

# Revised Australian national guidelines for colorectal cancer screening: family history

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**C**olorectal cancer is a major cause of morbidity and mortality in Australia. It is the second most common cancer diagnosed in both men and women (17 004 cases for 2018) and causes the second most cancer deaths (4129 deaths in 2018).<sup>1</sup> In 2017, Cancer Council Australia released the revised guidelines for the prevention, early detection and management of colorectal cancer which included consideration of family history.<sup>2</sup>

Family history of colorectal cancer is an important risk factor for developing the disease.<sup>3</sup> The best evidence for the association between colorectal cancer risk and family history comes from cohort and case-control studies that compare the risk of colorectal cancer for people with and without a family history of this disease. Such studies consistently report an elevated risk of colorectal cancer associated with family history.

Genes have been identified which, when inherited in a mutated form, substantially increase a person's risk of developing colorectal cancer. The best studied of these genes include the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2* (Lynch syndrome);<sup>4</sup> the *APC* gene (familial adenomatous polyposis);<sup>5</sup> and *MUTYH* (*MUTYH*-associated polyposis).<sup>6</sup> Mutations in these genes cause fewer than 5% of all colorectal cancer cases and, at most, only explain half of the reasons why family history is a risk factor for this disease.<sup>7</sup> The remainder of the observed increases in familial risk could be due in part to mutations in yet to be discovered colorectal cancer susceptibility genes, polygenic factors such as single-nucleotide polymorphisms,<sup>8,9</sup> or dietary and other lifestyle factors shared by family members.

The current practice in many countries is to recommend more intensive screening (in terms of frequency and procedure) for people with a stronger family history. The majority of screening guidelines recommend biennial faecal occult blood test (FOBT) or colonoscopy every 10 years for the lowest risk category; colonoscopy every 5 years for the moderate risk category; and annual or biennial colonoscopy for the highest risk category, which includes individuals with high risk familial syndromes.<sup>10-12</sup> Most screening guidelines recommend screening to begin at age 50 years for all risk categories or 10 years before the youngest age of colorectal cancer diagnosis in a relative, without explicitly considering risk of cancer for age and family history. The 10-year risk of colorectal cancer by age and family history can be estimated using the age-specific incidence rates for the Australian population and the level of increased risk afforded by each level of family history.

The revised guidelines provide estimates of risk of colorectal cancer and screening recommendations for people who have a family history of colorectal cancer who are not known or suspected to have a genetic syndrome.

## Abstract

**Introduction:** Screening is an effective means for colorectal cancer prevention and early detection. Family history is strongly associated with colorectal cancer risk. We describe the rationale, evidence and recommendations for colorectal cancer screening by family history for people without a genetic syndrome, as reported in the 2017 revised Australian guidelines.

**Main recommendations:** Based on 10-year risks of colorectal cancer, people at near average risk due to no or weak family history (category 1) are recommended screening by immunochemical faecal occult blood test (iFOBT) every 2 years from age 50 to 74 years. Individuals with moderate risk due to their family history (category 2) are recommended biennial iFOBT from age 40 to 49 years, then colonoscopy every 5 years from age 50 to 74 years. People with a high risk due to their family history (category 3) are recommended biennial iFOBT from age 35 to 44 years, then colonoscopy every 5 years from age 45 to 74 years.

**Changes in management as a result of the guidelines:** By 2019, the National Bowel Cancer Screening Program will offer all Australians free biennial iFOBT screening from age 50 to 74 years, consistent with the recommendations in these guidelines for category 1. Compared with the 2005 guidelines, there are some minor changes in the family history inclusion criteria for categories 1 and 2; the genetic syndromes have been removed from category 3 and, as a consequence, colonoscopy screening is now every 5 years; and for categories 2 and 3, screening begins with iFOBT for people aged 40 and 35 years, respectively, before transitioning to colonoscopy after 10 years.

## Methods

A systematic literature review of cohort studies since 2005 (when the previous guidelines were published<sup>13</sup>) was undertaken to update the colorectal cancer risk estimates for relatives of people with colorectal cancer.<sup>2,14,15</sup> Only cohort studies were considered for inclusion in the review, as they are less subject to recall misclassification compared with case-control studies, in which people with colorectal cancer are more likely to recall any existing family history than controls.

We identified six studies analysing the association between family history and colorectal cancer: one analysis of pooled data from two prospective cohort studies<sup>16</sup> and five cohort studies.<sup>17-21</sup> Overall, the studies reported that people with a family member diagnosed with colorectal cancer had an increased risk of colorectal cancer compared with the average population. The estimated increases in risk were greater the younger the relative was when diagnosed with colorectal cancer and the higher the number of first and second degree relatives diagnosed with this disease (Box 1).

