and its findings do not require further colonoscopy follow-up, the National Bowel Cancer Screening Program (NBCSP) participant should skip the next round of iFOBT screening through the NBCSP (in line with the Colonoscopy Surveillance Guidelines). Colorectal cancer will rarely occur within that interval.

Good practice statement

15. Practice Point

Participants with positive immunochemical faecal occult blood test (iFOBT) results should have follow-up investigation with the sole exception of cases in which there was a clear breach in sample collection protocol (i.e., menstrual blood contaminating the sample at collection). If there is a clear breach of protocol, repeat iFOBT testing is suggested within six weeks. However, this approach carries the risk of a misleading negative test result because low levels of bleeding from a cancer or adenoma may be intermittent, or unevenly distributed in the stools.

Good practice statement

16. Practice Point

To minimise the risk of psychological harm, colonoscopy should be performed promptly after a positive immunochemical faecal occult blood test. (Kirkøen et al, 2016*[133]*)

Good practice statement

17. Practice Point

There is evidence that colonoscopy should be done within 120 days from the day of the positive immunochemical faecal occult blood test to minimise risk of advancing the severity of disease if cancer is present.

5.3 Participation in population screening for colorectal cancer

Good practice statement

18. Practice Point

Encouragement by health care professionals (including general practitioners (GPs), Aboriginal Health Workers (AHWs), Aboriginal Health Practitioners (AHPs), nurses and other primary health care professionals substantially boosts participation in colorectal cancer screening. Health care professionals play a key role in providing patients with screening advice. GP or clinic endorsement messages in advance of receiving a test kit, the use of GP or clinic reminder systems, leadership of AHWs and AHPs in health promotion activities and practice audits can improve participation rates (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). Increased participation in the National Bowel Cancer Screening Program (NBCSP) through encouragement and access through a variety of NBCSP kit distribution avenues will increase the program's effectiveness and cost-effectiveness.

Good practice statement

19. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a very important role in managing the interface between population screening and personalised care (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). This role includes identifying and advising those who should opt out of the National Bowel Cancer Screening Program (NBCSP) because of the known elevated risk of colorectal cancer, presence of major comorbidities and limited life expectancy, those who should defer participation for several months because of recent surgery or major illness and the most appropriate avenue of NBCSP kit distribution available.

Good practice statement

20. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a key role in advising patients who are at average or slightly above average risk that immunochemical faecal occult blood test is the preferred method of screening. They can advise on the various avenues of kit distribution through the National Bowel Cancer Screening Program. They should also discuss the relative harms and benefits of and discourage inappropriate use of colonoscopy as a screening method.

Good practice statement

21. Practice Point

Ongoing efforts to identify methods to improve colorectal cancer screening participation, access to screening kits through various distribution avenues, modify testing strategies and evaluate existing and new population screening modalities are needed and should be informed by real-world data and other well-designed local and international research, as appropriate.

5.4 Colorectal cancer screening for Aboriginal and Torres Strait Islander peoples

Good practice statement

22. Practice Point

Local access to culturally safe, targeted advice and support for colorectal cancer screening, diagnostic services and treatment should be provided through health care professionals to improve equity for Aboriginal and Torres Strait Islander peoples.

Good practice statement

23. Practice Point

Health care professionals must be adequately supported to provide culturally safe and sensitive information, verbally and in written form, about colorectal cancer screening and local services (including colonoscopies) to promote engagement in the complete colorectal cancer screening pathway.

Good practice statement

24. Practice Point

Ongoing efforts to improve engagement of Aboriginal and Torres Strait Islander peoples in colorectal cancer screening must continue and occur in partnership with Aboriginal and Torres Strait Islander peak health bodies to ensure equitable access to colorectal cancer screening services is achieved, as well as build community awareness of the importance of screening.

6. Colorectal Cancer in Australia

6.1 Population screening of colorectal cancer

Colorectal cancer (CRC) screening is an exemplar for population screening because it is among the most preventable cancers and satisfies all 10 of the World Health Organization's principles of screening *[18][19][20]*:

1. It is an important health problem.
2. There is a recognisable latent or early symptomatic stage.
3. Its biology is generally well understood.
4. There should be an accepted treatment for patients with recognised disease.
5. Effective and accurate screening tests are available.
6. The screening test is considered acceptable to the population.
7. There is agreement on who should be screened.
8. Facilities for diagnosis and treatment are available.
9. There is an economical balance for screening in relation to overall healthcare expenditure.
10. Screening is a continuous process.

Population screening targets people who are healthy and at average risk, so that preventive measures or early treatment may be offered to improve health outcomes *[21]*. CRC screening is primarily directed at middle-aged people in good general health, with no symptoms that might indicate CRC. People who experience CRC symptoms should always be encouraged to consult a general practitioner (GP), regardless of their eligibility for population screening.

Population screening for CRC now has widespread acceptance internationally, although local circumstances affect program design and choice of screening test *[22]*. Many national programs, especially those in Europe, Canada, and Australia, conduct organised population screening *[23][24]*. Where population screening programs have not been established, health care professionals often practice opportunistic screening (i.e. offer individuals tests or examinations for the purposes of screening for cancer when they present for unrelated reasons) *[23]*.

6.1.1 Population colorectal cancer screening in Australia

In 1997, the Australian Health Technology Advisory Committee reviewed the evidence on screening and recommended that Australia develop a program for population screening of CRC using faecal occult blood testing in the average-risk population *[25]*. A pilot study conducted between 2002 and 2004 tested the feasibility, acceptability, and cost-effectiveness of CRC screening in Australia.

In 2006, the National Bowel Cancer Screening Program (NBCSP) was established to provide a mailed out immunochemical faecal occult blood test (iFOBT) to Australians turning 55 and 65 years from August 2006. During 2006–2020, the NBCSP underwent a phased rollout, expanding the program as health system capacity increased, with full implementation reached in 2020 when all eligible Australians aged 50–74 years were invited to screen every two years (see Table 4) *[5]*.

The NBCSP aims to:

- enable earlier detection of colorectal cancer
- prevent cancer through detection and removal of pre-malignant adenomas
- achieve participation levels that maximise the population benefit of early detection of CRC in the target population
- enable equitable access to NBCSP for men and women in the target population, irrespective of their geographic location, socioeconomic status, disability or cultural background, to achieve patterns of

participation that mirror the general population
- facilitate the provision of timely, appropriate, high-quality and safe diagnostic assessment services for NBCSP participants
- maximise the benefits and minimise burden to individuals participating in the NBCSP
- ensure the NBCSP is cost effective and maintains high standards of program management and accountability
- collect and analyse data to monitor participant outcomes and evaluate Program effectiveness.

The key elements of the NBCSP are *[26]*:

- the use of iFOBT as the screening test
- provision of iFOBT screening at no cost to eligible participants
- distribution of invitations and iFOBT kits by mail, with participating healthcare providers able to issue a kit directly to a participant from 2022
- analysis of iFOBT kits in a central laboratory
- follow-up of positive iFOBT results, mostly by colonoscopy, through the usual care pathway, backed up by a central reminder service
- central collation of data and reporting of NBCSP outcomes via regular reports
- the Participant Follow-up Function, which is delivered by the states and territories, to encourage individuals who have participated in the NBCSP with a positive iFOBT in their jurisdiction to continue along the screening pathway outlined in Figure 1 to diagnostic assessment.

Figure 1. NBCSP population screening pathway *[27]*

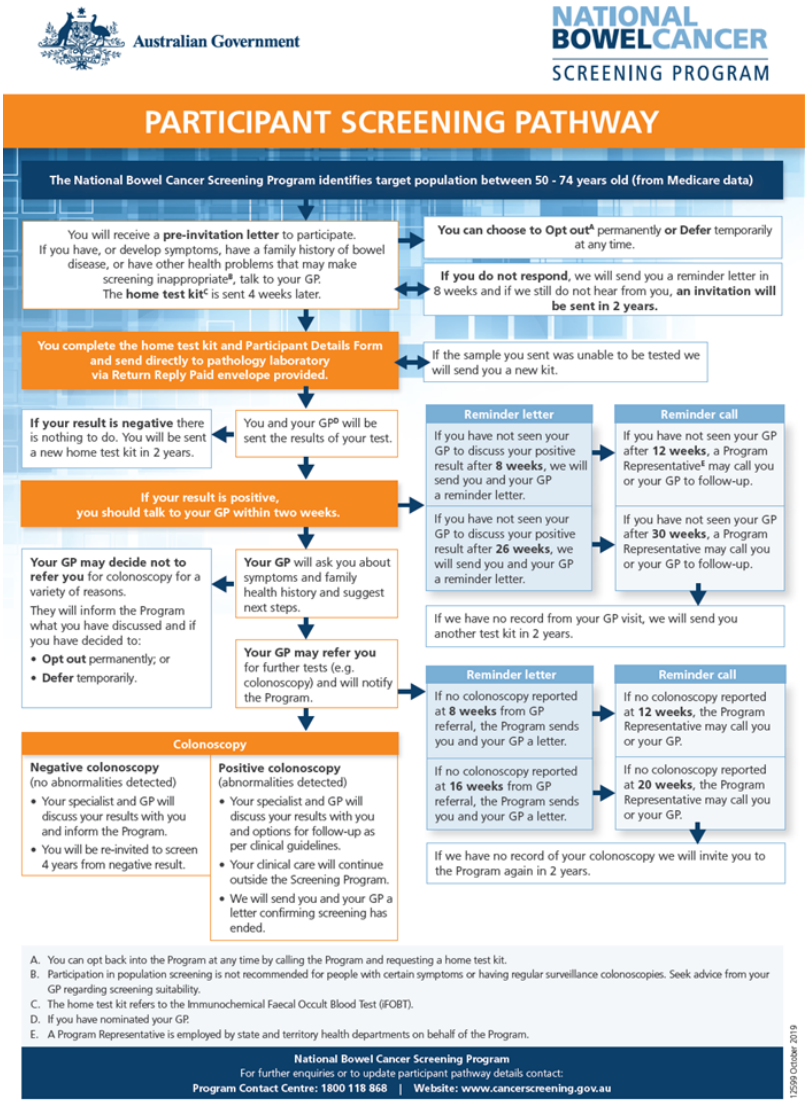

Table 4. Australian National Bowel Cancer Screening Program target populations in 2006–2022

Period	Target ages (years)
2006–2008	55 and 65
2008–2013	50, 55 and 65
2013–2014	50, 55, 60 and 65
2015	50, 55, 60, 65, 70 and 74
2016	50, 55, 60, 64, 65, 70, 72 and 74
2017	50, 54, 55, 58, 60, 64, 68, 70, 72 and 74
2018	50, 54, 58, 60, 62, 64, 66, 68, 70, 72 and 74
2019 onward	50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72 and 74

Source: Australian Institute of Health and Welfare *[5]*

6.1.2 Benefits of organised population colorectal cancer screening

Published research has shown that the NBCSP, even when it was still in its phased rollout, had an impact on reducing the CRC burden. Initial analyses found that the NBCSP had a measurable impact on CRC stage at diagnosis, with markedly earlier stage of CRC diagnosis and increased survival found in people participating

in the NBCSP *[28][29][30][31]*. A 2018 report found that non-NBCSP invitees from 2006–2015 had a 13% higher risk of CRC death by 2015 compared with NBCSP invitees. Of the NBCSP invitees, those who did not participate were at a two times higher risk of CRC-related death, with NBCSP participants having 171% higher odds of earlier CRC stage diagnosis than those who did not participate *[3]*.

Modelling studies predicted that, at approximately 40% NBCSP participation, 92,200 CRC cases and 59,000 deaths would to be prevented over the period 2015–2040 *[32]*, and that age-standardised CRC incidence and mortality could be reduced with increased diagnostic assessment rates and increased participation levels *[33]*.

Screening infrastructure in the NBCSP has been progressively strengthened to improve its efficiency and effectiveness, including the development of the National Cancer Screening Register (NCSR) and delivery of national public awareness campaigns *[5]*. The purpose of data collection for NBCSP is for monitoring, reporting, and evaluating effectiveness and to inform future iterations of the clinical practice guidelines. Where data is provided by proceduralists, it is collected by the NBCSP for monitoring, reporting, and evaluating effectiveness of the program to inform training within the health care sector related to the quality of colonoscopy. Robust and complete data collection to monitor and evaluate the NBCSP and its impact is also a requirement of the Australian Population-Based Screening Framework and critical for enabling monitoring of the performance of the NBCSP in accordance with the NBCSP aim of reducing the morbidity and mortality of bowel cancer in Australia through early detection and prevention of the disease *[26]*.

6.1.3 Interventions to improve participation in colorectal cancer screening

Existing evidence illustrates the impact of a range of interventions on increasing iFOBT screening participation in mail out programs, including telephone contact, simplified test procedures, advance notification, and general practitioner (GP) endorsement *[34]*. Further, evidence in the Australian context shows that population-wide strategies such as mass-media campaigns *[35]* and tailored interventions to culturally and linguistically diverse (CALD) communities and Aboriginal and Torres Strait Islander peoples have potential to increase participation in CRC screening *[36]*.

For example, in addition to the mailout method, the NBCSP enables healthcare providers to bulk-order NBCSP kits from the NCSR from 2022. Healthcare providers can issue kits directly to eligible participants during a routine consultation. This approach is based on the success of the National Indigenous Bowel Screening Pilot *[37]*, which showed that patients are more likely to complete the test after discussing it with a trusted healthcare provider. Alternative methods of kit distribution aim to improve NBCSP participation, especially in priority groups including Aboriginal and Torres Strait Islander peoples, people with disabilities, and those from CALD backgrounds *[38]*.

7. Colorectal cancer screening benefit

Colorectal cancer (CRC) in its early stages develops from mutations of benign polyps in the inner lining of the colon. The progressive mutation can eventually lead to malignant formations *[5]*. CRC screening can detect cancer at an earlier stage and reduce CRC-related mortality. Screening can be provided via organised population screening programs implementing one of many testing modalities, which include guaiac faecal occult blood test (gFOBT), immunochemical faecal occult blood test (iFOBT), flexible sigmoidoscopy, colonoscopy, computed tomography (CT) colonography, faecal biomarkers such as DNA, plasma biomarkers such as DNA, and/or a combination of these tests *[24]*.

Evidence of long-term effectiveness is not consistent across the testing modalities. The 2017 guidelines identified randomised control trial (RCT) level evidence for gFOBT and iFOBT dating back to the 1990s, as well as four flexible sigmoidoscopy RCTs *[39]*.

For the 2023 guideline update, a systematic review was conducted to assess updated evidence on the screening benefit of existing and emerging testing modalities for population screening.

