Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer: Risk and screening based on family history

Main editor
Mark Goulding

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Contact

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5. Summary of recommendations for risk and screening based on family history

5.1 Risk based on family history of colorectal cancer

Weak recommendation

1. Evidence-based recommendation

Category 1[#]

An individual should be advised that their risk of developing colorectal cancer is:

- near-average risk if they have no family history of colorectal cancer (no first-degree or second-degree relatives) (Ochs-Balcom 2021*[26]*)
- above average, but less than twice the average risk if they have only one first-degree relative with colorectal cancer diagnosed at age 60 or older (Tian 2019*[28]*).

[#]*Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer*

Weak recommendation

2. Evidence-based recommendation

Category 2#

An individual should be advised that their risk of developing colorectal cancer is at least two times higher than average, but could be up to four times higher than average, if they have any of the following:

- only one first-degree relative with colorectal cancer diagnosed before age 60 (Tian 2021*[29]*)
- one first-degree relative AND one or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*; Tian 2021*[29]*).
- two first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*, Tian 2021*[29]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Weak recommendation

3. Evidence-based recommendation

Category 3#

An individual should be advised that their risk of developing colorectal cancer is at least four times higher than average, but could be up to 20 times higher than average, if they have any of the following:

- two first-degree relatives AND one second-degree relative with colorectal cancer, with at least one diagnosed before age 50 (Tian 2019*[28]*)
- two first-degree relatives AND two or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*)
- three or more first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

5.2 Assessing family history

Good practice statement

4. Practice Point

Include both sides of the family when assessing an individual's risk category for colorectal cancer. Criteria for category 2 and category 3 can be met by inclusion of relatives from both sides of the family.

Good practice statement

5. Practice Point

Clinicians should be aware that medical information that patients provide about their relatives is often inaccurate (St John et al 1993*[22]*, Love et al 1985*[35]*, Douglas et al 1999*[40]*, Ruo et al 2001*[39]*, Mitchell et al 2004*[33]*, Tehranifar et al 2015*[34]*, Ziogas 2003*[36]*). For colorectal cancer, 86% of self reported family history is correct (positive predictive value). However, a high proportion of people appear to either be unaware that their relatives have had colorectal cancer or not connected to their family history, with the percentage of all colorectal cancers in first-degree relatives that are reported (sensitivity) being 27% (Mai 2011*[37]*).

Good practice statement

6. Practice Point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information on family history of colorectal cancer. An individual's knowledge of their family history may be unknown, they may not be connected to their family history, or it may change over time so it may be useful to repeat family history collection every few years.

Good practice statement

7. Practice Point

When there is uncertainty about an individual's family history, they should be encouraged to seek clarification within their family including details on which relatives have had colorectal cancer and their ages at diagnoses.

Good practice statement

8. Practice Point

If a family medical history appears to be significant but relatives' diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a family cancer clinic which has resources available to confirm cancer diagnoses.

Good practice statement

9. Practice Point

Because of the possibility of Lynch syndrome, the accuracy of the family history of cancer diagnoses and polyp pathology should be checked carefully and updated regularly (see Lynch syndrome).

5.3 Further testing and referrals

Good practice statement

10. Practice Point

As with all forms of screening for asymptomatic people, those at risk of colorectal cancer should be carefully checked for the presence of symptoms, and appropriate diagnostic investigation completed before entry into a screening program.

Good practice statement

11. Practice Point

For people with category 2 risk of colorectal cancer, genetic testing is not indicated at present.

Good practice statement

12. Practice Point

Consider tumour testing in affected relatives for Lynch syndrome-related changes using immunohistochemistry and microsatellite instability analysis. Where a mismatch repair deficiency and reflex testing for methylation of the MLH1 promoter (or a BRAF V600E mutation) is shown to be absent in the tumour of an affected relative, referral to a family cancer clinic should be considered for a patient with category 2 risk and their family (see Lynch syndrome).

Good practice statement

13. Practice Point

Referral to a family cancer clinic for people with category 3 risk should be prioritised to those whose family members with colorectal cancer are on the same side of the family.

5.4 Determining screening strategies for risk categories

Good practice statement

14. Practice Point

For people in category 2, CT colonography can be offered if the patient had an incomplete colonoscopy in the three months prior to the scan, there is a high-grade colonic obstruction or the service is requested by a specialist (Dachman 2003*[47]*, Sha 2020*[46]*).

Good practice statement

15. Practice Point

For people assessed as having category 1 risk of colorectal cancer:

- iFOBT screening should be performed in line with population screening every two years from age 45 to age 74.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Good practice statement

16. Practice Point

For people assessed as having category 2 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Good practice statement

17. Practice Point

For people assessed as having category 3 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health professional.
- referral to a culturally safe family cancer clinic should be considered. Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

6. Risk based on family history of colorectal cancer

6.1 Assessing family history and colorectal cancer risk

6.2 Clinical Question/PECO

6.3 Recommendations and practice points

Weak recommendation

1. Evidence-based recommendation

Category 1[#]

An individual should be advised that their risk of developing colorectal cancer is:

- near-average risk if they have no family history of colorectal cancer (no first-degree or second-degree relatives) (Ochs-Balcom 2021*[26]*)
- above average, but less than twice the average risk if they have only one first-degree relative with colorectal cancer diagnosed at age 60 or older (Tian 2019*[28]*).

#Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Weak recommendation

2. Evidence-based recommendation

Category 2[#]

An individual should be advised that their risk of developing colorectal cancer is at least two times higher than average, but could be up to four times higher than average, if they have any of the following:

- only one first-degree relative with colorectal cancer diagnosed before age 60 (Tian 2021*[29]*).
- one first-degree relative AND one or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*; Tian 2021*[29]*).
- two first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*, Tian 2021*[29]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Weak recommendation

3. Evidence-based recommendation

Category 3#

An individual should be advised that their risk of developing colorectal cancer is at least four times higher than average, but could be up to 20 times higher than average, if they have any of the following:

- two first-degree relatives AND one second-degree relative with colorectal cancer, with at least one diagnosed before age 50 (Tian 2019*[28]*)
- two first-degree relatives AND two or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*)
- three or more first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

7. Assessing family history

7.1 Collecting family history from patients

7.2 Recommendations and practice points

Good practice statement

4. Practice Point

Include both sides of the family when assessing an individual's risk category for colorectal cancer. Criteria for category 2 and category 3 can be met by inclusion of relatives from both sides of the family.

Good practice statement

5. Practice Point

Clinicians should be aware that medical information that patients provide about their relatives is often inaccurate (St John et al 1993*[22]*, Love et al 1985*[35]*, Douglas et al 1999*[40]*, Ruo et al 2001*[39]*, Mitchell et al 2004*[33]*, Tehranifar et al 2015*[34]*, Ziogas 2003*[36]*). For colorectal cancer, 86% of self reported family history is correct (positive predictive value). However, a high proportion of people appear to either be unaware that their relatives have had colorectal cancer or not connected to their family history, with the percentage of all colorectal cancers in first-degree relatives that are reported (sensitivity) being 27% (Mai 2011*[37]*).

Good practice statement

6. Practice Point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information on family history of colorectal cancer. An individual's knowledge of their family history may be unknown, they may not be connected to their family history, or it may change over time so it may be useful to repeat family history collection every few years.

Good practice statement

7. Practice Point

When there is uncertainty about an individual's family history, they should be encouraged to seek clarification within their family including details on which relatives have had colorectal cancer and their ages at diagnoses.

Good practice statement

8. Practice Point

If a family medical history appears to be significant but relatives' diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a family cancer clinic which has resources available to confirm cancer diagnoses.

Good practice statement

9. Practice Point

Because of the possibility of Lynch syndrome, the accuracy of the family history of cancer diagnoses and polyp pathology should be checked carefully and updated regularly (see Lynch syndrome).

8. Further testing and referrals

8.1 Recommendations and practice points

Good practice statement

10. Practice Point

As with all forms of screening for asymptomatic people, those at risk of colorectal cancer should be carefully checked for the presence of symptoms, and appropriate diagnostic investigation completed before entry into a screening program.

Good practice statement

11. Practice Point

For people with category 2 risk of colorectal cancer, genetic testing is not indicated at present.

Good practice statement

12. Practice Point

Consider tumour testing in affected relatives for Lynch syndrome-related changes using immunohistochemistry and microsatellite instability analysis. Where a mismatch repair deficiency and reflex testing for methylation of the MLH1 promoter (or a BRAF V600E mutation) is shown to be absent in the tumour of an affected relative, referral to a family cancer clinic should be considered for a patient with category 2 risk and their family (see Lynch syndrome).

Good practice statement

13. Practice Point

Referral to a family cancer clinic for people with category 3 risk should be prioritised to those whose family members with colorectal cancer are on the same side of the family.

9. Determining screening strategies for risk categories

9.1 Colorectal cancer screening modalities

9.2 Colorectal cancer screening timing

9.3 Absolute risk of colorectal cancer

9.4 Recommendations and practice points

Good practice statement

14. Practice Point

For people in category 2, CT colonography can be offered if the patient had an incomplete colonoscopy in the three months prior to the scan, there is a high-grade colonic obstruction or the service is requested by a specialist (Dachman 2003*[47]*, Sha 2020*[46]*).