7.1 Clinical question/PICO

The clinical question and population, intervention, comparator and outcome (PICO) question are shown in section 4.7.3 Systematic reviews and **Appendix B.**

7.2 Recommendations and practice points

Weak recommendation

1. Evidence-based recommendation

The recommended strategy for population screening in Australia, directed at those at average risk of colorectal cancer and without relevant symptoms, is immunochemical faecal occult blood testing every two years, starting at age 45 years and continuing to age 74 years. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Bretthauer, et al, 2022*[44]*, Juul, et al, 2022*[45]*)

Practical info

Evidence statements

Several RCTs evaluating gFOBT-based screening demonstrated a reduction in colorectal cancer-specific mortality, compared with no screening *[49][50][51][52][53][54][55]*.

A large study evaluating the combination of once-only iFOBT-based screening, with flexible sigmoidoscopy (but not colonoscopy) for those with a positive test, showed a 32% reduction in rectal cancer mortality but no statistically significant reduction in CRC-specific or colon cancer-specific mortality at 8-year follow-up*[40]*.

Four RCTs assessing flexible sigmoidoscopy as a screening modality, compared with usual care, reported a combined 26% (20–32%) reduction in CRC-specific mortality and a 22% (17–27%) reduction in CRC incidence in those randomised to screening, after median follow-up of at least 14.8 years, with greater benefits in males*[45]*. This benefit in CRC-specific mortality was attributed entirely to a reduction in distal CRC-specific mortality and not proximal CRC-specific mortality. Three out of four of the trials provided a once-only flexible sigmoidoscopy as the screening test *[40][41][42]*, the trial conducted in the US provided flexible sigmoidoscopy at baseline and at 3 or 5 years *[43]*.

One RCT assessed colonoscopy screening, compared with no screening *[43]*. This study had only 10 years' follow-up and a screening participation rate of 42% in the screening arm. It reported a numerical reduction in CRC-specific mortality (although the 95% confidence interval [CI] crossed 1.0), and a reduction in CRC incidence with a risk ratio of 0.82 (95% CI 0.70–0.93) *[43]*.

Only one RCT evaluated the combination of two screening modalities (flexible sigmoidoscopy and iFOBT) and reported a reduction in CRC-specific mortality of 27% after a median follow-up of 14.8 years *[41]*.

No RCTs were found that assessed screening with CT colonography, faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA, compared with no screening.

No studies were found that evaluated screening in participants aged younger than 50 years or older than 74 years.

Evidence to decision

Benefits and harms

Screening benefits have been assessed in terms of reductions in CRC incidence, mortality, and the incidence of metastases at diagnosis. These benefits should be weighed against the burden of screening procedures which, in the case of colonoscopy, can include the risk of perforation and bleeding. Data on screening-related harms were not extracted in the systematic review but have been assessed in the modelled evaluations (see section 4.4.2 Findings of modelling evaluation).

The age range of population screening also affects the balance of benefits versus harms. For those younger than 45 years, the risk of CRC is lower, so population screening would result in unnecessary testing for the average-risk population.

For those over age 74 years, there is little empirical evidence to support screening. The United States Preventive Services Task Force (USPSTF) maintained its recommendation for to stop screening at age 75 years *[56]*. Given that the balance of benefits and harms of CRC screening becomes less favourable in those aged 76–85 years due to the higher prevalence of colonoscopy-related serious adverse events *[57]*, the USPSTF recommended screening on a case-by-case basis in this age-group, and recommended against screening for people with significant comorbidity *[56]*. Modelling studies undertaken for the USPSTF estimated few additional life-years gained by extending screening beyond the 75 years among adults at average risk who had previously participated in screening *[58][59]*.

While the Australian population may have different comorbidity patterns, the US findings are likely relevant.

Certainty of the Evidence

CRC-specific mortality: The systematic review found that available studies reporting CRC-specific mortality provided a high certainty of evidence for flexible sigmoidoscopy overall and in male subgroups, and a moderate certainty of evidence in female subgroups. Studies reporting this outcome provided a moderate certainty of evidence for colonoscopy.

CRC incidence: Studies reporting CRC incidence provided a high certainty of evidence for colonoscopy.

Proportion of metastatic colorectal cancer at diagnosis: Studies reporting this outcome provided a low certainty of evidence for flexible sigmoidoscopy, and a moderate certainty of evidence for colonoscopy.

Values and preferences

Many countries, including Australia, New Zealand, Canada, and several European countries, have established national population-based CRC screening programs that use either gFOBT or iFOBT as a primary screening modality. The advantage of iFOBTs is that they specifically detect haemoglobin with no need to change diet or medication prior to testing *[60]*. Many iFOBT methods use automated analysis, and several allow quantitative analysis of haemoglobin. In contrast, flexible sigmoidoscopy and colonoscopy are invasive procedures, requiring a highly trained workforce and special facilities. There are particular concerns about the acceptability and feasibility of flexible sigmoidoscopy and colonoscopy as population screening modalities in the Australian setting, as well as their cost-effectiveness.

Resources and other considerations

Population screening based on colonoscopy and flexible sigmoidoscopy is not feasible in the Australian context, as the current healthcare system capacity could not meet the estimated demand on resources. Colonoscopy services in the public health system are already at capacity, and there are difficulties meeting the demand for diagnostic colonoscopy following a positive screening test result. However, the NBCSP with 2-year iFOBT offered to eligible participants from 50-74 years is predicted to contribute 10–14% of all MBS-funded colonoscopies by 2030 *[61]*.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen *[40][41][42]* and one reported on two screens *[43]*. The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial *[44]* reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up *[45]*. No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 *[40]*.

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678)

measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years *[41]*.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence *[43]*.

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years *[42]*.

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.74 (CI 95% 0.68 — 0.8) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	7.81 per 1000 Difference:	5.78 per 1000 **2.03 fewer per 1000** (CI 95% 2.5 fewer — 1.56 fewer)	High [1]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 50-74years
CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.8 (CI 95% 0.72 — 0.88) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	6.02 per 1000 Difference:	4.82 per 1000 **1.2 fewer per 1000** (CI 95% 1.69 fewer — 0.72 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 55-64years
CRC incidence (Age range 50-74) [measured as CRC incidence per 1000]	Hazard ratio 0.78 (CI 95% 0.73 — 0.83) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	25.3 per 1000 Difference:	19.7 per 1000 **5.6 fewer per 1000** (CI 95% 6.8 fewer	High [3]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 50-74years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
			— 4.3 fewer)		
CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.79 (CI 95% 0.75 — 0.83) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	21.7 per 1000 Difference:	17.1 per 1000 **4.6 fewer per 1000** (CI 95% 5.4 fewer — 3.7 fewer)	High [4]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 55-64years.
% CRC metastatic at diagnosis (Age range 55-74) [measured as metastatic disease at diagnosis per 100 CRC diagnoses] [5]	Relative risk 0.9 (CI 95% 0.76 — 1.07) Based on data from 154,887 participants in 1 studies. Follow up: N/A.	15.9 per 1000 Difference:	14.4 per 1000 **1.6 fewer per 1000** (CI 95% 3.8 fewer — 1.1 more)	Low High risk of bias due to deviations from intended interventions and missing outcome data; imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [6]	CRC screening with flexible sigmoidoscopy may reduce proportion of CRC metastatic at diagnosis for those in the age group 55-74years.

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with a median follow-up of at least 14.8 years show a reduced risk of CRC-specific mortality following FSG overall. Confidence intervals of individual trials overlapped, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR=0.74 (0.68-0.80) overall and HR = 0.69 (0.60-0.80). Power is unlikely to be an issue with > 400,000 participants and 3,188 events overall.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies.

Inconsistency: no serious. The point estimates for all 4 trials with over 15 years follow-up show a reduced risk of CRC-specific mortality following FSG. Confidence intervals of individual trials overlapped and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs limited to participants aged 55-64 years at 15 years follow-up was RR=0.80(0.72-0.88_ with narrow 95% C that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.

3. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected (I2 = 36.1%) but this is not statistically significant and point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.78 (0.73-0.83) for CRC incidence with a narrow 95% CI that did not include the null effect. The FSG meta-analysis results are likely to be adequately powered with > 400,000 participants and 10,495 events.
4. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. The point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to participants aged 55-64 years at 15 years follow-up was RR=0.79 (0.75-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.
5. undefined
6. **Risk of Bias: serious.** Single trial at high risk of bias due to deviations from intended interventions and missing outcome data. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome for this trial were relevant. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.76-1.07). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT

Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-64) [measured by CRC deaths per 1000]	Hazard ratio 0.75 (CI 95% 0.57 — 0.99) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	6.78 per 1000 Difference:	5.09 per 1000 **1.69 fewer per 1000** (CI 95% 2.91 fewer — 0.07 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for those in the age group 50-64years
CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.81 (CI 95% 0.7 — 0.93) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	22.4 per 1000 Difference:	18.1 per 1000 **4.3 fewer per 1000** (CI 95% 6.7 fewer — 1.6 fewer)	High [2]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for those in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population,

intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.75 (0.57-0.99) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). . **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant.. **Imprecision: no serious.** The HR is 0.81 (0.70-0.93) with a 95% CI that does not cross the null effect..

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with colonoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Nordic-European Initiative on Colorectal Cancer (NordICC): This population-based RCT (N=84,585) conducted in Poland, Norway and Sweden assessed single colonoscopy compared with usual care. Median follow-up was 10 years for CRC incidence and specific mortality. The study also reported on the percentage of metastatic CRC at diagnosis (44).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 55-64) [measured by CRC deaths per 1000]	Relative risk 0.9 (CI 95% 0.64 — 1.16) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	2.79 per 1000 Difference:	2.51 per 1000 **0.28 fewer per 1000** (CI 95% 1 fewer	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases	CRC screening with colonoscopy may reduce CRC-specific mortality for those in the age group 55-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
			— 0.45 more)	as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [1]	
CRC incidence (Age range 55-64) [measured by CRC incidence per 1000]	Relative risk 0.82 (CI 95% 0.7 — 0.93) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 3.3 fewer — 0.76 fewer)	High [2]	CRC screening with colonoscopy probably reduces CRC incidence for those in the age group 55-64years
% CRC metastatic at diagnosis (Age range 55-64) [measured by metastatic disease at diagnosis per 100 CRC diagnosis]	Relative risk 1.06 (CI 95% 0.77 — 1.44) Based on data from 84,585 participants in 1 studies. Follow up: NA.	17.2 per 100 Difference:	18.2 per 100 **1 more per 100** (CI 95% 4 fewer — 7.6 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [3]	CRC screening with colonoscopy may or may not reduce proportion of CRC metastatic at diagnosis for those in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that only 42% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.64-1.16) at 10 years follow-up. 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in CRC mortality so unsure as to the effect i.e. imprecise. The results were interim not mature results. The study was powered to detect 25% difference in CRC mortality at 15 years; it was not powered to detect difference of 25% or more at 10 years follow-up. The study was not powered to detect differences <25%.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions

resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: no serious.** Single study with risk ratio (95% CI) = 0.82 (0.70-0.93). The risk of CRC was 11.0/1000 in the control group and the upper limit of estimated absolute risk (upper limit of the 95% confidence interval) in the intervention arm was 10.3/1000. With 84,585 participants and 881 events power is unlikely to be an issue..
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 1.06 (0.77-1.44). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to the effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 (40).

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence (43).

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years (42).

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality (45).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.73 (CI 95% 0.64 — 0.83) Based on data from 135,452 participants in 4 studies. Follow up: 15yrs.	7.71 per 1000 Difference:	5.63 per 1000 **2.08 fewer per 1000** (CI 95% 2.78 fewer — 1.31 fewer)	High [1]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for males in the age group 55-64years
Male CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.69 (CI 95% 0.6 — 0.79) Based on data from 137,905 participants in studies. Follow up: >14.8yrs (median).	8.82 per 1000 Difference:	6.09 per 1000 **2.73 fewer per 1000** (CI 95% 3.52 fewer — 1.85 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for males in the age group 50-74years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Female CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.92 (CI 95% 0.78 — 1.08) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	5.51 per 1000 Difference:	5.07 per 1000 **0.44 fewer per 1000** (CI 95% 1.21 fewer — 0.44 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [3]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for females in the age group 50-74years
Female CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.91 (CI 95% 0.77 — 1.17) Based on data from 139,449 participants in 4 studies. Follow up: 15yrs.	4.37 per 1000 Difference:	3.98 per 1000 **0.39 fewer per 1000** (CI 95% 1.01 fewer — 0.74 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy may reduce CRC-specific mortality for females in the age group 55-64years
Male CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [5]	Hazard ratio 0.74 (CI 95% 0.64 — 0.86) Based on data from 137,905 participants in 3 studies. Follow up: >14.8yrs (median).	26.6 per 1000 Difference:	19.7 per 1000 **6.9 fewer per 1000** (CI 95% 9.6 fewer — 3.7 fewer)	High [6]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for males in the age group 50-74years
Male CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.75 (CI 95% 0.7 — 0.81) Based on data from 135,453 participants in 4 studies. Follow up: 15yrs.	26.3 per 1000 Difference:	19.7 per 1000 **6.6 fewer per 1000** (CI 95% 7.9 fewer — 5 fewer)	High [7]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for males in the age group 55-64years
Female CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [8]	Hazard ratio 0.88 (CI 95% 0.81 — 0.96) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	19.5 per 1000 Difference:	17.2 per 1000 **2.3 fewer per 1000** (CI 95% 3.7 fewer — 0.8 fewer)	High [9]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for females in the age group 50-74years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Female CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.84 (CI 95% 0.77 — 0.91) Based on data from 139,499 participants in 4 studies. Follow up: 15yrs.	17.3 per 1000 Difference:	14.5 per 1000 **2.8 fewer per 1000** (CI 95% 4 fewer — 1.6 fewer)	High [10]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for females in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. Inconsistency could not be assessed for FSG + FIT as only a single trial, however, results appeared consistent with those for FSG alone. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analysis of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to male participants aged 55-64 years at 15 years follow-up was RR=0.73 (0.64-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with > 100,000 participants.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials included in the meta-analysis were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** The point estimates for 3 trials with a median follow-up of at least 14.8 years included in the meta-analysis for males show a reduced risk of CRC-specific mortality following FSG Confidence intervals of individual trials overlapped including the female subgroup, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR = 0.69 (0.60-0.80) for males with narrow 95% CIs that did not include the null effect. Power is unlikely to be an issue with >100,000 participants and 1,100 events in the male subgroup analysis.
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.**

In the subgroup meta-analysis for females, the point estimate for 2 trials was consistent with a decrease whereas the point estimate for the third trial was consistent with an increased risk of CRC-specific mortality following FSG. However, confidence intervals of individual trials overlapped , no variability due to heterogeneity was detected and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled HR = 0.92 (0.78-1.08) for FSG alone crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.

4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled RR = 0.91 (0.77-1.17) crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.
5. undefined
6. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected in the male subgroup analysis (I2 = 63.3%) but did not reach statistical significance with confidence intervals overlapping and none of the upper CIs crossing 1.0. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.74 (0.64-0.86) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 3,412 events in the male subgroup analysis.
7. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate for males for FSG interventions was RR=0.75 (0.70-0.81) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.
8. undefined
9. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of the 3 FSG

trials included in this subgroup analysis were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 3 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens in the female subgroup analysis no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect do not vary widely. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.88 (0.81-0.96) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 2,600 events in the female subgroup analysis.

10. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was RR=0.84 (0.77-0.91) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no

screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.62 (CI 95% 0.42 — 0.91) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	7.85 per 1000 Difference:	4.87 per 1000 **2.98 fewer per 1000** (CI 95% 4.55 fewer — 0.71 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for males in the age group 50-64years
Female CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.94 (CI 95% 0.64 — 1.37) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	5.73 per 1000 Difference:	5.39 per 1000 **0.34 fewer per 1000** (CI 95% 2.06 fewer — 2.12 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [2]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC-specific mortality for females in the age group 50-64years
Male CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.72 (CI 95% 0.59 — 0.89) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	24.7 per 1000 Difference:	17.85 per 1000 **6.85 fewer per 1000** (CI 95% 10.05 fewer — 2.69 fewer)	High [3]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for males in the age group 50-64years
Female CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.91 (CI 95% 0.74 — 1.11) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	20.1 per 1000 Difference:	18.31 per 1000 **1.79 fewer per 1000** (CI 95% 5.19 fewer — 2.19 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC incidence for females in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.**

The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.72 (0.59-0.89) with a 95% CI that does not cross the null effect.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The population, intervention, comparator and outcome were relevant.

Weak recommendation

2. Evidence-based recommendation

The use of flexible sigmoidoscopy as a primary screening test is not recommended for population screening in the average-risk population. (Atkin, et al 2017*[40]*, Holme, et al, 2018*[41]*, Senore, et al, 2022*[42]*, Miller, et al, 2019*[43]*, Juul, et al, 2022*[45]*).

Practical info

Evidence statements

A large study evaluating the combination of once-only iFOBT-based screening, with flexible sigmoidoscopy (but not colonoscopy) for those with a positive test, showed a 32% reduction in rectal cancer mortality but no statistically significant reduction in CRC-specific or colon cancer-specific mortality at 8-year follow-up *[40]*.

Four RCTs assessing flexible sigmoidoscopy as a screening modality, compared with usual care, reported a combined 26% (20–32%) reduction in CRC-specific mortality and a 22% (17–27%) reduction in CRC incidence in those randomised to screening, after median follow-up of at least 14.8 years, with greater benefits in males *[45]*. This benefit in CRC-specific mortality was attributed entirely to a reduction in distal CRC-specific mortality and not proximal CRC-specific mortality. Three out of four of the trials provided a once-only flexible sigmoidoscopy as the screening test *[40][41][42]*, the trial conducted in the US provided flexible sigmoidoscopy at baseline and at 3 or 5 years *[43]*.

Only one RCT evaluated the combination of two screening modalities (flexible sigmoidoscopy and iFOBT) and reported a reduction in CRC-specific mortality of 27% after a median follow-up of 14.8 years *[41]*.

No studies were found that evaluated screening in participants aged younger than 50 years or older than 74 years.

Evidence to decision

Benefits and harms

Screening benefits have been assessed in terms of reductions in CRC incidence, mortality, and the incidence of metastases at diagnosis. These benefits should be weighed against the burden of screening procedures which can include the risk of perforation and bleeding.

Certainty of the Evidence

CRC-specific mortality: The systematic review found that available studies reporting CRC-specific mortality provided a high certainty of evidence for flexible sigmoidoscopy overall and in male subgroups, and a moderate certainty of evidence in female subgroups.

Proportion of metastatic colorectal cancer at diagnosis: Studies reporting this outcome provided a low certainty of evidence for flexible sigmoidoscopy.

Values and preferences

Flexible sigmoidoscopy, along with colonoscopy, is an invasive procedure, requiring a highly trained workforce and special facilities. There are particular concerns about the acceptability and feasibility of flexible sigmoidoscopy as population screening modalities in the Australian setting, as well as their cost-effectiveness.

Resources and other considerations

Population screening based flexible sigmoidoscopy is not feasible in the Australian context, as the current healthcare system capacity could not meet the estimated demand on resources.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen *[40][41][42]* and one reported on two screens *[43]*. The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial *[44]* reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up *[45]*. No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 *[40]*.

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years *[41]*.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence *[43]*.

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years *[42]*.

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.74 (CI 95% 0.68 — 0.8) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	7.81 per 1000 Difference:	5.78 per 1000 **2.03 fewer per 1000** (CI 95% 2.5 fewer — 1.56 fewer)	High [1]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 50-74years
CRC - specific mortality (Age range 55-64) [measured as CRC deaths per	Relative risk 0.8 (CI 95% 0.72 — 0.88) Based on data from 274,952 participants in 4 studies.	6.02 per 1000 Difference:	4.82 per 1000 **1.2 fewer per**	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for those in the age group 55-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
1000]	Follow up: 15yrs.		**1000** (CI 95% 1.69 fewer — 0.72 fewer)		
CRC incidence (Age range 50-74) [measured as CRC incidence per 1000]	Hazard ratio 0.78 (CI 95% 0.73 — 0.83) Based on data from 447,590 participants in 4 studies. Follow up: >14.8yrs (median).	25.3 per 1000 Difference:	19.7 per 1000 **5.6 fewer per 1000** (CI 95% 6.8 fewer — 4.3 fewer)	High [3]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 50-74years.
CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.79 (CI 95% 0.75 — 0.83) Based on data from 274,952 participants in 4 studies. Follow up: 15yrs.	21.7 per 1000 Difference:	17.1 per 1000 **4.6 fewer per 1000** (CI 95% 5.4 fewer — 3.7 fewer)	High [4]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for those in the age group 55-64years.
% CRC metastatic at diagnosis (Age range 55-74) [measured as metastatic disease at diagnosis per 100 CRC diagnoses] [5]	Relative risk 0.9 (CI 95% 0.76 — 1.07) Based on data from 154,887 participants in 1 studies. Follow up: N/A.	15.9 per 1000 Difference:	14.4 per 1000 **1.6 fewer per 1000** (CI 95% 3.8 fewer — 1.1 more)	Low High risk of bias due to deviations from intended interventions and missing outcome data; imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [6]	CRC screening with flexible sigmoidoscopy may reduce proportion of CRC metastatic at diagnosis for those in the age group 55-74years.

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with a median follow-up of at least 14.8 years show a reduced risk of CRC-specific mortality following FSG overall. Confidence intervals of individual trials overlapped, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no**

serious. Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR=0.74 (0.68-0.80) overall and HR = 0.69 (0.60-0.80). Power is unlikely to be an issue with > 400,000 participants and 3,188 events overall.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The point estimates for all 4 trials with over 15 years follow-up show a reduced risk of CRC-specific mortality following FSG. Confidence intervals of individual trials overlapped and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs limited to participants aged 55-64 years at 15 years follow-up was RR=0.80(0.72-0.88_ with narrow 95% C that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.
3. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected (I2 = 36.1%) but this is not statistically significant and point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.78 (0.73-0.83) for CRC incidence with a narrow 95% CI that did not include the null effect. The FSG meta-analysis results are likely to be adequately powered with > 400,000 participants and 10,495 events.
4. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. The point estimates of treatment effect do not vary widely ranging from 0.74 to 0.82, 95% confidence intervals mostly overlap and none of the upper confidence intervals cross 1.0 (null effect). **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analyses of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to participants aged 55-64 years at 15 years follow-up was RR=0.79 (0.75-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with >250,000 participants.
5. undefined
6. **Risk of Bias: serious.** Single trial at high risk of bias due to deviations from intended interventions and missing outcome data. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome for this trial were relevant. **Imprecision:**

serious. Single study with risk ratio (95% CI) = 0.90 (0.76-1.07). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 50-64) [measured by CRC deaths per 1000]	Hazard ratio 0.75 (CI 95% 0.57 — 0.99) Based on data from 88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	6.78 per 1000 Difference:	5.09 per 1000 **1.69 fewer per 1000** (CI 95% 2.91 fewer — 0.07 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for those in the age group 50-64years
CRC incidence (Age range 50-64)	Hazard ratio 0.81 (CI 95% 0.7 — 0.93) Based on data from	22.4 per 1000	18.1 per 1000	High [2]	CRC screening with flexible sigmoidoscopy and iFOBT probably

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
[measured by CRC incidence per 1000]	88,407 participants in 1 studies. Follow up: 14.8 yrs (median).	Difference:	**4.3 fewer per 1000** (CI 95% 6.7 fewer — 1.6 fewer)		reduces CRC incidence for those in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.75 (0.57-0.99) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). . **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant.. **Imprecision: no serious.** The HR is 0.81 (0.70-0.93) with a 95% CI that does not cross the null effect..

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: CRC screening with colonoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Nordic-European Initiative on Colorectal Cancer (NordICC): This population-based RCT (N=84,585) conducted in Poland, Norway and Sweden assessed single colonoscopy compared with usual care. Median follow-up was 10 years for CRC incidence and specific mortality. The study also

reported on the percentage of metastatic CRC at diagnosis (44).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with colonoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
CRC - specific mortality (Age range 55-64) [measured by CRC deaths per 1000]	Relative risk 0.9 (CI 95% 0.64 — 1.16) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	2.79 per 1000 Difference:	2.51 per 1000 **0.28 fewer per 1000** (CI 95% 1 fewer — 0.45 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [1]	CRC screening with colonoscopy may reduce CRC-specific mortality for those in the age group 55-64years
CRC incidence (Age range 55-64) [measured by CRC incidence per 1000]	Relative risk 0.82 (CI 95% 0.7 — 0.93) Based on data from 84,585 participants in 1 studies. Follow up: 10yrs.	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 3.3 fewer — 0.76 fewer)	High [2]	CRC screening with colonoscopy probably reduces CRC incidence for those in the age group 55-64years
% CRC metastatic at diagnosis (Age range 55-64) [measured by metastatic disease at diagnosis per 100 CRC diagnosis]	Relative risk 1.06 (CI 95% 0.77 — 1.44) Based on data from 84,585 participants in 1 studies. Follow up: NA.	17.2 per 100 Difference:	18.2 per 100 **1 more per 100** (CI 95% 4 fewer — 7.6 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases possibly due to inadequate power/ interim results - longer follow-up required [3]	CRC screening with colonoscopy may or may not reduce proportion of CRC metastatic at diagnosis for those in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of

reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that only 42% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 0.90 (0.64-1.16) at 10 years follow-up. 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in CRC mortality so unsure as to the effect i.e. imprecise. The results were interim not mature results. The study was powered to detect 25% difference in CRC mortality at 15 years; it was not powered to detect difference of 25% or more at 10 years follow-up. The study was not powered to detect differences <25%.

2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. There was a moderate risk of bias due to selection of reported results. Data were not analysed in accordance with a pre-specified analysis plan. Analysis plan was likely changed after unblinded outcome data were available for analysis but reason given for changing the plan is reasonable. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: no serious.** Single study with risk ratio (95% CI) = 0.82 (0.70-0.93). The risk of CRC was 11.0/1000 in the control group and the upper limit of estimated absolute risk (upper limit of the 95% confidence interval) in the intervention arm was 10.3/1000. With 84,585 participants and 881 events power is unlikely to be an issue..

3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. The risk of bias due to deviations from intended interventions for the single trial was low. **Inconsistency: no serious.** Not assessable - single study. **Indirectness: no serious.** The population, intervention, comparator and outcomes of this trial were relevant. However, it should be noted that < 50% of those in the screening arm underwent screening, a participation rate similar to that for the Australian CRC screening program. **Imprecision: serious.** Single study with risk ratio (95% CI) = 1.06 (0.77-1.44). 95% confidence interval crosses the null effect (1.0) including an increase as well as a decrease in % CRC metastatic at diagnosis so unsure as to the effect i.e. imprecise.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported

on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

Three of the RCT populations included males and females aged between 55 and 64 years (one trial had populations between 50 and 64 years, and one had a population aged 55–74 years). One study using pooled analysis of four flexible sigmoidoscopy trials in males and females aged 55–64 years. Outcomes of interest reported in these RCTs were CRC-specific mortality, CRC incidence, and proportion of CRC diagnosed when metastatic.

UK Flexible Sigmoidoscopy Screening Trial (UKFSST): This RCT included 170,432 average-risk participants followed 1995–1999 (40).

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): This RCT conducted in the USA assessed flexible sigmoidoscopy at baseline and repeated at 3 years or 5 years, compared with usual care. Participants were followed up for 16.8 years (median) for CRC mortality, and 15.8 years (median) for CRC incidence (43).

Screening for COlon REctum (SCORE); Italian Flexible Sigmoidoscopy Screening Trial: This RCT compared single flexible sigmoidoscopy with usual care in 34,292 participants, of which 10.9% had a family history of CRC but no individual history of CRC, adenomas nor irritable bowel disease, no more than one first-degree relative with CRC and no CRC-related endoscopies in the previous 2 years. Reported outcomes included CRC incidence after a median follow-up of 15.4 years and CRC-specific mortality at median 18.8 years (42).