Good practice statement

CATEGORY 1 – Those at near-average risk of colorectal cancer

15. Practice Point

For people assessed as having category 1 risk of colorectal cancer:

- iFOBT screening should be performed in line with population screening every two years from age 45 to age 74.
- low-dose (100mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Good practice statement

CATEGORY 2 – Those at moderately increased risk

16. Practice Point

For people assessed as having category 2 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Good practice statement

CATEGORY 3 – Those at potentially high risk

17. Practice Point

For people assessed as having category 3 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.
- referral to a culturally safe family cancer clinic should be considered. Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

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12. Appendices

1. Abbreviations

Acronym	Description
ACCHOs	Aboriginal and Torres Strait Islander community controlled health organisations
AIHW	Australian Institute of Health and Welfare
APC	Adenomatous polyposis coli
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
CRISP	Colorectal Cancer RISk Prediction
CT	Computed tomography
DNA	Deoxyribonucleic acid
EBR	Evidence-based recommendations
FAP	Familial adenomatous polyposis
g	Grams - unit of measurement
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
iFOBT	Immunochemical faecal occult blood test
MBS	Medicare Benefits Schedule
NBCSP	National Bowel Cancer Screening Program
NorTwinCan	Nordic Twin Study of Cancer
PECO	Population, Exposure, Comparator, Outcome
PP	Practice point
RACGP	Royal Australian College of General Practitioners
RR	Relative risk

2. Glossary

Absolute risk	The likelihood that a cancer-free person at a given age will develop that cancer over a certain period of time
Adenoma	A tumour that is not cancerous
Aspirin	A medicinal drug used to reduce pain or inflammation
Asymptomatic	Without any symptoms
Average risk	Not known to be at substantially increased risk, due to factors such as family history or comorbidities
Body mass index	A measure of body fat or healthy weight based on a person's height and weight
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
Cumulative risk	The total chance of an event to occur during a given period of time
Dizygotic	Unidentical twins
Evidence-based recommendation	Recommendation based on systematic review of medical data (e.g. results of clinical trials) conducted for these guidelines
Familial adenomatous polyposis	An inherited disorder that can lead to colorectal cancer
Family history	A history of disease and/or health conditions found in a person's biological family members
Generalisability	Whether results/findings of a study/report can be applied to other situations or people
High-risk familial syndromes	Inherited conditions that are passed on in the family that may predispose a person to developing cancer
Immunochemical faecal occult blood test	A test that checks for unseen blood in a stool sample
Immunohistochemical staining	A process that helps in selectively identifying specific proteins in cells and tissues
Incidence	The occurrence of newly diagnosed cases of a disease
Lesions	Abnormal growth or appearance of a tissue through injury or disease
Lynch Syndrome	A family inherited condition that can lead to an increased risk of some cancers, including colorectal cancer

Microsatellite Instability	A change that occurs in cells in which the number of repeated DNA bases in a short, repeated sequence of DNA (microsatellite) is different from when it was inherited.
MLH1	A gene that protects a person from cancer
Monozygotic	Identical twins
Mortality	Death rate; the number of deaths in a group of people
MSH2	A gene that protects a person from cancer by joining with the MSH6 gene to form a complex that detects and removes errors in DNA
MSH6	A gene that protects a person from cancer by providing instructions for making proteins to repair DNA
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
Neoplasia	Abnormal growth of cells or tissues
Opportunistic screening	Disease screening offered to patients by health professionals as additional examination or test during a health care visit, when screening was not the reason for the visit
Phenotype	A person's observable traits
PMS2	A gene that protects a person from cancer
Polygenic risk score	A scoring that estimates the total number of genetic variants on an individuals phenotype to assess their inherited risk of developing cancer (or other diseases)
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
Relative Risk	Ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group
Risk stratification	A combination of biometric and behavioural or lifestyle measures used to assign a patient to a certain risk level of getting cancer (or any other 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

Bowel cancer screening means testing healthy middle-aged people, with no known symptoms of bowel cancer, for early signs of bowel cancer. This can reduce the number of deaths due to bowel cancer. Most people who are eligible for bowel cancer screening have a small chance of getting bowel cancer. However, there are some people who have a higher chance of getting bowel cancer because a close relative in their family has or had bowel cancer.

The purpose of this guideline chapter is to help doctors recommend screening for bowel cancer in people with a family history of bowel cancer. This guideline chapter also helps doctors look after people before the person may get bowel cancer. It does not cover what happens after the screening process or bowel cancer treatment.

Bowel cancer in Australia

Bowel cancer, also known as colorectal cancer, is diagnosed in about 16,000 Australians each year and around 5,300 people die from bowel cancer each year. 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 a large amount 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 food. Bowel cancer can affect both men and women.

Some people can also have a higher risk of bowel cancer because it runs in their family, due to genetic changes (mutations that are passed down the family tree). Some inherited genetic mutations cause specific conditions, such as Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP.

A person's risk of bowel cancer depends on how many close relatives have bowel cancer, and those relatives' age at diagnosis. Someone with several close relatives with bowel cancer, especially if they were diagnosed before age 60, has a higher risk of bowel cancer than someone with no close relatives with bowel cancer.

How can Australia reduce deaths from bowel cancer?

Bowel cancer screening means testing healthy middle-aged people, with no known symptoms of bowel cancer, for early signs of bowel cancer. This can reduce the number of deaths due to bowel cancer.

Taking a small dose of aspirin every day can lower some people's risk of bowel cancer. People at risk of bowel cancer, or with a family history of bowel cancer, should talk to their doctor about whether this would be suitable for them.

Who should have regular screening for bowel cancer?

Bowel cancer screening is for people who do not already have bowel cancer, symptoms of bowel cancer, or any known reason to have a high risk of bowel cancer.

The Australian National Bowel Cancer Screening Program (NBCSP) provides bowel screening free of charge to all eligible people without symptoms or signs of bowel cancer every 2 years. The NBCSP uses the "poo test", which looks for invisible traces of blood (immunochemical faecal occult blood test or NBCSP test kit). The NBCSP test kit is mailed out every 2 years to all eligible people and can be done 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. If the test finds some blood (i.e., a positive screening result), the person's health care provider (e.g. doctor) 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.

Who should have special testing for bowel cancer?

The NBCSP is not suitable for people with a family history of bowel cancer in one or more close relatives, especially if they were diagnosed before age 60. These people can have a different type of regular testing to find bowel cancer early. This includes having a colonoscopy every 5 years from age 50, or earlier in some circumstances. The need for special testing depends on whether or not someone has a first-degree relative (i.e. mother, father, sister, or brother) with bowel cancer, whether they also have a second-degree relative (i.e. grandparent, aunt, or uncle) who had bowel cancer, and the age they were when they were first diagnosed.

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/app/uploads/2022/11/A-guide-for-health-professionals-FAQs-single-pages.pdf

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/app/uploads/2022/11/A-guide-for-community-members-FAQs-double-spread.pdf

Information for GPs. Bowel screening and Aboriginal and Torres Strait Islander people from: https://www.health.gov.au/sites/default/files/documents/2019/10/bowel-screening-and-aboriginal-and-torres-strait-islander-people-information-for-gps.pdf

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: Understanding the bowel cancer screening test in your language | Cancer Council

4. Introduction

4.1 Background

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 in 2022 *[1]*. According to the Australian Institute of Health and Welfare (AIHW), there were an estimated 15,713 new CRC cases and 5,326 CRC deaths in 2022 *[1]*. Key risk factors for CRC include tobacco consumption, excess alcohol consumption, excess body adiposity, and dietary factors including excess red and processed meat consumption, and insufficient dietary fibre intake *[2]*. Consumption of milk and dairy products and physical activity can reduce CRC risk *[2]*. In addition, CRC screening aims to facilitate the early detection and prevention of CRC with survival rates highest for those detected through screening *[3]*.

Family history of CRC is an important risk factor for developing the disease *[4]*. A family history of CRC means a person's probability of developing CRC could be several times higher than that of someone without a family history and may require CRC screening outside of population screening programs (i.e. targeted risk screening). Targeted screening involves screening of selected high-risk groups. In this chapter targeted screening is discussed and is applicable to those with an identified family history of colorectal cancer. This does not include an identified genetic syndrome or disorder.

This guideline chapter on Risk and screening based on family history has been updated from that developed in 2017 *[5]* in response to emerging evidence relevant to the target age range for population screening in Australia and the subsequent effect on targeted screening based on family history of CRC.

4.2 Intended users

This guideline chapter is intended for health professionals caring for people without symptoms or signs of CRC and with a family history 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 health care teams, including Aboriginal Health Practitioners and Aboriginal Health Workers.

It is not intended as health information for the general public.

4.3 Target populations

This guideline chapter covers a range of Australian populations. This chapter focuses on people with a family history of CRC.

Clinicians should consider the specific needs of priority/underrepresented groups nationally, as defined in annual AIHW National Bowel Cancer Screening Program (NBCSP) monitoring reports *[6]*, including Aboriginal and Torres Strait Islander peoples, people living with disabilities, and culturally and linguistically diverse people. For each systematic review, the 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 health care 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 health care 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: risk and screening based on family history)* provides information and recommendations to guide practice in CRC screening and the assessment pathway for people with a family history of CRC.

The first *Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer* were developed in 1999 *[7]* and, since then, have been widely used as a reference by health care professionals, 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: Risk and screening based on family history), 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 [5]* (the 2017 guidelines). Cancer Council Australia sub-contracted The Daffodil Centre, a joint venture between the University of Sydney and Cancer Council New South Wales, to perform the systematic reviews and predictive modelling, and provide project co-ordination 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 CRC (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 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 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 questions (see **Appendix B** for a full list of clinical questions):

> i) What is the strength of association between family history and CRC risk?
>
> ii) What screening strategies should be used for people with a family history, based on age, sex, number and relatedness of relatives with CRC?