Pooled analysis of the four flexible sigmoidoscopy trials: The pooled analysis study included data from four flexible sigmoidoscopy trials conducted in UK, Norway and USA (n=274,952). The analysis compared single flexible sigmoidoscopy, combination of flexible sigmoidoscopy and iFOBT and two flexible sigmoidoscopies, compared with usual care. Follow-up was 15 years for CRC incidence and CRC-specific mortality (45).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.73 (CI 95% 0.64 — 0.83) Based on data from 135,452 participants in 4 studies. Follow up: 15yrs.	7.71 per 1000 Difference:	5.63 per 1000 **2.08 fewer per 1000** (CI 95% 2.78 fewer — 1.31 fewer)	High [1]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for males in the age group 55-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.69 (CI 95% 0.6 — 0.79) Based on data from 137,905 participants in studies. Follow up: >14.8yrs (median).	8.82 per 1000 Difference:	6.09 per 1000 **2.73 fewer per 1000** (CI 95% 3.52 fewer — 1.85 fewer)	High [2]	CRC screening with flexible sigmoidoscopy reduces CRC-specific mortality for males in the age group 50-74years
Female CRC - specific mortality (Age range 50-74) [measured as CRC deaths per 1000]	Hazard ratio 0.92 (CI 95% 0.78 — 1.08) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	5.51 per 1000 Difference:	5.07 per 1000 **0.44 fewer per 1000** (CI 95% 1.21 fewer — 0.44 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [3]	CRC screening with flexible sigmoidoscopy probably reduces CRC-specific mortality for females in the age group 50-74years
Female CRC - specific mortality (Age range 55-64) [measured as CRC deaths per 1000]	Relative risk 0.91 (CI 95% 0.77 — 1.17) Based on data from 139,449 participants in 4 studies. Follow up: 15yrs.	4.37 per 1000 Difference:	3.98 per 1000 **0.39 fewer per 1000** (CI 95% 1.01 fewer — 0.74 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy may reduce CRC-specific mortality for females in the age group 55-64years
Male CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [5]	Hazard ratio 0.74 (CI 95% 0.64 — 0.86) Based on data from 137,905 participants in 3 studies. Follow up: >14.8yrs (median).	26.6 per 1000 Difference:	19.7 per 1000 **6.9 fewer per 1000** (CI 95% 9.6 fewer — 3.7 fewer)	High [6]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for males in the age group 50-74years
Male CRC incidence (Age range 55-64) [measured as CRC incidence	Relative risk 0.75 (CI 95% 0.7 — 0.81) Based on data from 135,453 participants in 4 studies.	26.3 per 1000 Difference:	19.7 per 1000 **6.6 fewer per**	High [7]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for males in the age group

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
per 1000]	Follow up: 15yrs.		**1000** (CI 95% 7.9 fewer — 5 fewer)		55-64years
Female CRC incidence (Age range 50-74) [measured as CRC incidence per 1000] [8]	Hazard ratio 0.88 (CI 95% 0.81 — 0.96) Based on data from 139,771 participants in 3 studies. Follow up: >14.8yrs (median).	19.5 per 1000 Difference:	17.2 per 1000 **2.3 fewer per 1000** (CI 95% 3.7 fewer — 0.8 fewer)	High [9]	CRC screening with flexible sigmoidoscopy reduces CRC incidence for females in the age group 50-74years
Female CRC incidence (Age range 55-64) [measured as CRC incidence per 1000]	Relative risk 0.84 (CI 95% 0.77 — 0.91) Based on data from 139,499 participants in 4 studies. Follow up: 15yrs.	17.3 per 1000 Difference:	14.5 per 1000 **2.8 fewer per 1000** (CI 95% 4 fewer — 1.6 fewer)	High [10]	CRC screening with flexible sigmoidoscopy probably reduces CRC incidence for females in the age group 55-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated “some concerns” i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. Inconsistency could not be assessed for FSG + FIT as only a single trial, however, results appeared consistent with those for FSG alone. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The estimate from the pooled analysis of the 4 RCTs (including FSG+FIT as well as FSG only) when limited to male participants aged 55-64 years at 15 years follow-up was RR=0.73 (0.64-0.83) with narrow 95% CI that did not include the null effect. Power is unlikely to be an issue with > 100,000 participants.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials included in the meta-analysis were rated “some concerns” i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. The risk of bias due to deviations from intended interventions for the single FST+ FIT trial was low. **Inconsistency: no serious.** The point estimates for 3 trials with a median follow-up of at least 14.8 years included in the meta-analysis for males show a reduced risk of CRC-specific mortality following FSG

Confidence intervals of individual trials overlapped including the female subgroup, no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** Pooled estimate from the meta-analysis for FSG alone with at least 15 years follow-up was HR = 0.69 (0.60-0.80) for males with narrow 95% CIs that did not include the null effect. Power is unlikely to be an issue with >100,000 participants and 1,100 events in the male subgroup analysis.

3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 trials were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** In the subgroup meta-analysis for females, the point estimate for 2 trials was consistent with a decrease whereas the point estimate for the third trial was consistent with an increased risk of CRC-specific mortality following FSG. However, confidence intervals of individual trials overlapped , no variability due to heterogeneity was detected and point estimates of treatment effect did not widely vary. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled HR = 0.92 (0.78-1.08) for FSG alone crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: serious.** For females the pooled RR = 0.91 (0.77-1.17) crossed the null effect including an increase as well as a decrease in CRC mortality, so unsure as to effect i.e. imprecise.
5. undefined
6. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of 3 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 4 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens. In the meta-analysis for FSG screening, some variability due to heterogeneity was detected in the male subgroup analysis (I2 = 63.3%) but did not reach statistical significance with confidence intervals overlapping and none of the upper CIs crossing 1.0. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.74 (0.64-0.86) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 3,412 events in the male subgroup analysis.
7. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in

contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for male subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate for males for FSG interventions was RR=0.75 (0.70-0.81) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.

8. undefined
9. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 1 of the 3 FSG trials included in this subgroup analysis were rated "some concerns" i.e. bias possible but unlikely (Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** The results from the 3 trials are consistent in that they all show a reduced risk of CRC incidence following one or two FSG screens in the female subgroup analysis no variability due to heterogeneity was detected (I2 = 0%) and point estimates of treatment effect do not vary widely. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was HR=0.88 (0.81-0.96) for CRC incidence with a narrow 95% CI that did not include the null effect. These results are likely to be adequately powered with >100,000 participants and 2,600 events in the female subgroup analysis.
10. **Risk of Bias: no serious.** Considered bias due to deviations from intended interventions resulting in contamination of the control group most important source of bias. For this source of bias 2 of 4 FSG trials were rated "some concerns" i.e. bias possible but unlikely (Atkin 2017, Senore 2022), low for one trial (Holme 2018) and high for one study, the PLCO trial (Miller 2019). The PLCO trial was the only study to be at high risk of bias due to missing data. Despite the PLCO trial being at high risk of bias for an important source of bias the results of this study did not differ from those of the other studies. **Inconsistency: no serious.** Point estimates and 95% confidence intervals for individual studies were not available for female subgroups for this analysis. **Indirectness: no serious.** The populations, interventions, comparators and outcomes of each of the 4 included trials were relevant. **Imprecision: no serious.** The pooled estimate from the meta-analysis of FSG interventions was RR=0.84 (0.77-0.91) for CRC incidence with a narrow 95% CI that did not include the null effect when limited to participants aged 55-64 years at 15 years follow-up.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC by sex
Intervention: CRC screening with flexible sigmoidoscopy +iFOBT
Comparator: No screening or usual care

Summary

The systematic reviews identified 16 potentially relevant guidelines, five of which were based on systematic reviews. However, none of these were considered for adoption or inclusion as evidence for

this guideline update as they did not match the relevant population, intervention, comparator and/or outcomes (see **Appendix E**1 for detail).

Five RCTs identified as updated evidence were included in the systematic reviews. Four RCTs (UKFSST, NORCCAP, PLCO and SCORE trials) reported on screening with flexible sigmoidoscopy: three reported on a single screen (40–42) and one reported on two screens (43). The NORCCAP trial also reported on a single flexible sigmoidoscopy + iFOBT screen. The NordICC trial (44) reported on a single colonoscopy screen. Also included was a pooled analysis of the data from the four flexible sigmoidoscopy trials for participants aged 55–64 years and with 15 years follow-up (45). No trials that included Aboriginal or Torres Strait Islander peoples were identified.

Included studies

The Norwegian Colorectal Cancer Prevention (NORCCAP): This population-based RCT (N=98,678) measured single flexible sigmoidoscopy or single flexible sigmoidoscopy and iFOBT against no screening in the control group. Participants were followed up for a median of 14.8 years (41).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Male CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.62 (CI 95% 0.42 — 0.91) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	7.85 per 1000 Difference:	4.87 per 1000 **2.98 fewer per 1000** (CI 95% 4.55 fewer — 0.71 fewer)	High [1]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC-specific mortality for males in the age group 50-64years
Female CRC - specific mortality (Age range 50-64) [measured as CRC deaths per 1000]	Hazard ratio 0.94 (CI 95% 0.64 — 1.37) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	5.73 per 1000 Difference:	5.39 per 1000 **0.34 fewer per 1000** (CI 95% 2.06 fewer — 2.12 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [2]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC-specific mortality for females in the age group 50-64years
Male CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.72 (CI 95% 0.59 — 0.89) Based on data from 44,006 participants in 1 studies. Follow up: 14.8 yrs (median).	24.7 per 1000 Difference:	17.85 per 1000 **6.85 fewer per 1000** (CI 95% 10.05 fewer — 2.69 fewer)	High [3]	CRC screening with flexible sigmoidoscopy and iFOBT probably reduces CRC incidence for males in the age group 50-64years

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening or usual care	**Intervention** CRC screening with flexible sigmoidoscopy +iFOBT	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Female CRC incidence (Age range 50-64) [measured by CRC incidence per 1000]	Hazard ratio 0.91 (CI 95% 0.74 — 1.11) Based on data from 44,401 participants in 1 studies. Follow up: 14.8 yrs (median).	20.1 per 1000 Difference:	18.31 per 1000 **1.79 fewer per 1000** (CI 95% 5.19 fewer — 2.19 more)	Moderate Imprecision as effect estimate 95% confidence interval crosses the null i.e. includes increases as well as decreases [4]	CRC screening with flexible sigmoidoscopy and iFOBT may reduce CRC incidence for females in the age group 50-64years

1. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
2. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The HR is 0.62 (0.42-0.91) with a 95% CI that does not cross the null effect.
3. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018) . **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: no serious.** The HR is 0.72 (0.59-0.89) with a 95% CI that does not cross the null effect.
4. **Risk of Bias: no serious.** Considered bias due to due to deviations from intended interventions resulting in contamination of the control group most important source of bias. This was rated low for this trial (Holme 2018). **Inconsistency: no serious.** Not assessable – single study. **Indirectness: no serious.** The population, intervention, comparator and outcome were relevant. **Imprecision: serious.** The population, intervention, comparator and outcome were relevant.

3. Evidence-based recommendation

The recommended age range for organised population screening is 45–74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all

eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see**Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges, expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

4. Evidence-based recommendation

Although modelling indicated that it may be cost-effective, starting screening at age 40 is not recommended for population screening because at this age range there is a less favourable benefits to burden balance compared to screening for 45-74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an

extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges, expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of

offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

5. Evidence-based recommendation

Extending the upper limit of the age range from 74 to 79 or 84 years is not recommended for population screening, because the likely benefits do not outweigh the burden (number of colonoscopies and associated risk), compared with screening for people aged 45–74 years.

Rationale

Additional evidence: screening age range – modelling evaluation

The National Bowel Cancer Screening Program (NBCSP) was established in 2006 and underwent a phased rollout, reaching full implementation in 2019-2020, at which point free 2-yearly screening was offered to all eligible Australians aged 50–74 years using an iFOBT. This age range for screening has been challenged, both due to the rise in CRC incidence rates among adults aged less than 50 years and the increasing life expectancy of Australians *[46][47][48]*.

Policy parameters for population-based cancer screening are informed by both primary scientific evidence and data-informed predictive modelling on screening-related health benefit, burden, harms and cost-effectiveness. The modelling study was undertaken to explore the health benefit, burden, harms, and cost-effectiveness of extending CRC age ranges at differing screening participation levels.

Aim and strategy of the modelling evaluations

The modelling evaluation assessed the health benefits (i.e., CRC incidence and mortality reductions and life-years saved), burden (i.e. the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of extending the recommended population screening age range from age 40 years to 84 years.

A modelled evaluation of the 2-yearly iFOBT screening at various age ranges was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**2 for detailed report).

In brief, nine age range strategies and three participation scenarios were modelled. These scenarios included the previous NBCSP screening age range of 50–74 years, and eight alternative screening strategies (assuming screening start ages of 40, 45 or 50 years and stop ages of 74, 79 or 84). The three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

Two cohorts with different CRC incidence rates were evaluated for all strategies and scenarios. Incidence rates for the cohorts were based on statistical projections of the CRC incidence trend in Australia; cohort A

were 1.03 times and cohort B were 1.21 times higher than the rates modelled in the evaluations undertaken for the 2017 guidelines. Cohort A is the cohort of people aged 45 years in 2024 and cohort B is the cohort of people aged 40 years in 2024.

Findings of the modelled evaluation

The modelled evaluation found that screening at ages 50–74 years would reduce CRC incidence and mortality by 17–47% and 34–75%, respectively, compared with no screening. Higher incidence and mortality reductions were found to be associated with only lowering the screening start age of 40 or 45 years (3-16% reduction in CRC incidence and 5-33% reduction in CRC mortality vs screening from 50-74), compared with only extending the screening stop age to 79 or 84 years (<1% and 3-12% reduction, respectively, vs screening from 50-74). Only lowering the screening start age to 40 or 45 years was found to result in relatively smaller increase in the lifetime colonoscopy utilisation and colonoscopy-related serious adverse events (12-33% increase in colonoscopy utilisation and 1-19% increase in colonoscopy-related adverse events), compared with only extending the screening stop age to 79 or 84 years (15-42% and 26-76% increase, respectively, vs screening from 50-74) (refer to table 3 in **Appendix E**2).

The quoted estimates in this section reflect findings for all participation scenarios.

The benefits-and-burden analysis compared the burden (assessed as number of colonoscopies performed) and health benefits (life-years saved) estimated for each strategy with different screening age ranges, expressed as the incremental number needed to colonoscope (INNC). This is shown in in Table 7. For wider screening age ranges, the INNC increased due to the relatively smaller increase in the life-years saved by screening compared with the increase in the number of colonoscopies required.

Table 7. Incremental number needed to colonoscopy by age group

Age group (years)	INNC (ACs/LYS)
50–74	1.6–2.5
45–74	1.9–5.1
40–74	2.6–6.7
40–79	5.7–14.5
40–84	11.4–26.2

ACs/LYS: Number of additional colonoscopies per life-year saved

The cost-effectiveness analysis compared the discounted lifetime costs and discounted life-years of each strategy, given the indicative willingness-to-pay thresholds of AUD$20,000/LYS, $30,000/LYS and $50,000/LYS (see Table 7 in **Appendix E**2). Offering population screening to people aged 50–74 years was the most cost-effective strategy, compared with other screening age ranges. Strategies offering 2-yearly iFOBT screening to people aged 45–74 or 45–79 years were found likely to be cost-effective, while strategies of offering 2-yearly iFOBT screening to people aged 40–74, 40–79, or 40–84 years were found to be only possibly cost-effective.

The screening age range of 50–74 years was found to be cost-saving, compared with no screening. Lowering the screening age range to 45–74 years or 40–74 years would also be cost-saving or very cost-effective (under the $20,000/LYS threshold) compared with no screening and would likely be incrementally cost-effective compared with screening at age 50–74 years while also preventing more CRC cases and deaths. Screening at age ranges 50–74, 45–74, or 40–74 years all had a favourable benefits-and-burden balance, with the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events per life-year saved. These findings indicated that lowering the starting age for screening to 45 or 40 years would increase the health benefits of screening and cause limited increases to the costs, resource demand, and potential harms of screening.

Good practice statement

6. Practice Point

For people aged 75-85 years who are fit, well and healthy, who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#].

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

7. Practice Point

In people aged 40-44 years who request screening after a discussion with their health care professional about the benefits and potential harms of testing, health care professionals could consider offering an immunochemical faecal occult blood test[#] every two years during the lead-up to the first routine National Bowel Cancer Screening Program invitation.

#Screening offered to people not eligible to screen under the National Bowel Cancer Screening Program means that screening tests are provided by private pathology, screening status is not centrally recorded and follow-up for future screening is not centrally provided.

Good practice statement

8. Practice Point

Every effort should be pursued to ensure equitable participation and ongoing quality improvement initiatives in population screening for colorectal cancer in the target age group of 45-74 years and ensure equity of access to culturally safe health care, including access to diagnostic assessment for National Bowel Cancer Screening Program participants with a positive screening test.

8. Colorectal cancer screening test accuracy

Colorectal cancer (CRC) screening can detect cancer at an earlier stage and reduce CRC-related mortality. Screening can utilise one of many testing modalities including guaiac faecal occult blood test (gFOBT), immunochemical faecal occult blood test (iFOBT), flexible sigmoidoscopy, colonoscopy, computed tomography colonography, faecal biomarkers such as DNA, plasma biomarkers such as DNA, and/or a combination of these tests *[24]*. These tests have differing diagnostic performance in terms of sensitivity and specificity for precancerous lesions and CRC as well as costs, acceptability and risks *[25]*. The National Bowel Cancer Screening Program (NBCSP) uses Eiken OC-Sensor kit (an iFOBT) to screen eligible people in the target population *[5]*.

During the 1990s, randomised controlled trials (RCTs) performed in the United States, United Kingdom and Denmark showed that faecal occult blood tests were an effective method of screening for CRC *[49][50][51][54][62]*. The Minnesota trial concluded that screening by yearly gFOBTs led to significantly lower CRC incidence and mortality rates, compared with 2-yearly gFOBT and usual care *[49][50]*; the trial reported that rehydration of the slides increased the sensitivity of the test from 80.8% to 92.2% and decreased the specificity from 97.7% to 90.4% *[62]*. The UK trial reported that, among CRCs diagnosed in the screening group (20% at stage A), 26% were detected by gFOBT *[51]*. In the control group, only 11% of diagnosed CRCs were detected at stage A. However, sensitivity and specificity of the test could not be calculated in this study due to limited follow-up interval *[51]*. The Denmark trial, assessing 2-yearly gFOBT with 10 years' follow-up, reported lower rates of CRC incidence and mortality in the screening group than the control group, *[54]* but did not report sensitivity or specificity of gFOBT. Subsequent meta-analyses provided Level I evidence that at least one RCT reported a 15–30% reduction in mortality for screening using gFOBT *[63][64]*. Later studies that assessed screening accuracy using iFOBT and DNA stool markers, compared with colonoscopy as gold standard, found that both of the non-invasive tests remain reliable and effective for CRC screening, with varying specificity and sensitivity *[65][66][67]*.

8.1 Clinical question/PICO

The clinical question and population, intervention, comparator and outcome (PICO) question are shown in section 4.7.3 Systematic reviews.

8.2 Recommendations and practice points

Weak recommendation

9. Evidence-based recommendation

An immunochemical faecal occult blood test is recommended as the screening modality for the detection of colorectal cancer in the average-risk population. (Burón et al, 2019*[72]*, Chang et al, 2017*[73]*, Brenner et al 2018*[70]*, Digby 2016*[76]*, Kim et al, 2017*[78]*, Ribbing et al 2022*[80]*, Shapiro et al, 2017*[83]*, Zorzi et al, 2018*[82]*)

Practical info

Evidence statement

The iFOBT performed best at detection of colorectal cancer and was also able to detect a proportion of advanced adenomas. The iFOBT was better at detecting colorectal cancer compared with advanced adenomas.

In a meta-analysis of four studies assessing iFOBT with a threshold of 10 µg haemoglobin per gram faeces (3/4 single sample only) the sensitivity for colorectal cancer was 92 (95% confidence interval [CI] 74–98)% and the specificity was 88 (95% CI 86–90)% *[69]*.

In a meta-analysis of 11 studies assessing iFOBT with a threshold of 20 µg haemoglobin per gram faeces (11/11 single sample only) the sensitivity for colorectal cancer was 84 (95% CI 82–86) % and the specificity was 95 (95% CI 94–96)% *[70]*.

At either threshold, iFOBT detected less than 50% of advanced adenomas, serrated lesions, advanced serrated lesions and advanced precancerous lesions.

Only one study identified in the systematic review directly compared the iFOBT performance of using 2-sample vs 1-sample within the same test technology. The study found that 2-sample has a higher mean test sensitivity in detecting advanced neoplasia than 1-sample. However, the study results were not statistically significant given the wide and overlapping confidence interval resulted from the small sample size *[81]*.

There is evidence from a single study that the sensitivity of iFOBT is higher for males *[79]*.

There is insufficient evidence to determine how the diagnostic performance of iFOBT assays may alter with participant age or risk of colorectal cancer.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For iFOBT, the sensitivity and specificity vary by the haemoglobin per gram of faeces threshold. The NBCSP uses a two-sample iFOBT with a 20 µg/g threshold which, based on current evidence, has a sensitivity of 84% and specificity of 95% for detection of CRC, with lower sensitivity (24%) for detection of advanced adenoma.

Certainty of the Evidence

The systematic review found that studies reporting CRC detection using an iFOBT threshold of 20 µg haemoglobin per grams of faeces provided evidence of moderate certainty overall and for data analysed by participant sex, but a low certainty of evidence for data analysed by age. Studies reporting CRC detection using an iFOBT threshold of 10 µg haemoglobin per gram of faeces provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

The NBCSP uses an iFOBT containing 2 sample (with a 20µg/g threshold) every 2 years. There has been consideration of both providing iFOBT with only one sample and modification of the threshold to account for one sample specificity and sensitivity. Exploratory analysis on the iFOBT threshold change has been conducted *[85]* but no change to the threshold has been recommended at this point. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Resources and other considerations

As of 2023, CRC population screening in Australia is offered via 2-yearly iFOBT screening through the NBCSP. The NBCSP is estimated to contribute 10-14% of MBS-recorded colonoscopies as of 2023, and is projected to continue contributing 10-14% of MBS-recorded colonoscopies every year to 2030 *[61]*. The

health system is under strain to meet the demands of colonoscopy services. Increasing the frequency of iFOBT screening and/or modifying the threshold is not feasible at this time.

Colonoscopies performed following a positive iFOBT should be of high quality. A high-quality colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care *[86]*. This is defined as adequate bowel preparation, complete intubation, and preferably done by a proceduralist with current certification by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. On completion of the colonoscopy, a proceduralist's report is produced with an indication of its quality based on the standards. Based on this information, a proceduralist identifies whether the standard has been met and, if not met, the proceduralist would request a repeat procedure. Using the report, health care practitioners can confirm that the colonoscopy has met the appropriate standards.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Internationally, population screening for CRC is typically offered using 2-yearly iFOBT screening, as is the case in Australia; however, a small number of countries instead offer yearly iFOBT screening.(84) In the analysis undertaken for the 2017 guidelines, yearly iFOBT screening was found to be potentially cost-effective at a 40–60% participation level, but with a less favourable benefits-and-burden balance compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of yearly iFOBT compared to 2-yearly iFOBT screening.

A modelled evaluation of yearly iFOBT and 2-yearly iFOBT screening was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of yearly iFOBT , compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03 times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that yearly iFOBT would reduce CRC incidence by 9–10% and mortality by 15% at 40% screening participation; these were further reduced to 21–22% and 26–29%, respectively, with a participation level of 100% (see **Appendix E**5 table 3). However,

yearly iFOBT would lead to significant increase in colonoscopy demand (54–63%) and related adverse events (47–57%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS. Yearly iFOBT screening had a much higher INNC of 4.1–14.8 ACs/LYS across all participation rates and cohorts analysed.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Yearly iFOBT (40%, 60%, and 100%)	4.1–14.8

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Yearly iFOBT had an incremental cost-effectiveness ratio (ICER) under $20,000 per life-year saved at a 40% participation rate but was not cost-effective at 100% participation with an ICER above $50,000 per life-year saved.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. Yearly iFOBT was found to be incrementally cost-effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*,

and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Weak recommendation

10. Evidence-based recommendation

The emerging faecal, blood or serum tests for cancer-specific biomarkers such as DNA are not recommended as population screening modalities for colorectal cancer at this time. (Bosch et al, 2019*[66]*, Bretagne et al, 2021*[71]*, Chiu et al, 2016*[75]*, Imperiale et al, 2021*[68]*, Jin et al 2022*[65]*, Shapiro et al, 2017*[83]*)

Practical info

Evidence statement

With only one or two studies reporting on the diagnostic accuracy of the different biomarker assays there is insufficient evidence to fully assess the diagnostic performance of the various non-FOBT faecal or blood-based cancer-specific biomarker assays.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For multitarget stool DNA tests, the sensitivity and

specificity vary with sensitivity ranging from 85.7%-92.9% and specificity of 84.9%-88.5% for detection of CRC, with lower sensitivity (47.8%) for detection of advanced adenoma.

Certainty of the Evidence

Studies reporting CRC detection using multitarget stool DNA provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

In the Australian context, multitarget stool DNA tests are not commonly used or available. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Stool biomarker screening (also known as faecal DNA screening or multitarget stool DNA testing) is an alternative stool testing modality available for CRC screening. In the analysis undertaken for the 2017 guidelines, 5-yearly stool biomarker testing was found not to be cost-effective compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of 5-yearly stool biomarker screening, compared to 2-yearly iFOBT screening.

A modelled evaluation of 2-yearly iFOBT and 5-yearly stool biomarker screening was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see**Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of 5-yearly stool biomarker screening, compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03 times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that five-yearly stool biomarker

screening resulted in modest different in CRC incidence and mortality compared with 2-yearly iFOBT (see **Appendix E**5 table 1). However, 5-yearly stool biomarker would lead to a slight reduction in colonoscopy demand (0–3%) but a small increase in colonoscopy-related serious adverse events (6–9%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT and five-yearly stool biomarker screening had very similar colonoscopy burden and life-years saved (Table 11). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS; five-yearly stool biomarker testing had a favourable benefits-and-burden balance at 100% participation, with an INNC of 2.2–2.5 ACs/LYS.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Five-yearly stool biomarker (100%)	2.2–2.5

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Five-yearly stool biomarker testing was more expensive and less cost-effective compared with 2-yearly and/or yearly iFOBT at all participation rates and in both cohorts.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels, whereas 5-yearly stool biomarker was found to have most favourable benefits-and-burden balance at a participation level of 100%. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. 5-yearly stool biomarker was more expensive and less effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*, and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Weak recommendation

11. Evidence-based recommendation

Population screening for colorectal cancer using immunochemical faecal occult blood testing every two years is recommended. It is not recommended that the frequency of screening within the National Bowel Cancer Screening Program be increased to yearly. (Bretagne et al, 2021*[71]*, Burón, et al, 2019*[72]*, Digby et al, 2016*[76]*, Jensen et al, 2016*[77]*, Ribbing et al, 2022*[80]*)

Practical info

Evidence statement

The iFOBT performed best at detection of colorectal cancer and was also able to detect a proportion of advanced adenomas. The iFOBT was better at detecting colorectal cancer compared with advanced adenomas.

In a meta-analysis of four studies assessing iFOBT with a threshold of 10 µg haemoglobin per gram faeces (3/4 single sample only) the sensitivity for colorectal cancer was 92 (95% confidence interval [CI] 74–98)%

and the specificity was 88 (95% CI 86–90)% *[69]*.

In a meta-analysis of 11 studies assessing iFOBT with a threshold of 20 µg haemoglobin per gram faeces (11/11 single sample only) the sensitivity for colorectal cancer was 84 (95% CI 82–86) % and the specificity was 95 (95% CI 94–96)% *[70]*.

At either threshold, iFOBT detected less than 50% of advanced adenomas, serrated lesions, advanced serrated lesions and advanced precancerous lesions.

Only one study identified in the systematic review directly compared the iFOBT performance of using 2-sample vs 1-sample within the same test technology. The study found that 2-sample has a higher mean test sensitivity in detecting advanced neoplasia than 1-sample. However, the study results were not statistically significant given the wide and overlapping confidence interval resulted from the small sample size *[81]*.

There is evidence from a single study that the sensitivity of iFOBT is higher for males *[79]*.

There is insufficient evidence to determine how the diagnostic performance of iFOBT assays may alter with participant age or risk of colorectal cancer.

With only one or two studies reporting on the diagnostic accuracy of the different biomarker assays there is insufficient evidence to fully assess the diagnostic performance of the various non-FOBT faecal or blood-based cancer-specific biomarker assays.

Evidence to decision

Benefits and harms

The short-term benefits and harms of diagnostic accuracy are reported in terms of test sensitivity and specificity. The benefit is illustrated through true positive and true negative results and harms can arise from false positive and false negative results. For iFOBT, the sensitivity and specificity vary by the haemoglobin per gram of faeces threshold. The NBCSP uses a two-sample iFOBT with a 20 µg/g threshold which, based on current evidence, has a sensitivity of 84% and specificity of 95% for detection of CRC, with lower sensitivity (24%) for detection of advanced adenoma.

Certainty of the Evidence

The systematic review found that studies reporting CRC detection using an iFOBT threshold of 20 µg haemoglobin per grams of faeces provided evidence of moderate certainty overall and for data analysed by participant sex, but a low certainty of evidence for data analysed by age. Studies reporting CRC detection using an iFOBT threshold of 10 µg haemoglobin per gram of faeces provided evidence of very low certainty. Studies reporting CRC detection using multitarget stool DNA provided evidence of very low certainty. See **Appendix E**6 for more details.

Values and preferences

The NBCSP uses an iFOBT containing 2 sample (with a 20µg/g threshold) every 2 years. There has been consideration of both providing iFOBT with only one sample and modification of the threshold to account for one sample specificity and sensitivity. Exploratory analysis on the iFOBT threshold change has been conducted *[85]* but no change to the threshold has been recommended at this point. There is not sufficient evidence to patient preferences or support guidance for population screening in Australia.

Resources and other considerations

As of 2023, CRC population screening in Australia is offered via 2-yearly iFOBT screening through the NBCSP. The NBCSP is estimated to contribute 10-14% of MBS-recorded colonoscopies as of 2023, and is projected to continue contributing 10-14% of MBS-recorded colonoscopies every year to 2030 *[61]*. The health system is under strain to meet the demands of colonoscopy services. Increasing the frequency of iFOBT screening and/or modifying the threshold is not feasible at this time.

Colonoscopies performed following a positive iFOBT should be of high quality. A high-quality colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care *[86]*. This is defined as adequate bowel preparation, complete intubation, and preferably done by a proceduralist with current certification by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. On completion of the colonoscopy, a proceduralist's report is produced with an indication of its quality based on the standards. Based on this information, a proceduralist identifies whether the standard has been met and, if not met, the proceduralist would request a repeat procedure. Using the report, health care practitioners can confirm that the colonoscopy has met the appropriate standards.

Rationale

Additional Evidence: screening modalities – modelling evaluation

Internationally, population screening for CRC is typically offered using 2-yearly iFOBT screening, as is the case in Australia; however, a small number of countries instead offer yearly iFOBT screening.(84) Stool biomarker screening (also known as faecal DNA screening or multitarget stool DNA testing) is an alternative stool testing modality available for CRC screening. In the analysis undertaken for the 2017 guidelines, 5-yearly stool biomarker testing was found not to be cost-effective, and yearly iFOBT screening was found to be potentially cost-effective at a 40–60% participation level, but with a less favourable benefits-and-burden balance compared with 2-yearly iFOBT screening.