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

4.8.3 Systematic reviews

The recommendations were informed by a systematic review (FHS1) conducted based on the PECO question in Table 1 and outlined in **Appendix E**.

Table 1. Systematic review question.

PECO	Systematic Review Question
FHS1	For asymptomatic individuals, is a family history of CRC associated with an increase in risk of occurrence of or death from CRC when compared to individuals who do not have a family history of CRC; and how does this association vary by age and sex of the asymptomatic individuals, and with age, sex, number, and relatedness of relatives with CRC.

4.8.4 Evidence appraisal and synthesis

A technical report of the systematic review was completed, and the Working Party appraised the evidence by considering the body of evidence (design, number, and size of studies and their risk of bias), consistency of findings, clinical impact of outcomes, and the generalisability and applicability of evidence to the Australian population.

For this clinical question, the Working Party did not use Grading of Recommendations, Assessment,

Development and Evaluations (GRADE) methodology to assess the certainty of evidence or guide the development of recommendations based on the identified body evidence. GRADE was primarily designed for intervention clinical questions, and there is limited experience applying it to questions looking at risks associated with different degrees of an exposure within asymptomatic populations.

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 (EBRs) 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) based on consideration of the body of evidence and its consistency, potential unwanted effects of implementing the guidance, values and preferences of people applying or affected by the recommendation, and implications for resource use (see Table 2). The type of recommendation and wording reflects the assessment of evidence.

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 (see Table 1). 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 2. Types of recommendations included in these guidelines.

Type	Process
Evidence-based recommendation (EBR)	Recommendation based on 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 the 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. The recommendations and practice points were circulated to the Working Party for comments and a voting process was used, both in meetings and offline correspondence, to reach consensus. 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 peoples. 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 guides have been developed to support health care providers to provide 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]*, and 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 updated chapter of the 2017 guidelines (referred to as the 2023 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 the management of CRC risk in individuals with a family history of CRC, the Working Party will reconvene 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: Risk and screening based on family history. September 2023. Sydney: Cancer Council Australia. Available from **Magicapp**

5. Summary of recommendations for risk and screening based on family history

To dowload a PDF of the summary of recommendations click here

This section covers screening for colorectal cancer (CRC) in asymptomatic individuals who are at higher-than-average risk based on their family history of CRC, so that preventative measures or early treatment may be offered to improve health outcomes.

These recommendations are intended to guide decision-making in determining who should take part in targeted screening for CRC based on their family history. 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 the recommendations in these guidelines.

The 2023 guideline chapter includes evidence-based recommendations (EBR) and practice points. For each EBR, the Working Party assigned a strength (weak or strong), after considering the volume, consistency, generalisability, applicability, and clinical impact of the body of evidence. Recommendations and practice points were developed by Working Party members. The choice of recommendation and wording reflects the assessment of the evidence.

5.1 Risk based on family history of colorectal cancer

Weak recommendation

1. Evidence-based recommendation

Category 1[#]

An individual should be advised that their risk of developing colorectal cancer is:

- near-average risk if they have no family history of colorectal cancer (no first-degree or second-degree relatives) (Ochs-Balcom 2021*[26]*)
- above average, but less than twice the average risk if they have only one first-degree relative with colorectal cancer diagnosed at age 60 or older (Tian 2019*[28]*).

[#]*Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer*

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC

    - no first-degree relatives diagnosed with CRC
    - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.

- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
    - one first-degree relative and one second-degree relative diagnosed with CRC
    - only two first-degree relatives (other than both parents) diagnosed with CRC
    - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
    - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.

- RRs were greater than 4.00 for each of the following scenarios:
    - three or more first-degree relatives diagnosed with CRC
    - both parents diagnosed with CRC
    - two first-degree relatives and two or more second-degree relatives diagnosed with CRC
    - two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
    - one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before 50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC in category 1 are near-average or slightly above average risk. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, individuals in category 1 should perform iFOBT screening in line with population screening. This would be expected to reduce demand on colonoscopy.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

Of the studies, three were deemed to have a high risk of bias *[25][26][31]* and four were deemed to have a moderate risk of bias *[27][28][29][30]*.

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

The three large data linkage studies were from: 1) the Utah Population Database *[25][26]*, 2) the Swedish Family Cancer dataset *[28][29]*, and 3) the Nordic Twin Study of Cancer (NorTwinCan) *[27]* using data from Denmark, Finland, Norway, and Sweden.

From the Utah Population Database, there were two retrospective cohort analyses. Individuals with at least three generations of genealogy with follow-up for cancer up to 2014 were included *[25][26]*. One study looked at risk factors in combination with family history of CRC, focusing on body mass index (BMI). The outcomes for this study included measuring standardised incidence ratios for overweight/obese and underweight/normal weight probands *[25]*.The second study focused on the risk of early-onset CRC (people diagnosed at younger than age 50 years) with first-, second- and third-degree relatives with CRC. This study also investigated the location of CRC. Reported outcomes included relative risk of specific CRC phenotype *[26]*.

Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

A small Italian prospective cohort study *[31]* included individuals who underwent a screening colonoscopy in the Trentino district between December 2005 and November 2009 (N=2017). The exposures of interest were one or more first-degree relatives diagnosed with CRC, ascertained from a centralised CRC screening database for first-degree relatives (N=1252). The comparator population was individuals with no family history of CRC ascertained by gastroenterologists (N=765). The outcome of interest was CRC incidence with a mean follow up of 52 months (exposed) and 53 months (comparator)*[31]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

Weak recommendation

2. Evidence-based recommendation

Category 2#

An individual should be advised that their risk of developing colorectal cancer is at least two times higher than average, but could be up to four times higher than average, if they have any of the following:

- only one first-degree relative with colorectal cancer diagnosed before age 60 (Tian 2021*[29]*)
- one first-degree relative AND one or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*; Tian 2021*[29]*).
- two first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*, Tian 2021*[29]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC
  - no first-degree relatives diagnosed with CRC
  - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.
- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
  - one first-degree relative and one second-degree relative diagnosed with CRC

    - only two first-degree relatives (other than both parents) diagnosed with CRC
    - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
    - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.

- RRs were greater than 4.00 for each of the following scenarios:
    - three or more first-degree relatives diagnosed with CRC
    - both parents diagnosed with CRC
    - two first-degree relatives and two or more second-degree relatives diagnosed with CRC
    - two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
    - one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before 50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC

incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC are generally recognised as a high-risk group for CRC and recognised in many international CRC guidance. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, the updated categorisation of those at moderate to high risk of CRC based on family history (category 2 and category 3) now represent approximately 10% of the population. This would be expected to contribute minimal extra demand on existing colonoscopy demand.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

Of the studies, three were deemed to have a high risk of bias *[25][26][31]* and four were deemed to have a moderate risk of bias *[27][28][29][30]*.

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

The three large data linkage studies were from: 1) the Utah Population Database *[25][26]*, 2) the Swedish Family Cancer dataset *[28][29]*, and 3) the Nordic Twin Study of Cancer (NorTwinCan) *[27]* using data from Denmark, Finland, Norway, and Sweden.

From the Utah Population Database, there were two retrospective cohort analyses. Individuals with at least three generations of genealogy with follow-up for cancer up to 2014 were included *[25][26]*. One study looked at risk factors in combination with family history of CRC, focusing on body mass index (BMI). The outcomes for this study included measuring standardised incidence ratios for overweight/obese and underweight/normal weight probands *[25]*.The second study focused on the risk of early-onset CRC (people diagnosed at younger than age 50 years) with first-, second- and third-degree relatives with CRC. This study also investigated the location of CRC. Reported outcomes included relative risk of specific CRC phenotype *[26]*.

Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

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Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

Weak recommendation

3. Evidence-based recommendation

Category 3#

An individual should be advised that their risk of developing colorectal cancer is at least four times higher than average, but could be up to 20 times higher than average, if they have any of the following:

- two first-degree relatives AND one second-degree relative with colorectal cancer, with at least one diagnosed before age 50 (Tian 2019*[28]*)
- two first-degree relatives AND two or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*)
- three or more first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC
  - no first-degree relatives diagnosed with CRC
  - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.
- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
  - one first-degree relative and one second-degree relative diagnosed with CRC

    - only two first-degree relatives (other than both parents) diagnosed with CRC
    - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
    - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.

- RRs were greater than 4.00 for each of the following scenarios:
    - three or more first-degree relatives diagnosed with CRC
    - both parents diagnosed with CRC
    - two first-degree relatives and two or more second-degree relatives diagnosed with CRC
    - two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
    - one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before 50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC

incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC are generally recognised as a high-risk group for CRC and recognised in many international CRC guidance. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, the updated categorisation of those at moderate to high risk of CRC based on family history (category 2 and category 3) now represent approximately 10% of the population. This would be expected to contribute minimal extra demand on existing colonoscopy demand.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

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The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

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Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

A small Italian prospective cohort study *[31]* included individuals who underwent a screening colonoscopy in the Trentino district between December 2005 and November 2009 (N=2017). The exposures of interest were one or more first-degree relatives diagnosed with CRC, ascertained from a centralised CRC screening database for first-degree relatives (N=1252). The comparator population was individuals with no family history of CRC ascertained by gastroenterologists (N=765). The outcome of interest was CRC incidence with a mean follow up of 52 months (exposed) and 53 months (comparator)*[31]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

5.2 Assessing family history

Good practice statement

4. Practice Point

Include both sides of the family when assessing an individual's risk category for colorectal cancer. Criteria for category 2 and category 3 can be met by inclusion of relatives from both sides of the family.