New evidence on population CRC risk has become available since publication of the 2017 guidelines. In line with international findings, recent Australian studies found CRC incidence increased in people aged under 50 years in the past decades (46–48), potentially necessitating updated evaluations to identify the optimal population screening modality.

Aim and strategy of modelling evaluations

The aim of modelling was to evaluate the health benefits (as measured by CRC incidence and mortality reduction and life-years saved), burden (as measured by the number of colonoscopies performed), harms (i.e. the number of colonoscopy-related adverse events), and cost-effectiveness of yearly iFOBT or 5-yearly stool biomarker screening, compared to 2-yearly iFOBT screening.

A modelled evaluation of yearly iFOBT, 2-yearly iFOBT and 5-yearly stool biomarker screening was conducted using an extensively calibrated and validated microsimulation model of CRC and screening, *Policy1-Bowel* (see **Appendix E**5 for detailed report). In brief, *Policy1-Bowel* was used to evaluate CRC incidence and mortality reduction and life-years saved (as health benefits), number of colonoscopies (as burden), number of colonoscopy-related adverse events (as harms), and cost-effectiveness of yearly iFOBT or 5-yearly stool biomarker screening, compared with 2-yearly iFOBT screening. Three participation scenarios were assessed for the indicated age ranges:

- Scenario 1: approximately 40% overall participation rate (observed NBCSP participation rate as of 2019-2020)
- Scenario 2: approximately 60% overall participation rate
- Scenario 3: 100% participation rate (perfect adherence).

The modalities and participation scenarios were modelled in two cohorts with an overall CRC incidence 1.03

times (cohort A) and 1.21 times (cohort B) higher than the rate used in the 2017 guidelines. This was done to reflect observed and projected CRC incidence trends.

Findings of modelled evaluation

Compared with 2-yearly iFOBT screening, the modelled evaluation found that yearly iFOBT would reduce CRC incidence by 9–10% and mortality by 15% at 40% screening participation; these were further reduced to 21–22% and 26–29%, respectively, with a participation level of 100% (see **Appendix E**5 table 3). However, yearly iFOBT would lead to significant increase in colonoscopy demand (54–63%) and related adverse events (47–57%) (see **Appendix E**5 table 2). Five-yearly stool biomarker resulted in modest different in CRC incidence and mortality compared with 2-yearly iFOBT (see **Appendix E**5 table 1). However, 5-yearly stool biomarker would lead to a slight reduction in colonoscopy demand (0–3%) but a small increase in colonoscopy-related serious adverse events (6–9%) (see **Appendix E**5 table 2).

The benefits-and-burden analysis estimated the number of additional colonoscopies required per life-year saved (ACs/LYS). 2-yearly iFOBT and five-yearly stool biomarker screening had very similar colonoscopy burden and life-years saved (Table 11). 2-yearly iFOBT screening had a favourable benefits-and-burden balance at 40% and 60% participation in both cohorts, with an incremental number-needed-to-colonoscope (INNC) ranging between 1.8 and1.9 ACs/LYS; five-yearly stool biomarker testing had a favourable benefits-and-burden balance at 100% participation, with an INNC of 2.2–2.5 ACs/LYS. Yearly iFOBT screening had a much higher INNC of 4.1–14.8 ACs/LYS across all participation rates and cohorts analysed.

Table 11. Incremental number needed to colonoscopy by age group

Screening modality (screening participation rate)	INNC (ACs/LYS)
Two-yearly iFOBT (40% and 60%)	1.8–1.9
Five-yearly stool biomarker (100%)	2.2–2.5
Yearly iFOBT (40%, 60%, and 100%)	4.1–14.8

ACs/LYS: Number of additional colonoscopies per life-year saved

Two-yearly iFOBT was cost-saving and saved lives, compared with no screening. Yearly iFOBT had an incremental cost-effectiveness ratio (ICER) under $20,000 per life-year saved at a 40% participation rate but was not cost-effective at 100% participation with an ICER above $50,000 per life-year saved. Five-yearly stool biomarker testing was more expensive and less cost-effective compared with 2-yearly and/or yearly iFOBT at all participation rates and in both cohorts.

Two-yearly iFOBT was found to have the most favourable benefit-and-burden balance at 40% and 60% participation levels, whereas 5-yearly stool biomarker was found to have most favourable benefits-and-burden balance at a participation level of 100%. Nonetheless, 2-yearly iFOBT was cost-saving, compared with no screening. Yearly iFOBT was found to be incrementally cost-effective, and 5-yearly stool biomarker was more expensive and less effective, compared with 2-yearly iFOBT.

Clinical question/ PICO

Population: Persons without a CRC diagnosis or symptoms that might indicate CRC (with a family history of CRC or no family history of CRC)

Intervention: Index Test 1: Screening for CRC with any of the following: • iFOBT • Faecal biomarkers • Blood-based biomarkers • Any combinations Index Test 2: An alternative screening test or no screening

Comparator: Colonoscopy findings or follow-up outcomes

Summary

A systematic review was undertaken to assess the diagnostic accuracy of iFOBT, faecal biomarkers, blood-based biomarker or any combinations of these, compared with an alternative screening test or no screening. Colonoscopy or follow-up was used as the reference standard.

Sixteen potentially relevant guidelines were identified, of which five were based on systematic reviews. None were considered for adoption, as they either addressed different population, intervention, comparator, outcomes (PICOs) and/or did not include recent evidence.

During title and abstract screening of literature search results, most of the identified systematic reviews were excluded, mainly due to study design (case-control studies). One systematic review met the study inclusion criteria but was later excluded due to errors in the data extraction for the sensitivity and specificity calculations. Instead, data extracted from relevant included primary studies were used to calculate summary estimates.

Included studies

A total of 18 primary studies met the inclusion criteria. One study screened participants with one iFOBT and two faecal DNA tests *[65]*; one study screened participants with one iFOBT and one faecal DNA test *[66]*, one study screened participants (aged 45-49 years) with one faecal DNA test *[68]*, 14 studies screened participants with one iFOBT *[69][70][71][72][73][74][75][76][77][78][79][80][81][82]*, and one study screened participants with two iFOBTs *[83]*. Two studies used a two-sample iFOBT *[81][83]*; all other studies used a single-sample iFOBT. Sensitivity and specificity were reported or calculable in 15 studies for detection of CRC, four for advanced adenoma, three for serrated lesion, three for advanced serrated lesion and four for advanced precancerous lesion. One study reported subgroup analyses by sex *[79]*, one by age less or more than 50 years in males *[78]* and for participants aged 45–49 years *[68]*, and one by first or second screen *[77]*. None of the included studies reported subgroup analyses for participants aged older than 74 years, with and without a family history of CRC, or by number of index tests. Studies of blood-based biomarkers such as methylated septin 9 (mSEPT9) and multi-cancer early detection tests did not meet criteria for inclusion primarily due to no population of interest, study design or inadequacy or irrelevancy of the reference standard (refer **Appendix E**4 for detail).

Outcome Timeframe	**Study results and measurements**	**Comparator** Colonoscopy findings or follow-up outcomes	**Intervention** Index Test 1: Screening for CRC with any of the following: •	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Test accuracy		For details of the test accuracy please click here			

Good practice statement

12. Practice Point

Participation in a population screening program is not recommended for people with symptoms such as rectal bleeding or persistent change in bowel habit or with iron-deficiency anaemia, nor for those who should be having regular surveillance or screening based on colonoscopy (e.g., for past colorectal cancer or adenoma, chronic inflammatory bowel disease, a strong family history of colorectal cancer, or a high-risk genetic cancer syndrome). (Chiu et al, 2016*[75]*, Kim et al 2017*[78]*)

Good practice statement

13. Practice Point

It is important that individuals undergo a high-quality diagnostic colonoscopy after a positive immunochemical faecal occult blood test (Aniwan et al, 2017*[69]*, Njor et al, 2022*[79]*, Chiu et al 2016*[75]*, Digby et al 2016*[76]*, Ribbing et al, 2019*[81]*). A colonoscopy which does not meet the clinical care standard warrants a repeat procedure usually initiated by the proceduralist. A high-quality colonoscopy is defined as adequate bowel preparation, complete intubation, as documented and made available in the proceduralist's report. The proceduralist should ensure that the colonoscopy aligns with the colonoscopy clinical care standard from the Australian Commission on Safety and Quality in Health Care (see ACSQHC).

Good practice statement

14. Practice Point

If a diagnostic colonoscopy after a positive immunochemical faecal occult blood test (iFOBT) is performed and its findings do not require further colonoscopy follow-up, the National Bowel Cancer Screening Program (NBCSP) participant should skip the next round of iFOBT screening through the NBCSP (in line with the Colonoscopy Surveillance Guidelines). Colorectal cancer will rarely occur within that interval.

Good practice statement

15. Practice Point

Participants with positive immunochemical faecal occult blood test (iFOBT) results should have follow-up investigation with the sole exception of cases in which there was a clear breach in sample collection protocol (i.e., menstrual blood contaminating the sample at collection). If there is a clear breach of protocol, repeat iFOBT testing is suggested within six weeks. However, this approach carries the risk of a misleading negative test result because low levels of bleeding from a cancer or adenoma may be intermittent, or unevenly distributed in the stools.

Good practice statement

16. Practice Point

To minimise the risk of psychological harm, colonoscopy should be performed promptly after a positive immunochemical faecal occult blood test. (Kirkøen et al, 2016*[133]*)

Good practice statement

17. Practice Point

There is evidence that colonoscopy should be done within 120 days from the day of the positive immunochemical faecal occult blood test to minimise risk of advancing the severity of disease if cancer is present.

9. Preferences for colorectal cancer screening modalities

Individual preferences for colorectal cancer (CRC) screening modality are important considerations in determining the acceptability and feasibility of screening. Importantly, patient preferences can impact test uptake. Australia is one of the only countries where two samples are required as part of its organised population-based program, the National Bowel Cancer Screening Program (NBCSP). As part of the NBCSP, a 2-sample immunochemical faecal occult blood test (iFOBT) is provided by mail to all eligible participants *[5]*. A short review was conducted to characterise patient preferences for existing CRC screening tests when undergoing CRC screening as part of an organised population-based program (full report available in **Appendix E**7). The review assessed studies published between 2017 and 2022 specifically reporting on patient test preferences for the CRC screening tests of interest (colonoscopy, flexible sigmoidoscopy, and iFOBT/guaiac faecal occult blood test).

The studies reviewed concluded no clear preference for a specific CRC screening test *[87][88][89][90][91][92][93][94][95][96][97][98][99][100][101]*. However, there was evidence of a slight preference for colonoscopy due to the high accuracy and reliability *[87][90][91][93][94][97]*, followed by iFOBT due to the ease, convenience, and lower cost *[87][88][94][95][96][99]* and lastly flexible sigmoidoscopy due to the accuracy *[96][97]*. The studies included in this review were from a variety of countries and used various methodologies for assessing preferences which limited their applicability to Australia.

Two studies identified in the review explicitly assessed the number of iFOBT samples and their impact on patient preferences which showed an indicative preference for a single sample test *[22][23]*. Pre-2017 studies assessing the number of iFOBT samples found mixed results, with no clear preference for sample number but some evidence of higher uptake for a single sample *[24][25][26][27]*. The higher participation rates observed in some international screening programs that offered 1-sample iFOBT could not be attributed to the number of test samples alone and were likely a result of multiple factors such as participants having already been screened through colonoscopy or another test, forgetting about the kits, hygienic concerns, did not believe in the test's accuracy, etc *[102]*.

In Australia, the provision of 2 samples (i.e. the requirement of storing the stool sample in the fridge) has been identified as a barrier to NBCSP participation *[102]*. While, to date, there is no direct evidence to illustrate the impact of shifting from 2-sample to 1-sample in terms of NBCSP participation or CRC outcomes, there have been calls to further explore these issues as it may address known barriers to screening relating to refrigeration of stool samples and lack of time to complete the test *[34]*. This is particularly important in never- or under-screened groups to improve equity, especially in Aboriginal and Torres Strait Islander peoples *[103]*.

This review highlighted that both colonoscopy and iFOBT were the preferred/acceptable screening modalities as part of organised CRC screening programs, with no consistent preference for the number of samples used in an iFOBT.

10. Participation in population screening for colorectal cancer

In order to improve the preventative health benefit of population screening, considerable focus needs to be placed on improving participation in screening to achieve the National Bowel Cancer Screening Program's (NBCSP) target of 53%, as referenced in the National Preventative Health Strategy 2021-2030 *[39][104]*. Over time, NBCSP participation has stabilised, with a slightly lower rate of 40.9% reported for 2020-2021 *[5]*. To better understand equity of access to the NBCSP, participation is monitored and reported for various population groups, including subpopulations defined by geographical location, socioeconomic area, Indigenous status, language spoken at home, and disability *[5]*. Participation rates have been historically lower for participants who identified as Aboriginal or Torres Strait Islander, those living in very remote areas, and those living in low socioeconomic areas *[5]*. A previous evaluation of the NBCSP showed that, as participation in the NBCSP increased, CRC outcomes were estimated to improve *[32]*. Key components for improving participation and ensuring equity are feasibility and acceptability of CRC screening and the NBCSP to the Australian population, regardless of demographics.

10.1 Factors associated with participation in colorectal cancer screening

Participation in population screening for colorectal cancer (CRC) can be facilitated by knowledge/awareness of screening and the NBCSP among general practitioners (GPs), reinforcing simplicity of the test, perceived usefulness of screening or the screening test in the community *[105][106][107]*. Other reported facilitators include individuals' health status, family history, experiences with health services, good health care professional–patient relationship, social support, and awareness of CRC, including encouragement to participate by nurses, Aboriginal Health Workers, and Aboriginal Health Practitioners *[37][105][106]*. A study in South Australia reported that one of the major facilitators of CRC screening in Australia is that it is free of cost *[108]*.

Several factors have already been found to be associated with non-participation in screening, including sociodemographic, lifestyle factors, geographic location and misconceptions and lack of awareness with respect to colorectal cancer *[109][110]*. A short review conducted to inform the current update assessed studies published between 2017 and 2022 to identify reasons for non-participation in population screening in Australia through the NBCSP (full report available in **Appendix E**7).

The review identified a variety of reasons why people may not participate in CRC screening in Australia, which were largely consistent with previous research *[111]*. The reasons ranged from individual response to screening, such as fear and anxiety, to a lack of time to complete the test *[102][112][113][114][115][116]*. Lifestyle factors, such as low consumption of dietary fibre and high alcohol consumption, were also found to be associated with reduced likelihood of participating in CRC screening *[111]*. Other reasons for non-participation were specifically related to the test and challenges in performing the test. Additional external reasons for not participating highlighted the lack of health professional advice *[89][101][114][115][117][118]*.