Good practice statement

5. Practice Point

Clinicians should be aware that medical information that patients provide about their relatives is often inaccurate (St John et al 1993*[22]*, Love et al 1985*[35]*, Douglas et al 1999*[40]*, Ruo et al 2001*[39]*, Mitchell et al 2004*[33]*, Tehranifar et al 2015*[34]*, Ziogas 2003*[36]*). For colorectal cancer, 86% of self reported family history is correct (positive predictive value). However, a high proportion of people appear to either be unaware that their relatives have had colorectal cancer or not connected to their family history, with the percentage of all colorectal cancers in first-degree relatives that are reported (sensitivity) being 27% (Mai 2011*[37]*).

Good practice statement

6. Practice Point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information on family history of colorectal cancer. An individual's knowledge of their family history may be unknown, they may not be connected to their family history, or it may change over time so it may be useful to repeat family history collection every few years.

Good practice statement

7. Practice Point

When there is uncertainty about an individual's family history, they should be encouraged to seek clarification within their family including details on which relatives have had colorectal cancer and their ages at diagnoses.

Good practice statement

8. Practice Point

If a family medical history appears to be significant but relatives' diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a family cancer clinic which has resources available to confirm cancer diagnoses.

Good practice statement

9. Practice Point

Because of the possibility of Lynch syndrome, the accuracy of the family history of cancer diagnoses and polyp pathology should be checked carefully and updated regularly (see Lynch syndrome).

5.3 Further testing and referrals

Good practice statement

10. Practice Point

As with all forms of screening for asymptomatic people, those at risk of colorectal cancer should be carefully checked for the presence of symptoms, and appropriate diagnostic investigation completed before entry into a screening program.

Good practice statement

11. Practice Point

For people with category 2 risk of colorectal cancer, genetic testing is not indicated at present.

Good practice statement

12. Practice Point

Consider tumour testing in affected relatives for Lynch syndrome-related changes using immunohistochemistry and microsatellite instability analysis. Where a mismatch repair deficiency and reflex testing for methylation of the MLH1 promoter (or a BRAF V600E mutation) is shown to be absent in the tumour of an affected relative, referral to a family cancer clinic should be considered for a patient with category 2 risk and their family (see Lynch syndrome).

Good practice statement

13. Practice Point

Referral to a family cancer clinic for people with category 3 risk should be prioritised to those whose family members with colorectal cancer are on the same side of the family.

5.4 Determining screening strategies for risk categories

Good practice statement

14. Practice Point

For people in category 2, CT colonography can be offered if the patient had an incomplete colonoscopy in the three months prior to the scan, there is a high-grade colonic obstruction or the service is requested by a specialist (Dachman 2003*[47]*, Sha 2020*[46]*).

Good practice statement

15. Practice Point

For people assessed as having category 1 risk of colorectal cancer:

- iFOBT screening should be performed in line with population screening every two years from age 45 to age 74.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Rationale

A number of organisations, including the American Cancer Society and the American Gastroenterological Association, do not consider that risk of CRC based on weak family history of CRC justifies more invasive screening than that recommended for the average population *[51][52]*. More invasive screening is generally done using colonoscopy.

Given that the yield of clinically significant lesions at screening with colonoscopy is low (approximately 14%) *[53][54][55][56][57][58]*, colonoscopy screening is not warranted in a population with a weak family history. Approximately 90% of the population are in this category.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-examined via a systematic review for the 2023 update.

Good practice statement

16. Practice Point

For people assessed as having category 2 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Rationale

For people in category 2, the risk of CRC at age 40 years is similar to that of the average population at age 50 years. Their 10-year absolute risk of CRC at age 40 is approximately 1%, which is equivalent to the risk for people in category 1 at age 50. Approximately 10% of the population are in this category.

Given that their 10-year absolute risk of CRC is higher than the average population at age 50, a 5-yearly colonoscopy screening strategy is recommended for those in Category 2. Prior to the recommended start age for colonoscopy screening, people with Category 2 risk should screen in line with population screening program recommendations.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional, to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-examined via a systematic review for the 2023 update.

Good practice statement

17. Practice Point

For people assessed as having category 3 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health professional.
- referral to a culturally safe family cancer clinic should be considered. Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

Rationale

The risk for some people with three (or more) relatives with CRC may be difficult to categorise, especially if all cases of CRC occur at an advanced age, are confined to one generation of the family, and if no-one in the family has had any of the extra-colonic cancers associated with Lynch syndrome *[59]*. If there is uncertainty about their mutation status, it may be safer to categorise people as having suspected (or possible) Lynch syndrome (see Lynch syndrome). New diagnoses of cancer in the family or results of microsatellite instability, immunohistochemical staining, or genetic testing may clarify the situation.

For people in category 3, their risk of CRC at age 35 years is as high as that of the average population at age 50. Their 10-year absolute risk of CRC at age 35 is approximately 1.2%, which is equivalent to the risk for people in category 1 at age 50. Less than 1% of the population are in this category.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional, to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-

examined via a systematic review for the 2023 update.

6. Risk based on family history of colorectal cancer

Family history of colorectal cancer (CRC) is an important risk factor for developing CRC *[4]*. The probability of developing CRC could be several times higher for a person with a family history of CRC than that of someone without a family history.

Research has identified several genes for which inherited mutations substantially increase a person's CRC risk. Those best understood include:

- the DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2, mutations of which cause the hereditary cancer predisposition of Lynch syndrome (previously known as hereditary non-polyposis CRC) *[18][19]*
- the APC gene, mutation of which causes familial adenomatous polyposis (FAP)*[19]*
- the DNA base excision repair gene *MUTYH*, biallelic mutation of which causes *MUTYH*-associated polyposis *[19]*.

These genetic disorders have either an autosomal-dominant mode of transmission (mismatch repair genes and APC) or autosomal-recessive mode of transmission (*MUTYH*) within families and are associated with a very high cancer risk (risk based on genetic syndromes and disorders are out of scope for the current chapter. See High-risk familial syndromes) *[19]*. However, mutations in these genes cause fewer than 5% of all CRC cases and, at most, only explain half of the reasons why family history is a risk factor for CRC *[20]*.

Assessment of family history of CRC has two roles in cancer prevention and early detection:

- to prioritise who should be tested for mutations in these genes
- to inform decisions about the optimal timing, frequency, and modality of screening.

6.1 Assessing family history and colorectal cancer risk

The best evidence for the association between CRC risk and family history of CRC comes from cohort studies that compare the risk of CRC for people with and without a family history of CRC. Ideally, these studies should control for any differences between people with and without a family history for CRC risk factors.

Such studies consistently report an elevated risk of CRC associated with family history. The strength of this association increases with the number of relatives with CRC, the closeness of genetic relationship of the relative(s) with CRC, and the diagnosis age of relative(s) with CRC.

Early case control studies and cohort studies in Denmark *[21]*, Australia *[22]*, and the USA *[23][24]* included individuals with first-, second- and/or third-degree relatives with CRC. These studies reported that the risk of CRC was approximately two times higher in individuals with first-, second- and/or third-degree relatives with CRC, compared with individuals at average risk (no family history) *[21][22][23][24]*.

CRC risk was even greater for those with a first-degree relative with CRC diagnosed at an early age (below age 55) or for those with two close relatives who had CRC (irrespective of the age at diagnosis) *[23][24]*.

For the 2023 guideline chapter, a systematic review was undertaken to identify cohort and nested case-control studies estimating the risk of CRC among relatives of patients with CRC, published since 1 January 2016, which was the end of the search period for the systematic review undertaken for the 2017 edition of these guidelines *[5]*. Cohort studies are less subject to recall misclassification than case-control studies, in which people with CRC are more likely to report any existing family history than controls.

6.2 Clinical Question/PECO

See section 4.7.3 Systematic reviews or **Appendix B** for the clinical questions and population, exposure, comparator, and outcome (PECO) question.

Please note: A systematic review was conducted based on a PECO (population, exposure, comparator, and outcome) question

6.3 Recommendations and practice points

Weak recommendation

1. Evidence-based recommendation

Category 1#

An individual should be advised that their risk of developing colorectal cancer is:

- near-average risk if they have no family history of colorectal cancer (no first-degree or second-degree relatives) (Ochs-Balcom 2021*[26]*)
- above average, but less than twice the average risk if they have only one first-degree relative with colorectal cancer diagnosed at age 60 or older (Tian 2019*[28]*).

#Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC
  - no first-degree relatives diagnosed with CRC
  - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.
- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
  - one first-degree relative and one second-degree relative diagnosed with CRC
  - only two first-degree relatives (other than both parents) diagnosed with CRC
  - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
  - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.
- RRs were greater than 4.00 for each of the following scenarios:
  - three or more first-degree relatives diagnosed with CRC

- both parents diagnosed with CRC
- two first-degree relatives and two or more second-degree relatives diagnosed with CRC
- two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
- one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before 50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC in category 1 are near-average or slightly above average risk. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, individuals in category 1 should perform iFOBT screening in line with population screening. This would be expected to reduce demand on colonoscopy.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

Of the studies, three were deemed to have a high risk of bias *[25][26][31]* and four were deemed to have a moderate risk of bias *[27][28][29][30]*.

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

The three large data linkage studies were from: 1) the Utah Population Database *[25][26]*, 2) the Swedish Family Cancer dataset *[28][29]*, and 3) the Nordic Twin Study of Cancer (NorTwinCan) *[27]* using data from Denmark, Finland, Norway, and Sweden.

From the Utah Population Database, there were two retrospective cohort analyses. Individuals with at least three generations of genealogy with follow-up for cancer up to 2014 were included *[25][26]*. One study looked at risk factors in combination with family history of CRC, focusing on body mass index (BMI). The outcomes for this study included measuring standardised incidence ratios for overweight/ obese and underweight/normal weight probands *[25]*.The second study focused on the risk of early-onset CRC (people diagnosed at younger than age 50 years) with first-, second- and third-degree relatives with CRC. This study also investigated the location of CRC. Reported outcomes included

relative risk of specific CRC phenotype *[26]*.

Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

A small Italian prospective cohort study *[31]* included individuals who underwent a screening colonoscopy in the Trentino district between December 2005 and November 2009 (N=2017). The exposures of interest were one or more first-degree relatives diagnosed with CRC, ascertained from a centralised CRC screening database for first-degree relatives (N=1252). The comparator population was individuals with no family history of CRC ascertained by gastroenterologists (N=765). The outcome of interest was CRC incidence with a mean follow up of 52 months (exposed) and 53 months (comparator)*[31]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

Weak recommendation

2. Evidence-based recommendation

Category 2#

An individual should be advised that their risk of developing colorectal cancer is at least two times higher than average, but could be up to four times higher than average, if they have any of the following:

- only one first-degree relative with colorectal cancer diagnosed before age 60 (Tian 2021*[29]*).
- one first-degree relative AND one or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*; Tian 2021*[29]*).
- two first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*, Tian 2021*[29]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC
  - no first-degree relatives diagnosed with CRC
  - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.
- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
  - one first-degree relative and one second-degree relative diagnosed with CRC
  - only two first-degree relatives (other than both parents) diagnosed with CRC
  - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
  - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.
- RRs were greater than 4.00 for each of the following scenarios:
  - three or more first-degree relatives diagnosed with CRC
  - both parents diagnosed with CRC
  - two first-degree relatives and two or more second-degree relatives diagnosed with CRC
  - two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
  - one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before

50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC are generally recognised as a high-risk group for CRC and recognised in many international CRC guidance. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, the updated categorisation of those at moderate to high risk of CRC based on family history (category 2 and category 3) now represent approximately 10% of the population. This would be expected to contribute minimal extra demand on existing colonoscopy demand.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

Of the studies, three were deemed to have a high risk of bias *[25][26][31]* and four were deemed to have a moderate risk of bias *[27][28][29][30]*.

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

The three large data linkage studies were from: 1) the Utah Population Database *[25][26]*, 2) the Swedish Family Cancer dataset *[28][29]*, and 3) the Nordic Twin Study of Cancer (NorTwinCan) *[27]* using data from Denmark, Finland, Norway, and Sweden.

From the Utah Population Database, there were two retrospective cohort analyses. Individuals with at least three generations of genealogy with follow-up for cancer up to 2014 were included *[25][26]*. One study looked at risk factors in combination with family history of CRC, focusing on body mass index (BMI). The outcomes for this study included measuring standardised incidence ratios for overweight/ obese and underweight/normal weight probands *[25]*.The second study focused on the risk of early-onset CRC (people diagnosed at younger than age 50 years) with first-, second- and third-degree relatives with CRC. This study also investigated the location of CRC. Reported outcomes included relative risk of specific CRC phenotype *[26]*.

Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The

study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

A small Italian prospective cohort study *[31]* included individuals who underwent a screening colonoscopy in the Trentino district between December 2005 and November 2009 (N=2017). The exposures of interest were one or more first-degree relatives diagnosed with CRC, ascertained from a centralised CRC screening database for first-degree relatives (N=1252). The comparator population was individuals with no family history of CRC ascertained by gastroenterologists (N=765). The outcome of interest was CRC incidence with a mean follow up of 52 months (exposed) and 53 months (comparator)*[31]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

Weak recommendation

3. Evidence-based recommendation

Category 3#

An individual should be advised that their risk of developing colorectal cancer is at least four times higher than average, but could be up to 20 times higher than average, if they have any of the following:

- two first-degree relatives AND one second-degree relative with colorectal cancer, with at least one diagnosed before age 50 (Tian 2019*[28]*)
- two first-degree relatives AND two or more second-degree relatives with colorectal cancer diagnosed at any age (Tian 2019*[28]*)
- three or more first-degree relatives with colorectal cancer diagnosed at any age (Ochs-Balcom 2021*[26]*, Tian 2019*[28]*).

 # Excludes an individual known to have or known to be related to someone with a genetic predisposition to colorectal cancer

Practical info

Evidence statement

Multiple studies report that a family history of CRC is associated with an increased risk of CRC.

Two large data linkage Swedish and Utah studies examining CRC risk associated with multiple family history constellations, with follow-up to 2005 and 2015, reported that the relative risk (RR) of a CRC diagnosis at any age increases with the increasing strength and extent of family history of CRC and with decreasing age of family members at diagnosis, compared with either average risk or risk in the absence of first-degree and second-degree relatives diagnosed with CRC.

Reported RRs of CRC associated with a family history were:

- Less than 2.00 for each of the following scenarios:
  - no first-degree relatives or second-degree relatives diagnosed with CRC
  - no first-degree relatives diagnosed with CRC
  - only one first-degree relative diagnosed with CRC and they were diagnosed at age 60 years or over.
- RRs were greater than 2.00 and less than 4.00 for each of the following scenarios:
  - one first-degree relative and one second-degree relative diagnosed with CRC
  - only two first-degree relatives (other than both parents) diagnosed with CRC
  - two first-degree relatives (other than both parents) and one second-degree relative all diagnosed aged 50 years or older
  - one first-degree relative and two second-degree relatives, all of whom were diagnosed aged 50 years or older.
- RRs were greater than 4.00 for each of the following scenarios:
  - three or more first-degree relatives diagnosed with CRC
  - both parents diagnosed with CRC
  - two first-degree relatives and two or more second-degree relatives diagnosed with CRC
  - two first-degree relatives and one second-degree relative, at least one of whom was diagnosed before aged 50 years
  - one first-degree relative and two second-degree relatives, at least one of whom was diagnosed before aged 50 years.

In the Swedish study, estimates of RR associated with having only one first-degree relative diagnosed before

50 years depended on the analysis:

- 2.00 when family histories in which there were relatives diagnosed with colorectal carcinoma in situ were not excluded
- 1.90 excluding family histories in which there were relatives diagnosed with colorectal carcinoma in situ. In this analysis, the risk was the same whether the first-degree relative was diagnosed aged less than 50 years or aged 50–59 years.

Results from the large Swedish data linkage study suggest that the risks associated with several family history constellations may be slightly higher for males.

The RR associated with family history was greater for earlier-onset disease and highest for CRC diagnosed before age 50 years; in both the Swedish and Utah cohorts, RR of a CRC diagnosis before the age of 50 was greater than 4.00 for individuals with one first-degree relative diagnosed with CRC before the age of 50.

The risk of CRC increases with additional risk factors e.g., body mass index (BMI).

Evidence to decision

Benefits and harms

The risk of CRC based on family history increases with the number of first- and second-degree relatives diagnosed, as well as the age at which they were diagnosed. An assessment of family history can benefit individuals by identifying an increased risk, and subsequent objective categorisation of risk level can inform decisions about participating in more intensive screening strategies that may prevent CRC. The harms associated with risk categorisation begin with the associated psychological distress or harm stemming from the knowledge that an individual is at increased risk. Data on potential harms associated with risk categorisation are limited and were out of scope in the systematic review undertaken for this guideline update.

Certainty of the Evidence

The current update identified an additional small prospective cohort study, a cross-sectional study, and five articles reporting on three data-linkage cohort studies, including additional analyses of data from the Utah study which was included in the 2017 guidelines update. Included studies were mostly consistent, but with some inconsistencies between comparisons of different family history exposures for CRC incidence at any age, calculated according to type and extent of family history, affected relatives' ages at diagnosis, and by sex. The clinical impact of the evidence was assessed as substantial for CRC incidence at any and all ages and CRC-specific mortality for those with a family history of CRC (see Practical info - Evidence statement for detail).

Values and preferences

Individuals with a family history of CRC are generally recognised as a high-risk group for CRC and recognised in many international CRC guidance. Individuals are generally comfortable to disclose their family history of CRC, if known, or obtain this information in order to guide screening recommendations specific to their individual circumstances. In some instances, ascertaining family history of CRC can be challenging for cultural reasons and individuals may not want to be informed of their potentially above-average risk of CRC.

Resources and other considerations

Colonoscopy services in the public system are already at capacity and strain to meet demands of diagnostic colonoscopy following a positive immunochemical faecal occult blood test. The recommendations align closely with current practice. However, the updated categorisation of those at moderate to high risk of CRC based on family history (category 2 and category 3) now represent approximately 10% of the population. This would be expected to contribute minimal extra demand on existing colonoscopy demand.

Clinical question/ PICO

Population: People without a CRC diagnosis or symptoms that might indicate CRC
Intervention: Exposure - Presence of a family history of CRC
Comparator: No known family history of CRC or general population

Summary

Evidence Summary

The systematic review identified seven studies (based on five datasets): three large data linkage studies*[25][26][27][28][29]*, one cross-sectional study *[30]*, and one small prospective cohort study *[31]*. Each of the studies assessed risk of CRC according to the individual's independently confirmed history of CRC (including first- and second- degree relatives). Reported outcomes included CRC incidence, CRC prevalence, and CRC diagnosis at different ages.