Included studies also identified key personal characteristics that were associated with a higher likelihood of non-participation which related to risk factors or geographic location *[111][117]*. These findings reinforced the need to continue to support population screening for CRC and improve participation in the NBCSP. This could be supported through additional focus and encouragement on CRC screening in primary care *[103][113][114][119]*. Involvement from the primary care sector could include not only GPs but also Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other health workers. Examples of successful interventions in primary care that have improved CRC screening uptake are GP endorsement letters issued before invitations to participate in population screening, the use of GP reminders to encourage discussions of CRC screening, health promotion activities led by primary care, professional association and not-for-profit associations, and practice audits *[34][35][107][114][120]*.

Existing evidence on participation in population screening for CRC does not commonly include people under the age of 50. The United States Preventive Services Task Force (USPSTF) 2021 recommendation expanded the eligible age range for CRC screening to 45 *[56]*. It has been suggested that the USPSTF update could have the

benefit of increasing participation among individuals 50 years and older, as more people will be participating from an earlier age *[121]*.

Conversely, between the ages of 45-49 years, participation may be lower than observed for those aged 50-54 years and this differential participation could impact the real net benefit of population screening. To address this, ongoing efforts to improve screening participation through evidence-based interventions should continue.

10.2 Recommendations and practice points

Good practice statement

18. Practice Point

Encouragement by health care professionals (including general practitioners (GPs), Aboriginal Health Workers (AHWs), Aboriginal Health Practitioners (AHPs), nurses and other primary health care professionals) substantially boosts participation in colorectal cancer screening. Health care professionals play a key role in providing patients with screening advice. GP or clinic endorsement messages in advance of receiving a test kit, the use of GP or clinic reminder systems, leadership of AHWs and AHPs in health promotion activities and practice audits can improve participation rates (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*). Increased participation in the National Bowel Cancer Screening Program (NBCSP) through encouragement and access through a variety of NBCSP kit distribution avenues will increase the program's effectiveness and cost-effectiveness.

Good practice statement

19. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a very important role in managing the interface between population screening and personalised care. (Dodd et al 2019*[107]*, Goodwin et al 2020*[114]*, Lee et al 2021*[119]*) This role includes identifying and advising those who should opt out of the National Bowel Cancer Screening Program (NBCSP) because of the known elevated risk of colorectal cancer, presence of major comorbidities and limited life expectancy, those who should defer participation for several months because of recent surgery or major illness and the most appropriate avenue of NBCSP kit distribution available.

Good practice statement

20. Practice Point

Health care professionals (including general practitioners, Aboriginal Health Workers, Aboriginal Health Practitioners, nurses and other primary health care professionals) have a key role in advising patients who are at average or slightly above average risk that immunochemical faecal occult blood test is the preferred method of screening. They can advise on the various avenues of kit distribution through the National Bowel Cancer Screening Program. They should also discuss the relative harms and benefits of and discourage inappropriate use of colonoscopy as a screening method.

Good practice statement

21. Practice Point

Ongoing efforts to identify methods to improve colorectal cancer screening participation, access to screening kits through various distribution avenues, modify testing strategies and evaluate existing and new population screening modalities are needed and should be informed by real-world data and other well-designed local and international research, as appropriate.

11. Colorectal cancer screening for Aboriginal and Torres Strait Islander peoples

Cancer is the leading cause of all deaths among Aboriginal and Torres Strait Islander peoples and, of these, colorectal cancer (CRC) is the fourth most common cancer *[122]*. Structural barriers that impact the social and cultural determinants of health result in Aboriginal and Torres Strait Islander peoples experiencing inequitable health outcomes and lower life expectancy than non-Indigenous Australians *[123]*. Once diagnosed with CRC, there are disparities in outcomes, including earlier age of cancer onset of up to 9 years (mean age 61 years versus 70 years), a higher rate of cancer diagnosed at advanced or unknown stage (64.1% versus 53.6%) and a lower 5-year survival rate (57.3% versus 67.3%) among Aboriginal and Torres Strait Islander peoples, compared with non-Indigenous Australians *[124]*.

The National Bowel Cancer Screening Program (NBCSP) participation rate among Aboriginal and Torres Strait Islander peoples was 31.3% in 2020-2021 compared to 41.4% in non-Indigenous people *[5]*. A modelling study was conducted to estimate the health outcomes and cost-effectiveness of 2-yearly iFOBT screening from age 50-74 (the NBCSP target screening frequency and age range as of 2023) and the potential extensions to include Aboriginal and Torres Strait Islander people under the age of 50 years *[7]*. The study found that, at 23-42% participation, 2-yearly immunochemical faecal occult blood test (iFOBT) screening at 50–74 years for Aboriginal and Torres Strait Islander peoples was predicted to reduce lifetime CRC incidence by 14–24% and mortality by 23–39%, be cost-effective (incremental cost-effectiveness ratio (ICER) <$13,000/life-year saved), and be associated with a benefits-and-burden balance of 51–53 number-needed-to-colonoscope (NNC) per CRC death prevented. Lowering the screening start age to 40 or 45 years would further reduce CRC incidence by 7–11 and CRC mortality by 4–5 percentage points, be cost-effective under an indicative willingness-to-pay threshold of $50,000/life-year saved, and be associated with an incremental NNC of 62-103 per CRC-specific death prevented (i.e. a ~1.2-fold to ~2.0-fold higher than the NNC estimated for screening from age 50-74 for Aboriginal and Torres Strait Islander peoples). These findings were broadly similar to the modelling evaluation findings for the general population (Section 4.4 and **Appendix E**2). For the general population, it was estimated that lowering the screening start age to 40 or 45 years would further reduce CRC incidence by 3-16 and CRC mortality by 5-33 percentage points, possibly and likely be cost-effective under a range of willingness-to-pay thresholds of $20,000-50,000/life-year saved, and be associated with an incremental NNC that was ~1.2-fold to ~2.6-fold higher from the NNC estimated for screening from age 50-74. The modelling study for Aboriginal and Torres Strait Islander peoples concluded that the previous practice is cost-effective, and more CRC cases and deaths could be prevented by increasing participation and/or lowering the screening start age to 40 or 45 years, which was predicted to further reduce CRC incidence and CRC mortality by 7–11 and 4–5 percentage points for Aboriginal and Torres Strait Islander peoples. The study findings highlight a need to increase NBCSP participation whilst exploring the feasibility and acceptability of lowering the NBCSP start age for Aboriginal and Torres Strait Islander peoples *[7]*.

A review of the barriers and facilitators to NBCSP participation in Aboriginal and Torres Strait Islander peoples highlighted the lack of available culturally appropriate information as well as the lack of awareness of bowel cancer and screening, embarrassment associated with completing a test, and issues of inadequate housing and homelessness affecting feasibility of screening using a mailed at-home test kit *[103]*. A review of international literature on strategies to increase CRC screening rates amongst Indigenous populations identified providing culturally appropriate information and education resources, support from community clinics and health workers, providing alternative access to iFOBTs as possible ways of improving participation in population screening *[125]*. The National Indigenous Bowel Screening Pilot was conducted to design and pilot a possible alternative pathway to accessing the NBCSP kit *[37]*. The outcomes of the pilot showed increased NBCSP participation rates among the Aboriginal and Torres Strait Islander patients who participated *[37]*. This evidence-based avenue of kit distribution has been scaled up and rolled out by the NBCSP nationally. Efforts to reduce these barriers are ongoing and warrant continued support to improve participation in population screening via the most appropriate pathways to reduce inequities.

Rurality has impacted the accessibility and availability of colonoscopies to Aboriginal and Torres Strait Islander people, with the provision of colonoscopies in Australia inversely proportionate to the degree of rurality *[126]*. An

observational cohort study has demonstrated ongoing inequities in colonoscopy accessibility in the Northern Territory, especially in remote and very remote communities, where Aboriginal and Torres Strait Islander peoples had lower colonoscopy rates compared with non-Indigenous people *[127]*.

11.1 Recommendations and practice points

Good practice statement

22. Practice Point

Local access to culturally safe, targeted advice and support for colorectal cancer screening, diagnostic services and treatment should be provided through health care professionals to improve equity for Aboriginal and Torres Strait Islander peoples.

Good practice statement

23. Practice Point

Health care professionals must be adequately supported to provide culturally safe and sensitive information, verbally and in written form, about colorectal cancer screening and local services (including colonoscopies) to promote engagement in the complete colorectal cancer screening pathway.

Good practice statement

24. Practice Point

Ongoing efforts to improve engagement of Aboriginal and Torres Strait Islander peoples in colorectal cancer screening must continue and occur in partnership with Aboriginal and Torres Strait Islander peak health bodies to ensure equitable access to colorectal cancer screening services is achieved, as well as build community awareness of the importance of screening.

12. Population screening: implications

12.1 Considerations in making these recommendations

The recommendation for population screening for colorectal cancer (CRC) using immunochemical faecal occult blood test (iFOBT) every 2 years, starting at age 45 years and continuing to age 74 years, is based on effectiveness, cost-effectiveness, and the balance of benefits to harms and feasibility within the Australian healthcare system.

We used an up-to-date comprehensive validated model to simulate the National Bowel Cancer Screening Program (NBCSP), *Policy1-Bowel*. The analysis of three screening scenarios assessed 2-yearly iFOBT screening at three levels of participation (40%, 60% and 100%) across various age ranges. The modelling evaluation found that, in comparison with no screening, screening for those aged 50–74 years would reduce CRC incidence by 17–46% and mortality 34-75%. The model evaluation found that, among screening strategies that offered similar rounds of screening invitations (e.g. screening at 45–74 years versus screening at 50–79 years which both cover 30 years of screening), strategies that started screening from an earlier age were found to be associated with higher health benefits, with lower colonoscopy burden and colonoscopy-related serious adverse events, hence a more favourable benefits-and-harms balance, compared with strategies that stopped screening at a later age.

Of all the screening age ranges considered in the analysis, screening at 45–74, and 40–74 years were found to have a more favourable benefits-and-burden balance compared to screening at 50-74, were potentially cost-effective, and had the smallest increase in lifetime colonoscopy utilisation and associated serious adverse events.

Also using *Policy-Bowel*, iFOBT screening provided every 2 years was assessed and found to be cost-effective at three levels of participation (40%, 60% and 100%) while yearly iFOBT screening was likely to be cost-effective.

12.2 Applicability to the Australian setting

The *Policy1-Bowel* model was used to simulate the NBCSP. This included analysis of the 50-74 target age range with 2-yearly iFOBT screening delivered by the NBCSP as of 2023, as well as alternative screening approaches. Calculated rates of CRC incidence and mortality, survival figures for CRC, the probability of dying from other causes and population size and projected size, were all derived from updated Australian data. The costs of screening, colonoscopy investigation and stage-specific CRC treatment all related to Australia. The colonoscopy surveillance management was simulated based on the Australian Clinical practice guidelines for surveillance colonoscopy *[128]*. In addition, cost-effectiveness assessment related to three possible indicative willingness-to-pay thresholds of $AUD 20,000, $AUD 30,000 and $AUD 50,000 per life–year saved which have all been previously used in Australia.

These findings relate to population screening in Australia. Their applicability to other countries will depend on similarities to Australia, including level of risk for CRC and the design and costs of their health services.

12.3 Harms and benefits-and-burden balance

The modelling conducted for this update included an evaluation of the screening-related harms and benefits-and-burden balance. Harms were defined as colonoscopy-related serious adverse event and the benefits-and-burden balance was derived from the number of colonoscopies performed (burden) and the life-years saved (the health benefits).

Potential psychological adverse effects can also be considered screening-related risks or harms. They can result from the trauma and distress of identifying disease in symptom-free, healthy individuals, stress experienced by

people in whom cancer is suspected although later discounted, and more subtle concerns of participants during the screening process *[129]*. However, several studies have shown no evidence of long-term psychological harm after screening *[130][131][132][133]*. The NBCSP has a Participant Follow-Up Function delivered by the states and territories to support NBCSP participants with a positive iFOBT result to continue on the screening pathway to diagnostic assessment. This service may alleviate anxiety for some program participants.

Additionally, culturally sensitive and safe health systems and health services are required to reduce harm to individuals and demonstrate respect to an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics and values. They also address racism and inequity to ensure that all are welcome, safe and protected. The guidelines encourage and support the provision of screening in a culturally safe and sensitive manner based on existing frameworks, guides and manuals in Australia *[10][11][134][135][136][137]*. Health care professionals must recognise the potential adverse psychological effects of screening and alleviate this potential through clear and culturally sensitive and safe communication of CRC screening.

12.4 Choice of target age range for population screening

The recommended age range for organised population screening is 45–74 years, based on considerations of effectiveness, cost-effectiveness and the benefits-and-burden balance from modelled evaluations as randomised controlled trial (RCT) evidence was limited.

When assessing screening age ranges, screening at 40-74 was cost-effective, but with a less favourable benefits-and-burden balance than for 45–74 years, which would require a higher number of colonoscopies for each extra life-year saved.

Every effort should be pursued by health care professionals, professional associations, not-for-profit organisations and other key stakeholders to ensure equitable participation and ongoing quality improvement initiatives in population screening for CRC. These efforts should focus on the target age group of 45–74 years rather than starting from the age of 40 years and ensure equity of access to culturally safe health care. Population screening after 74 years of age could potentially prevent additional CRC cases and deaths, but it is less cost-effective and has a less favourable benefits-and-burden balance. Extending the exit age to those over 74 would require a substantially higher number of colonoscopies. These colonoscopies would be associated with a higher number of colonoscopy-related serious adverse events, which increases with age *[138]*.

CRC screening can commence from age 40 or continue after 74 outside of the NBCSP for those who are fit, well and healthy and request screening. The decision to undergo screening should be a shared decision between the individual and their health care professional, in context of an individual's health status, after an assessment of the potential benefits of screening and the potential harms of a colonoscopy following a positive screening result.

12.5 Choice of testing interval for population screening

The recommendation not to increase the frequency of testing from 2-yearly to yearly is based on the modelling study findings that yearly testing with iFOBTs would be effective and potentially cost-effective but would also be associated with significant increases in colonoscopy demand.

Modelling indicated that testing with iFOBTs every 2 years is a very cost-effective screening strategy for colorectal cancer in the Australian setting, regardless of the indicative willingness to pay threshold.

12.6 Choice of immunochemical faecal occult blood test as preferred test for population screening

12.6.1 Faecal occult blood tests versus flexible sigmoidoscopy or colonoscopy

Population-based screening using faecal occult blood tests or flexible sigmoidoscopy, or colonoscopy can reduce CRC-specific mortality. While both methods of screening are effective, there are major concerns about feasibility, acceptability, and cost-effectiveness with colonoscopy or flexible sigmoidoscopy.