Of the studies, three were deemed to have a high risk of bias *[25][26][31]* and four were deemed to have a moderate risk of bias *[27][28][29][30]*.

The literature searches conducted as part of the systematic reviews were designed to capture priority groups including Aboriginal and Torres Strait Islander peoples. Although, no evidence for priority groups was identified for inclusion. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report (see **Appendix E**1).

Included studies

The three large data linkage studies were from: 1) the Utah Population Database *[25][26]*, 2) the Swedish Family Cancer dataset *[28][29]*, and 3) the Nordic Twin Study of Cancer (NorTwinCan) *[27]* using data from Denmark, Finland, Norway, and Sweden.

From the Utah Population Database, there were two retrospective cohort analyses. Individuals with at least three generations of genealogy with follow-up for cancer up to 2014 were included *[25][26]*. One study looked at risk factors in combination with family history of CRC, focusing on body mass index (BMI). The outcomes for this study included measuring standardised incidence ratios for overweight/ obese and underweight/normal weight probands *[25]*.The second study focused on the risk of early-onset CRC (people diagnosed at younger than age 50 years) with first-, second- and third-degree relatives with CRC. This study also investigated the location of CRC. Reported outcomes included relative risk of specific CRC phenotype *[26]*.

Two retrospective cohort analyses were based on the Swedish Family Cancer dataset *[28][29]*. The first study explored the risk of CRC for people with family history of CRC, with an emphasis on second-degree relatives, especially half-siblings. The study included people born after 1931 and followed them up from 1958 to 2015. Main reported outcomes included lifetime (0–79 years) cumulative risk of CRC, and standardised incidence ratio of CRC among first- and second-degree relatives *[28]*. The second study investigated the risk of invasive CRC for people with family history of invasive CRC. The

study followed the same cohort of people born in 1931 and followed up from 1958 to 2015. Reported outcomes included lifetime cumulative risk of CRC at different ages for those with first-degree relatives diagnosed with invasive CRC at different ages *[29]*.

From the NorTwinCan cohort, Graff et al 2017 *[27]* conducted a retrospective analysis of same-sex monozygotic or dizygotic twins (N = 202,866) between 1943 and 2010 . Participants were followed up for 31.9 years (median) with an exposure of a monozygotic and dizygotic co-twin with CRC diagnosis and an outcome of CRC incidence *[27]*.

A cross-sectional analysis using data from 12 Asia-Pacific countries *[30]* included data from asymptomatic individuals aged above 40 years who underwent screening colonoscopy at CRC screening centres or medical outpatient clinics between December 2011 and December 2013 (N = 11,797). The study exposures were combinations of first-degree relatives (N=2,006), compared with individuals without a self-reported family history of CRC (N = 9791). The outcome of interest was CRC prevalence *[30]*.

A small Italian prospective cohort study *[31]* included individuals who underwent a screening colonoscopy in the Trentino district between December 2005 and November 2009 (N=2017). The exposures of interest were one or more first-degree relatives diagnosed with CRC, ascertained from a centralised CRC screening database for first-degree relatives (N=1252). The comparator population was individuals with no family history of CRC ascertained by gastroenterologists (N=765). The outcome of interest was CRC incidence with a mean follow up of 52 months (exposed) and 53 months (comparator)*[31]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No known family history of CRC or general population	**Intervention** Presence of a family history of CRC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Assessing family history and colorectal risk		To review family history outcomes please click **here**			

7. Assessing family history

Family history is often used to stratify people without a diagnosis or symptoms of colorectal cancer (CRC) into risk categories in which the number of expected CRC or adenoma is high enough to warrant more intensive screening than the average population. For those with an affected first-degree relative, risk is double the average risk, although most of the elevated risk is expressed after the age of 60 years. When the affected relative is second-degree (e.g. a grandparent, uncle or aunt), lifetime risk is up to 1.5 times higher than average *[24][32]*. However, family history is only a proxy measure for elevated risk of CRC (see Ongoing research studies). Using family history to guide screening practices depends on the accuracy of the information collected from the individual.

7.1 Collecting family history from patients

Collecting family history of cancer is often a challenging process and family history is not always reported or recorded accurately. In most clinical settings, family history is only collected for first-degree relatives, with varied accuracy, and the collection of second- and third-degree relatives is often unavailable or reported with lower accuracy *[22][33][34][35][36][37][38][39]*. Other relevant factors, like relationship to the individual, cancer type, and age at diagnosis also contribute to accuracy of family history reporting *[36][37][40]*. Evidence from studies assessing the accuracy and limitations of family cancer history has shown that the addition of multiple relatives (i.e. collecting family cancer history from multiple relatives) and a follow-up interview at a later date may improve the completeness and accuracy of collection of family cancer history *[34][39]*. Collection of information on family history of Lynch Syndrome related cancers other than CRC are also important in assessment of risk (see Lynch syndrome).

Culturally safe and sensitive care and consideration are essential when ascertaining family history for Aboriginal and Torres Strait Islander peoples as concepts and understandings of 'family' may vary for Aboriginal and Torres Strait Islander peoples *[41][42]*. This may involve an emphasis on sensitivity in discussions about family history, offering the involvement of Aboriginal and Torres Strait Islander Health Workers or interpreters, and the provision of educational resources *[41][42]*.

Previous Australian guidelines specified that relatives with cancer needed to be on the same side of the family in order to meet eligibility of this risk category. This restriction has been removed because updated evidence provides data suggesting that a similar level of risk applies if the relatives with cancer are on opposite sides of the family *[32]*.

7.2 Recommendations and practice points

Good practice statement

4. Practice Point

Include both sides of the family when assessing an individual's risk category for colorectal cancer. Criteria for category 2 and category 3 can be met by inclusion of relatives from both sides of the family.

Good practice statement

5. Practice Point

Clinicians should be aware that medical information that patients provide about their relatives is often inaccurate (St John et al 1993*[22]*, Love et al 1985*[35]*, Douglas et al 1999*[40]*, Ruo et al 2001*[39]*, Mitchell et al 2004*[33]*, Tehranifar et al 2015*[34]*, Ziogas 2003*[36]*). For colorectal cancer, 86% of self reported family history is correct (positive predictive value). However, a high proportion of people appear to either be unaware that their relatives have had colorectal cancer or not connected to their family history, with the percentage of all colorectal cancers in first-degree relatives that are reported (sensitivity) being 27% (Mai 2011*[37]*).

Good practice statement

6. Practice Point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information on family history of colorectal cancer. An individual's knowledge of their family history may be unknown, they may not be connected to their family history, or it may change over time so it may be useful to repeat family history collection every few years.

Good practice statement

7. Practice Point

When there is uncertainty about an individual's family history, they should be encouraged to seek clarification within their family including details on which relatives have had colorectal cancer and their ages at diagnoses.

Good practice statement

8. Practice Point

If a family medical history appears to be significant but relatives' diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a family cancer clinic which has resources available to confirm cancer diagnoses.

Good practice statement

9. Practice Point

Because of the possibility of Lynch syndrome, the accuracy of the family history of cancer diagnoses and polyp pathology should be checked carefully and updated regularly (see Lynch syndrome).

8. Further testing and referrals

In Australia, approximately 75% of cases of colorectal cancer (CRC) are diagnosed after a person presents with symptoms that indicate investigation is required. The majority of people with symptomatic CRC first present to general practice. General practitioners (GPs) are faced with the challenge of identifying people with symptoms that are due to CRC amongst the many people with similar symptoms that are caused by benign conditions. Accurate early identification of CRC may be hampered by reduced community health literacy and symptom awareness, delayed presentation to primary health care, or limited access to culturally safe colonoscopy services *[43]*.

Extra care and consideration are necessary in the management of those in category 2 and category 3, given their higher level of risk. It is important to rule out both the presence of any symptoms and/or the possibility of genetic mutations through additional testing (i.e. using microsatellite instability analysis and immunohistochemical staining) or referral.

People with a known or probable high-risk familial syndrome due to a genetic predisposition to CRC require more intensive screening. These people may have a much higher risk of CRC and are excluded from categories 2 and 3. They should undergo testing, surveillance, and management based on clinical advice. For guidance on managing risk in people in category 3 with a known or suspected genetic syndrome, see High-risk familial syndromes.

Risk categories 1–3 exclude the following:

- a person who has a relative in whom a pathogenic mutation in a gene associated with a high-risk familial syndrome has been confirmed
- a person with a relative in whom familial adenomatous polyposis (FAP) has been diagnosed
- a person with at least three first-degree or second-degree relatives with a Lynch syndrome-related cancer (endometrial, ovarian, stomach, small bowel, renal pelvis or ureter, biliary tract, brain), with at least one diagnosed before age 50 years
- a person with a first-degree relative in whom multiple colorectal cancers have been diagnosed.

All the above should be referred to a family cancer clinic for testing for a high-risk familial syndrome.

8.1 Recommendations and practice points

Good practice statement

10. Practice Point

As with all forms of screening for asymptomatic people, those at risk of colorectal cancer should be carefully checked for the presence of symptoms, and appropriate diagnostic investigation completed before entry into a screening program.

Good practice statement

11. Practice Point

For people with category 2 risk of colorectal cancer, genetic testing is not indicated at present.

Good practice statement

12. Practice Point

Consider tumour testing in affected relatives for Lynch syndrome-related changes using immunohistochemistry and microsatellite instability analysis. Where a mismatch repair deficiency and reflex testing for methylation of the MLH1 promoter (or a BRAF V600E mutation) is shown to be absent in the tumour of an affected relative, referral to a family cancer clinic should be considered for a patient with category 2 risk and their family (see Lynch syndrome).

Good practice statement

13. Practice Point

Referral to a family cancer clinic for people with category 3 risk should be prioritised to those whose family members with colorectal cancer are on the same side of the family.

9. Determining screening strategies for risk categories

9.1 Colorectal cancer screening modalities

The majority of colorectal cancer (CRC) screening guidelines recommend 2-yearly immunochemical faecal occult blood test (iFOBT) or 10-yearly colonoscopy for the lowest risk category, 5-yearly colonoscopy for the middle risk category, and yearly or 2-yearly (every 2 years) colonoscopy for the highest risk category, which includes those with high-risk familial syndromes *[44][45]*.

Colonoscopy is considered to be the gold standard for CRC detection *[46]*. However, it is an invasive procedure that requires sedation *[46]*. It also carries various risks, including bowel perforation and bleeding, and increased risk of adverse effects associated with sedation for patients in older age groups. Computed tomography (CT) colonography offers an alternative which does not require sedation and has a high sensitivity for detecting polyps by external imaging *[46][47]*. In line with the existing Medical Benefits Schedule *[48]*, item number 56553 covers CT colonography for a symptomatic or high risk patient if:

(a) one or more of the following applies:

> (i) the patient has had an incomplete colonoscopy in the 3 months before the scan;
>
> (ii) there is a high grade colonic obstruction;
>
> (iii) the service is requested by a specialist or consultant physician who performs colonoscopies in the practice of the specialist's or consultant physician's speciality; and

(b) the service is not a service to which item 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies.

For the purposes of a CT colonography, a high risk patient is someone who is asymptomatic but has either: i) three or more first-degree or a combination of first-degree and second-degree relatives on the same side of the family diagnosed with bowel cancer (suspected hereditary non-polyposis CRC), or ii) two or more first-degree or second-degree relatives on the same side of the family diagnosed with bowel cancer, including any of the following high-risk features, or iii) multiple bowel cancers in the one person, or iv) bowel cancer before the age of 50 years, or v) at least one relative with cancer of the endometrium, ovary, stomach, small bowel, ureter, biliary tract or brain, or vi) at least one first-degree relative with a large number of adenomas throughout the large bowel (suspected familial adenomatous polyposis or familial adenomatous polyposis), or vii) somebody in the family in whom the presence of a high-risk mutation in the adenomatous polyposis coli gene or one of the mismatch repair genes has been identified.

9.2 Colorectal cancer screening timing

The majority of screening guidelines recommend screening to begin at age 50 for all risk categories or 10 years before the youngest age of CRC diagnosis in a relative. Early (2005) Australian clinical practice guidelines recommended, alongside other guidance on CRC, that screening should begin at 10 years younger than the age of first diagnosis of CRC in the family *[49]*. This was no longer recommended in the 2017 guidelines, due to a lack of published evidence to support this strategy *[5]*.

The 2017 guidelines *[5]* recommended colonoscopy for people with a family history of CRC assessed to be at moderately increased risk (category 2) or high risk (category 3). The 2017 guideline recommendations for people with category 2 risk included 2-yearly iFOBT starting at age 40 years, followed by 5-yearly colonoscopy beginning at age 50 years, with CT colonography offered when colonoscopy was contraindicated. The 2017 guideline recommendations for people with category 3 risk included 2-yearly iFOBT starting at age 35 years, followed by 5-yearly colonoscopy starting at age 45 years, with CT colonography offered when colonoscopy was

contraindicated.

Tian and colleagues *[29]* used the Swedish Family Cancer Database to estimate risk-adapted effects of recommendations on CRC screening start ages on CRC outcomes for individuals with differing family histories. Of 12,829,251 individuals with genealogy information followed up from 1958 to 2015, 173,796 developed CRC *[29]*.

The 10-year cumulative risk for CRC for the average-risk population was 0.44% for screening starting at age 50 years *[29]*. The same risk level of 0.44% was reached at age 45 years for people with only one first-degree relative, at age 35 years for those with both one first-degree relative and one or more second-degree relatives with CRC, and at age 22 years for those with two or more first-degree relatives and with any number of second-degree relatives with CRC. For those with only one second-degree relative with CRC, 0.44% risk was reached at age 47 years, except for those with one half-sibling with CRC, for whom the same risk level would be reached 6 years earlier. Those with two or more second-degree relatives with CRC would reach 0.44% risk at 46 years *[29]*.

The 10-year cumulative risk for CRC for the average-risk population starting screening at 45 years was 0.25% *[29]*. In comparison, this risk level was reached at age 39 years for those with only one first-degree relative with CRC diagnosed at any age, at age 22 years for those with one first-degree relative but more than two second-degree relatives with CRC, and at age 21 years for those with more than two first-degree relatives and any number of second-degree relatives with CRC. The same risk level of 25% was reached at age 43 years by people with no first-degree relative and one second-degree relative with CRC, and at age 40 years in those with no first-degree relative and more than two second-degree relatives with CRC *[29]*.

9.3 Absolute risk of colorectal cancer

Population-based data can be used to calculate the 10-year risk of CRC for the average-risk population and those under two-fold increased risk (both category 1), those at three- to six-fold increased risk (category 2), and those at seven- to ten-fold increased risk (category 3) (Table 3). The 10-year CRC risk for a 40-year-old at three- to six-fold increased risk is the same as the 10-year CRC risk for a 35-year-old at seven- to ten-fold increased risk, and the same as the 10-year CRC risk for a 50-year-old at average risk. For people in category 2, the 10-year risk of CRC from age 50 is 3% or higher.

Table 3. Ten-year absolute risks of colorectal cancer (%) based on age and level of increased risk due to family history

Number of first-degree relatives with colorectal cancer	**RR due to family history**	**10-year absolute risk of CRC**				
		Age (years)				
		30	35	40	45	50
0	0.9	0.07%	0.12%	0.25%	0.50%	0.90%
1	2	0.15%	0.29%	0.59%	1.10%	1.90%
2	3-6	0.30%	0.60%	1.20%	2.20%	3.80%
3+	7-10	0.60%	1.20%	2.40%	4.80%	7.60%

***RR**: relative risk; the risk of colorectal cancer relative to the average risk in the population. Source: Incidence data from AIHW Australian colorectal cancer incidence for males and females combined for the year 2000 [50].Estimates are based on the assumption that the relative risk is the same for all age groups. The ranges provided are based on the ranges of the familial relative risks in each category from Taylor et al 2011 [32]. Note: The year 2000 is used as a proxy for an Australian screening naïve population. It is noted that opportunistic screening was available in Australia at this time and this may underestimate the 'natural' risk of disease.*

9.4 Recommendations and practice points

Good practice statement

14. Practice Point

For people in category 2, CT colonography can be offered if the patient had an incomplete colonoscopy in the three months prior to the scan, there is a high-grade colonic obstruction or the service is requested by a specialist (Dachman 2003*[47]*, Sha 2020*[46]*).

CATEGORY 1 – Those at near-average risk of colorectal cancer

Good practice statement

15. Practice Point

For people assessed as having category 1 risk of colorectal cancer:

- iFOBT screening should be performed in line with population screening every two years from age 45 to age 74.
- low-dose (100mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Rationale

A number of organisations, including the American Cancer Society and the American Gastroenterological Association, do not consider that risk of CRC based on weak family history of CRC justifies more invasive screening than that recommended for the average population *[51][52]*. More invasive screening is generally done using colonoscopy.

Given that the yield of clinically significant lesions at screening with colonoscopy is low (approximately 14%) *[53][54][55][56][57][58]*, colonoscopy screening is not warranted in a population with a weak family history. Approximately 90% of the population are in this category.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-examined via a systematic review for the 2023 update.

CATEGORY 2 – Those at moderately increased risk

Good practice statement

16. Practice Point

For people assessed as having category 2 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.

Rationale

For people in category 2, the risk of CRC at age 40 years is similar to that of the average population at age 50

years. Their 10-year absolute risk of CRC at age 40 is approximately 1%, which is equivalent to the risk for people in category 1 at age 50. Approximately 10% of the population are in this category.

Given that their 10-year absolute risk of CRC is higher than the average population at age 50, a 5-yearly colonoscopy screening strategy is recommended for those in Category 2. Prior to the recommended start age for colonoscopy screening, people with Category 2 risk should screen in line with population screening program recommendations.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional, to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-examined via a systematic review for the 2023 update.

CATEGORY 3 – Those at potentially high risk

Good practice statement

17. Practice Point

For people assessed as having category 3 risk of colorectal cancer:

- colonoscopy should be offered every five years starting at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40, whichever is earlier, to age 74.
- CT colonography may be offered if clinically indicated.
- low-dose (100 mg) aspirin daily should be considered from age 45 to 70 (see Aspirin) in consultation with a health care professional.
- referral to a culturally safe family cancer clinic should be considered. Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

Rationale

The risk for some people with three (or more) relatives with CRC may be difficult to categorise, especially if all cases of CRC occur at an advanced age, are confined to one generation of the family, and if no-one in the family has had any of the extra-colonic cancers associated with Lynch syndrome *[59]*. If there is uncertainty about their mutation status, it may be safer to categorise people as having suspected (or possible) Lynch syndrome (see Lynch syndrome). New diagnoses of cancer in the family or results of microsatellite instability, immunohistochemical staining, or genetic testing may clarify the situation.