Systematic reviews identified new literature which confirmed the diagnostic accuracy of iFOBTs *[65][66][69][70][72][73][74][75][77][78][79][81][82][83]* and effectiveness of flexible sigmoidoscopy and colonoscopy for CRC screening *[40][41][42][43][44][45]*. No RCT evidence was found that assessed screening with computed tomography colonography, faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA, compared with no screening.

The 2017 guidelines determined that population screening based on flexible sigmoidoscopy or colonoscopy would not be feasible in Australia because of the lack of dedicated facilities and support staff, the high capital cost of developing those facilities, and problems of access related to travel times for participants living outside urban and regional hubs. Previous modelling indicated that screening based on colonoscopy and flexible sigmoidoscopy would not be cost-effective *[139]* and the modelling analyses were not updated.

12.6.2 Immunochemical versus guaiac occult blood tests

There is high-level evidence from three large RCTs and case-control studies evaluating screening with guaiac faecal occult blood test (gFOBT) from the 1990s *[49][51][54]*. While trial data on iFOBT based screening are more limited, a recent systematic review found that iFOBTs had a similar specificity and higher sensitivity in detecting CRCs and advanced neoplasia than gFOBT *[140]*.

The success of iFOBT screening, as part of the NBCSP, for CRC in the Australian population was reported in the 2018 Analysis of Bowel Cancer Outcomes for the National Bowel Cancer Screening Program *[3]*. In this report, CRC incidence and mortality was compared between people in the NBCSP invitee and the never-invited groups in an intention-to-screen CRC mortality analysis. Of the 36,378 never-invited people with a CRC diagnosis, 9,582 (26.3%) had died of CRC before 2016. Of the 15,454 people in the NBCSP invitee group with a CRC diagnosis, 3,064 (19.8%) had died of CRC by the same date: hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.19–1.29. When corrected for potential lead-time bias in screen-detected cancers, the risk of death from CRC was still significantly higher in the never-invited group (HR 1.13, 95% CI: 1.08–1.19). The mean follow-up time to bowel cancer death for all diagnoses was 21.3 months (range 0–117.8 months, standard deviation 19.0 months).

To date, there has been only one high-level published RCT that compared iFOBT-based screening with no screening *[141]*. The recent systematic review found that the diagnostic accuracy of iFOBT was superior to that of gFOBT *[140]*. Moreover, with the widespread availability of evidence-based CRC screening in many countries including Australia (through the NBCSP), it would be unethical to initiate new randomised controlled trials to compare screening by iFOBT with no screening *[142]*. Ongoing trials compare screening modalities or evaluate screening in screening-naïve populations (see section 1.9.2).

Whilst population-based trials of iFOBT have not been as comprehensive as for gFOBT, the European guidelines for quality assurance in CRC screening and diagnosis *[143]* recommend population screening with iFOBT over gFOBT on the basis of *[144]*:

- superior performance (e.g. sensitivity and specificity) in detecting cancers and adenomas
- greater acceptability to participants

- comparable complication rates and costs.

iFOBTs used as a screening modality for CRC will also detect a significant proportion of advanced adenomas in the average-risk population. Removal of advanced adenomas at colonoscopy can reduce the future CRC incidence.

12.7 Health system implications of the recommendations

12.7.1 Clinical practice

Implementation of the recommendation to modify population screening for CRC in the average-risk population, to iFOBT screening every 2 years at age 45–74 years will result in a change to clinical practice. This will include a new cohort of people aged 45 to 49, compared with the previous 2017 recommended target age-group of 50–74 years. Inclusion of the 45- to 49-year-old cohort will require updated advice from primary care and other health care professionals and the addition of colorectal cancer screening to the topics covered as part of a Medicare Benefits Schedule Health assessment for people aged 45 to 49 years who are at risk of developing chronic disease. Additionally, other differences in recommendations and practice points from those in the 2017 guidelines are outlined in **Appendix I.**

Health care professionals play a critical role in managing the interface between population screening and personalised care. In this context, health care professionals include general practitioners, primary health care nurses, Aboriginal Health Workers, and healthcare workers in Aboriginal and Torres Strait Islander community-controlled healthcare organisations and other primary care. Their role requires the ability to identify and advise:

- people who should opt out of the population screening (the NBCSP) because of:
  - major co-morbidities and limited life expectancy
  - the presence of special risk factors
  - recent colonoscopy for whatever reason.
- those who should defer the screening until they recover from recent surgery or major illness.

Evidence shows that healthcare professionals are able to promote and substantially boost participation in the NBCSP *[107][145]*. Trusted health care professionals are well placed to explain the significance of positive screening test results, arrange colonoscopies, discuss any further action that needs to be taken, and interact with the National Cancer Screening Register on an individual's behalf, either by phone or via the Healthcare Provider Portal *[146]*.

For average-risk asymptomatic Australians, prioritising screening through a population-based organised program (in this case the NBCSP) using an iFOBT, can help reduce low-value colonoscopies and therefore colonoscopy service demand which is already under considerable strain *[86]*. Healthcare usage data suggest that colonoscopy patterns may not correlate with disease prevalence in some areas *[147]*. Ensuring colonoscopy usage is in line with guideline recommendations and Colonoscopy Clinical Care Standard will support appropriate use of colonoscopy services, equity of access and reduce colonoscopy-related harms or risk *[147]*. Updated booking systems to manage demand within a model of care that give priority to NBCSP participants and other high-risk groups (e.g. Direct Access Colonoscopy Services) are being explored and have shown promising results in terms of reduced waiting times for colonoscopies and reduced direct costs to patients *[148][149][150]*.

12.7.2 Resourcing

Implementation of the recommendations and practice points included in these guidelines is important to maximise the overall population benefit with implications for many, including health care professionals, professional associations, not for profit organisations and other key stakeholders. Considerations could include:

- updated awareness campaigns and promotion of population screening for CRC, with adaptations for priority populations, to communicate updated advice and boost participation
- support health care professionals to endorse population screening for CRC through specialised education
- access to population screening availability through primary care for priority populations identified among culturally and linguistically diverse communities or in regional and remote communities *[37]*.

12.7.3 Barriers to population screening

A scoping review of reasons for non-participation in population screening (including the NBCSP) revealed several existing barriers that can be broadly categorised into individual barriers, test-related barriers, external barriers, and personal characteristics. Individual barriers included personal emotional or psychological reasons such as disgust with performing the test or fear or anxiety of the result *[102][116]*, and misconceptions or attitudes regarding screening or bowel cancer in general *[115][116][119]*. Test-related barriers specific to the iFOBT included being unaware that the test must be repeated after 2 years or difficulty performing the test *[118][119]*. External barriers included people either receiving general practitioner (GP) advice against screening, difficulty staying up to date with bowel examinations, or expecting their GP to tell them if they needed to undergo the test *[102][113][114][119]*. Personal characteristics that represented barriers to screening included geographical location of the non-participants and/or risk factors *[111][117]*. Recent studies have demonstrated that several of these barriers can be at least partially overcome to improve participation *[151][152][153]*.

The use of iFOBTs, simplifying the method of stool sampling, and endorsement of screening by a person's own health care professional could all result in improvements in participation *[151][152][153]*.

Appropriate public education and promotion is usually necessary to support participation in population screening and build awareness of eligibility criteria. This should take into consideration key stakeholders and population groups, incorporating the central tenet of equity, and consideration of the alignment of initiatives to the existing frameworks and strategies, including the Australian Cancer Plan, the Aboriginal and Torres Strait Islander Cancer Plan and the Four Priority Reform Areas of the National Agreement on Closing the Gap *[154][155]*.

Current evidence has found that iFOBT kits may be less accurate when exposed to higher temperatures for prolonged periods, due to the degradation or denaturing of the sample haemoglobin in temperatures beyond 30°C (156). As a result, the NBCSP delays distribution of kits to postcodes where the average monthly temperature exceeds 30°C *[157]*; this is referred to as the *hot zone policy*. People living in affected areas are instead mailed their kits in the cooler months of the year. However, healthcare providers and participants can override this policy and request a kit during hotter months. In doing this, they are required to acknowledge the importance of and commit to keeping collected samples as cool as possible until they are posted to the laboratory for testing. Careful consideration and understanding of the hot zone policy and potential deterioration of faecal samples by healthcare providers and participants is therefore critical to implementation considerations for the NBCSP, particularly in regional and remote areas or locations with high populations of Aboriginal and Torres Strait Islander people *[158]*. Activities focused on increasing participation in hot zone affected areas would benefit from considered timing to maximise the opportunity to screen.

12.8 Ensuring equity in population screening for colorectal cancer

Participation in population screening for CRC varies by population group. In Australia, NBCSP participation, as reported in the annual monitoring reports, is markedly lower in groups based on geographical location,

socioeconomic area, Indigenous status, language spoken at home and disability *[5]*. Equity in population screening is critical to a program's success and often interconnected with large-scale social and health system issues. Especially in relation to population screening changes (e.g., expanding the target age range), inequities can be exacerbated if screening rates are already low. In the American context, commentators suggest that investment in preventive care infrastructure is a key factor in addressing issues of systemic racism and, in turn, improve data collection, health service provision and reduce inequities in CRC care *[159]*.

Issues of equity in the Australian context as a whole of population concept should be addressed as part of an integrated approach to health care in Australia. In relation to cancer care in Australia, the Australian Cancer Plan includes more appropriate guidance to improve equity that can also be applied to population screening for CRC *[154]*. An Aboriginal and Torres Strait Islander Cancer Plan is also in development which will provide further guidance in this area. Within the remit of the clinical guidelines, specific Practice Points have been developed and included in an effort to encourage equity for population screening in Aboriginal and Torres Strait Islander peoples (Practice Points 21-23). Continued efforts to improve participation and ongoing monitoring of screening rates by population group should be facilitated to support ongoing improvements in equity.

13. Population screening: discussion

13.1 Unresolved issues

There is currently insufficient evidence from appropriately designed studies to determine the following:

- the diagnostic performance of immunochemical faecal occult blood test (iFOBT) using one stool sample vs two stool samples
- the diagnostic performance of non-FOBT faecal or blood-based cancer-specific biomarker assays, and whether these are influenced by participant age, sex, or risk of colorectal cancer
- the effectiveness and cost-effectiveness of population screening based on faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA
- the effectiveness and cost-effectiveness of population screening based on combinations of screening modalities.

Other unresolved issues include:

- potential roles of new screening modalities based on faecal DNA and emerging blood-based screening tests including methylated Septin 9 (mSEPT9) and multi-cancer early detection tests. More evidence is needed.
- the optimal screening modality for sessile serrated lesions, given the diagnostic performance of the iFOBT has low sensitivity
- whether the high rate of colonoscopy in Australia reduces efficiency of population screening, given people may be undergoing screening via colonoscopies when they are at average risk and could be screened via iFOBT through the National Bowel Cancer Screening Program (NBCSP)
- how to optimise public health interventions to maximise participation in population screening
- possible inequities that may arise with changing target age ranges for population screening programs
- likely participation rates of people aged 45–49 years, as this is not an age group that has been systematically offered population screening for CRC. These recommendations are limited by the assumption that the participation rate of 45–49-year-olds in the NBCSP will be the same as that for 50-year-olds.

13.2 Studies currently underway

Several potentially relevant ongoing randomised controlled trials have been identified. The studies listed below may resolve the acknowledged issues relating to diagnostic accuracy of the iFOBT at varying thresholds and the performance of other non-iFOBT screening modalities. Findings from ongoing studies may also identify new approaches to increasing population screening participation which, if successful, may be implemented more broadly in Australia.

13.2.1 iFOBT/colonoscopy screening versus usual care

- Scaling CRC screening through Outreach, Referral and Engagement (SCORE),USA *[160]*
- Effectiveness of an integrated colorectal cancer screening in Saudi Arabia: A pragmatic randomized trial (CRCScreen), Saudi Arabia *[161]*
- Colonoscopy and FOBT as colorectal cancer screening test in the average risk population (SCREESCO – screening of Swedish colons), Sweden *[162]*
- Colonoscopy or faecal occult blood test in screening healthy participants for colorectal cancer (00-046), USA *[163]*
- The Nordic-European Initiative on Colorectal Cancer (NordICC) *[44]*

13.2.2 Colonoscopy versus iFOBT

- Colonoscopy or faecal occult blood test in screening healthy participants for CRC (00-046), USA *[163]*
- Colonoscopy versus faecal immunochemical test in reducing mortality from CRC (CONFIRM), USA *[164]*
- Comparative evaluation of novel strategies for CRC screening in China: a multicentre randomized controlled trial (TARGET-C study), China *[165]*
- Colorectal cancer screening in average-risk population: iFOBT versus colonoscopy, Spain *[166]*
- Augmentation of screening colonoscopy with faecal immunochemical testing (ASC-FIT), USA *[167]*

13.2.3 Sigmoidoscopy versus iFOBT

- Pilot study of a national screening programme for bowel cancer in Norway *[168]*
- Screening for CRC in the Netherlands: a study comparing attendance and feasibility of two different forms of faecal occult blood testing and sigmoidoscopy, Netherlands *[169]*

13.2.4 iFOBT versus iFOBT

- Will using a low threshold faecal immunochemical test compared to the higher threshold test used in the Bowel Cancer Screening Programme reduce the number of bowel cancer cases? UK *[170]*

13.2.5 Studies in Australia

- BEST Bowel Project – Stepped randomised control trial aimed at identifying tools and techniques to increase participation in the NBCSP. It is an ongoing project set to be completed by 2027 approximately.
- SMARTerScreen – a trial of patient SMS reminders from GPs in improving NBCSP participation in Australia.
- MAIL, GP and SCALE – an assessment of interventions to improve NBCSP participation and the optimal combination to maximise screening in the Australian population.
- Co-design of an education intervention to improve bowel cancer awareness and screening in a rural Tasmanian community *[171]*.

13.3 Future research priorities

Future research opportunities include:

- studies assessing the potential for extending population screening of CRC to extended age groups, i.e., 40-45 years
- studies assessing the place of combinations of screening tests (e.g. iFOBT every 2 years and colonoscopy every 10 years at ages 55, 65 and 75 years)
- studies on screening tailored to the presence of special risk factors (e.g. adjusting the starting age of screening, using more sensitive iFOBT conditions or combining screening tests tailored to factors such as sex, body mass index (BMI), history of cigarette smoking)
- evaluation of the performance characteristics of new versions of tests for faecal and blood-based cancer-specific biomarkers
- exploring pragmatic approaches to encouraging participation in the NBCSP for areas affected by the hot zone policy *[158]*. People living in hot zone affected areas are more likely to belong to groups with historically low NBCSP participation rates, such as those from areas with significant socioeconomic disadvantage and Aboriginal and Torres Strait Islander peoples.
- studies evaluating screening in Aboriginal and Torres Strait Islander peoples and other priority populations to improve approaches to enhance screening and participation rates, which may be informed by international experiences.

14. Appendices

Click below for each appendix:

Appendix A

Appendix B

Appendix C

Appendix D

Appendix E

Appendix F

AppendixG

Appendix H

Appendix I

Appendix J

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