For people in category 3, their risk of CRC at age 35 years is as high as that of the average population at age 50. Their 10-year absolute risk of CRC at age 35 is approximately 1.2%, which is equivalent to the risk for people in category 1 at age 50. Less than 1% of the population are in this category.

Daily use of low-dose aspirin should also be considered, in consultation with a health care professional, to prevent CRC for those aged 45 to 70 (see Aspirin). Evidence on aspirin use and the effect on CRC was not re-examined via a systematic review for the 2023 update.

10. Risk and screening based on family history: Implications

10.1 Health system implications of the recommendations

10.1.1 Clinical practice

The 2023 guideline chapter for population screening of colorectal cancer (CRC) recommends population screening for CRC in the average-risk population at ages 45-74 years. This update recommends that all people in Category 1 avail themselves of population screening, which will be sufficient given their risk of CRC.

In Australia, a comprehensive family history is not systematically recorded and depends on a health care professional, including the general practitioner (GP), practice nurse or other primary care worker, collecting the relevant information as part of a regular consultation. Although the Royal Australian College of General Practitioners (RACGP) recommends the use of a validated family history screening questionnaire *[60]*, this can be time-intensive to complete and not always achievable in a standard GP consultation. Under-ascertainment of family history of any cancer is known. This highlights the need for more proactive approaches in primary care which take into consideration the burden on GPs and the possibility of including other health care professionals in this determination.

Culturally safe and sensitive care and consideration are essential when ascertaining family history for Aboriginal and Torres Strait Islander peoples as concepts and understandings of 'family' may vary for Aboriginal and Torres Strait Islander peoples *[41][42]*. This may involve an emphasis on sensitivity in discussions about family history, offering the involvement of Aboriginal and Torres Strait Islander Health Workers or interpreters and the provision of educational resources *[41][42]*.

These guidelines differ from the 2017 guidelines in several ways (see **Appendix I**). There have been some changes in the family history inclusion criteria across all categories to provide clearer descriptions. Also, for people in category 2, screening using colonoscopy is recommended at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 50, whichever is earlier, to age 74. For people in category 3, screening using colonoscopy is also recommended at 10 years younger than the earliest age of diagnosis of colorectal cancer in a first-degree relative or age 40, whichever is earlier, to age 74.

Screening colonoscopies for people in categories 2 and 3 are currently subsidised under the Medicare Benefits Schedule (MBS). The updated definition of these categories requires modifications of MBS criteria to ensure that colonoscopies remain subsidised for the expanded groups. Any submissions to the Medical Services Advisory Committee regarding future modifications to MBS criteria, are the responsibility of the Department of Health and Aged Care once the guidelines are endorsed. To ensure the updated recommendations are used in clinical practice, updated education modules and communications are required to ensure that GPs are aware of the change. This could take the form of traditional education avenues such as training courses, webinars, and news articles, as well as quick-access or reference guides.

10.1.2 Resourcing

Current GP software systems do not support systematic collection of family history of cancer or the integration of risk assessment tools to identify people at higher-than-average risk. The Colorectal Cancer RISk Prediction (CRISP) trial aimed to test the effectiveness of a precision screening instrument in primary care practice in 10 general practices in Melbourne, Australia to enhance risk-appropriate CRC screening *[61]*. The trial determined the cost-effectiveness and balance of benefits and harms of a risk-stratified approach to CRC screening *[62]*. An increase in risk-appropriate screening was recorded in the intervention, compared with the control group: 71.6% versus 65%; odds ratio 1.36 (95% CI: 0.99–1.86); p = 0.057 *[62]*.

Another trial currently underway, SCRIPT, is testing the implementation of tailored precision screening using polygenic risk scores and risk reports in six to 10 general practices. The primary objective is to evaluate the impact of the intervention after 12 months. Secondary objectives include measuring participants' CRC risk perceptions, cancer-specific anxiety, factors influencing screening behaviour, screening intentions, and health care utilisation *[63]*.

Risk categorisation and the relating screening strategy may appear complex to implement in practice and their administration with a patient may take considerable time, which is not always available during a regular consult.

10.1.3 Barriers to implementation

Current GP software systems in Australia do not support systematic family history collection or risk assessment.

There may be some resistance to the change in recommendations that have been in place for over 10 years from health professionals and the community. To overcome these barriers, tailored education campaigns and messaging for primary care workers to outline the updated recommendations for people with a family history could be implemented by professional associations. Any messaging should also be culturally safe and sensitive, especially as screening would be provided via colonoscopy which requires preparation and has associated harms.

11. Risk and screening based on family history: Discussion

11.1 Unresolved issues

In the absence of trials and observational studies for the effectiveness of screening strategies in people at elevated risk of colorectal cancer (CRC) due to family history, cost-effectiveness analysis is appropriate to determine screening guidelines for the risk categories. A modelling study based on a large simulated cohort *[64]* estimated the costs, benefits, and harms of varied screening strategies varying by screening start age (40, 46, 50 ,54, or 60 years), test (immunochemical faecal occult blood test [iFOBT] or colonoscopy), and interval (yearly, 2-yearly, or 3-yearly for iFOBT screening and 5- or 10-yearly for colonoscopy screening), along with risk stratification of the population polygenic risk and family history using a microsimulation model in the Australian population (MISCAN-Colon). The results found, based on risk groups, yearly iFOBT screening from age 54 to 74 years was effective for all risk groups, but the incremental cost effectiveness ratios ranged from $86,929 (for the 'very low risk' group, i.e. people with the lowest quintile for polygenic risk and first-degree relatives diagnosed with CRC) to $3,687 (for the 'very high risk' group, i.e., people with the second highest and the highest quintile for polygenic risk and have one or more first-degree relatives diagnosed with CRC). Two-yearly iFOBT screening from age 50 to 74 years was effective for the very-low-risk group, whereas the optimal strategy for the very-high-risk group was 5-yearly colonoscopy from age 50 to 74 years *[64]*. Personalised screening, which offered different optimal screening strategies according to people's CRC risk level, could reduce CRC incidence by 4%-68% (3–57 fewer CRC cases per 1,000 individuals) and mortality by 5%–79% (2–23 fewer deaths per 1,000 individuals) but would increase colonoscopy demand by 45–6,698 per 1,000 individuals *[64]*.

Health economic research is needed to assess the cost-effectiveness of screening for various categories of family history, evaluate the screening strategies, and further examine the relationship between risk and age.

11.2 Evidence limitations

Included studies identified for this guideline chapter were conducted in Western countries, with no evidence for priority groups, including Aboriginal and Torres Strait Islander peoples, identified for inclusion. The genetic factors, in particular the high-risk factors that contribute to increased CRC risk, are not necessarily present in Aboriginal and Torres Strait Islander peoples and may be limited in their applicability across all population groups. Moreover, the generalisability of these studies to an Australian population may be limited. This is due to the CRC incidence in Australia being higher than in the USA or Sweden; the age-standardised incidence in 2020 per 100,000 was 33.1 for Australia compared with 27.8 for Sweden and 25.6 for the USA *[65]*. These differences were greater at the time of the 2017 guidelines update and may reflect differences in CRC screening practices and the roll-out of screening programs. The optimal age to start and stop screening is not known for those with a family history of CRC in Australia. Health economic research and predictive modelling can help inform the benefits, harms, and costs of iFOBT screening or colonoscopy screening in those with family history of CRC and guide decision making.

11.3 Ongoing research studies

One study identified in this review assessed the use of body mass index (BMI) in conjunction with family history of CRC to determine risk. The results suggest that other risk factors can increase relative risk of disease and may need to be considered when deciding on how to screen an individual in the future *[25]*.

It has been noted that family history is a proxy measure for elevated risk of CRC. However, more advanced methods of determining risk at the individual level to guide risk-based screening may better predict risk *[66]* and are under development. Some of these studies include:

- CRISP, SCRIPT– Ongoing randomised control trials aimed at identifying risk-based tools and polygenic risk score implementation in a general practice patient population. The primary outcome of these projects is participation and the identification of colorectal neoplasia by risk stratification.
- Australian Cancer Risk Study: The study will generate a germline genomic data linked with lifestyle and health data from participants of the Australian 45 and Up cohort and develop a validated genomic risk tool for breast, prostate, melanoma, and colorectal cancer for the Australian population. The study will also identify and incorporate public preferences in genomics-informed risk-tailored screening and perform health economics evaluation to determine 'best buy' risk-tailored screening and early detection strategies.

The potential implications of these trials on the current guideline recommendations are not immediately evident. Their results, however, may indicate the viability of sophisticated risk-based screening approaches for CRC in Australia which could be integrated into future iterations of the guidelines.

11.4 Future research priorities

Future research on Aboriginal and Torres Strait Islander populations is a priority. This must be conducted in an ethical and culturally safe manner and co-designed with Aboriginal and Torres Strait Islander peoples.

Inherent difficulties in deciding the demarcation between categories or the number of categories argues for an algorithm that summarises the family history of CRC into a risk score, which can then be used to decide age and modality of screening. These algorithms should also assess the effect on the accuracy of risk stratification of including personal risk factors for CRC other than family history (e.g. obesity, smoking, excessive alcohol intake, etc.). Ongoing research may support the development of algorithms and their implementation in practice, but this remains a future research priority.

Additionally, identifying the causes for familial risk of CRC will assist the evaluation of risk within these risk categories, so that more personalised screening can be recommended based on more precise estimates of risk.

12. Appendices

Appendix A

Appendix B

Appendix C

Appendix D

Appendix E

Appendix F

Appendix G

Appendix H

Appendix I

Appendix J

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