The screening recommendations in the guidelines were based on the colorectal cancer risk according to family history recommendations and the evidence for population screening. To date, no

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**1 Risk of colorectal cancer based on family history: examples of estimates from cohort studies published since 2005**

Family history of colorectal cancer	Colorectal cancer risk relative to the average population risk	Increase or decrease in risk for colorectal cancer	References
No family history	0.83	17% decrease	21
One or more first degree relative diagnosed at any age	1.4–2.1	40–110% increase	18,20,21
One first degree relative diagnosed before age 50 years	3.3	230% increase	21
One first degree relative diagnosed between ages 50 and 60 years	2.2–2.5	120–150% increase	20,21
Two first degree relatives	3.0	200% increase	21
No first degree relative, at least one second degree relative	1.1–1.5	10–50% increase	21

published peer-reviewed articles were identified assessing colorectal cancer screening by strength of family history.

**Risk categories**

There are three categories defined in the revised guidelines (Box 2) which are similar to the categories defined for the 2005 guidelines,<sup>13</sup> with some minor changes to the definitions of family history for each category based on recent studies assessing familial risk of colorectal cancer (Box 3).

All categories exclude people known to have, or with a high probability of having, a genetic predisposition to colorectal cancer due to a familial syndrome. These people have a much higher risk of colorectal cancer and are therefore recommended more intensive screening strategies. The risk categories considered in these guidelines exclude people who have:

- a relative confirmed as carrying a pathogenic mutation in a gene associated with a high risk familial syndrome who have not themselves been tested negative for the mutation;
- a relative with multiple colorectal cancers;
- a relative with familial adenomatous polyposis; or
- 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 relative diagnosed before age 55 years.

People suspected of a genetic syndrome need assessment at a family cancer clinic. There are specific guidelines for those with a hereditary cancer syndrome.<sup>31</sup>

**2 Colorectal cancer risk categories by family history, including degree of relationship, number of diagnoses in relatives and the ages of diagnoses**

Risk category*	Examples of asymptomatic people fitting into each category (full description in Box 3)	Lifetime risk (to age 75 years if no screening)	Risk compared with the population average
1 — People at near average risk	<ul style="list-style-type: none"> <li>• No first or second degree relative with colorectal cancer</li> </ul>	5–10%	<ul style="list-style-type: none"> <li>• Risk is about 10% lower than the average risk</li> </ul>
	<ul style="list-style-type: none"> <li>• One first degree or one first and one second degree relative with colorectal cancer diagnosed at age <math>\geq 55</math> years<sup>16,18,20,22–26</sup></li> </ul>		<ul style="list-style-type: none"> <li>• Risk is about double the average risk, although most of that extra risk is expressed after the age of 60 years</li> </ul>
2 — People at moderately increased risk	<ul style="list-style-type: none"> <li>• One first degree relative with colorectal cancer diagnosed before the age of 55 years<sup>21,25–29</sup></li> <li>• Two first degree relatives or one first degree relative and at least two second degree relatives diagnosed with colorectal cancer at any age<sup>21,28–30†</sup></li> </ul>	15–30%	<ul style="list-style-type: none"> <li>• When the affected relative is second degree (eg, a grandparent, uncle or aunt), lifetime risk is only up to 1.5 times higher than average<sup>21,25</sup></li> <li>• Risk is about 3–6 times average risk. For the majority of people in this category, the risk of colorectal cancer is 3–4 times higher than average†</li> </ul>
3 — People at high risk	<ul style="list-style-type: none"> <li>• At least three first degree relatives diagnosed with colorectal cancer at any age<sup>21</sup></li> <li>• At least three first degree or three second degree relatives with colorectal cancer, with at least one relative diagnosed before age 55 years</li> </ul>	15–30%	<ul style="list-style-type: none"> <li>• Risk is about 7–10 times average risk. For the majority of people in this category, the risk of colorectal cancer is 7 times higher than average</li> </ul>

\* People suspected of having a hereditary cancer syndrome are not included in these risk categories. There are specific guidelines for individuals with a hereditary cancer syndrome.<sup>31</sup> † Previous 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. Recent data suggest that a similar level of risk occurs if the relatives with cancer are on opposite sides of the family;<sup>21</sup> therefore, this restriction has now been omitted. ♦

### 3 Colorectal cancer risk categories by detailed family history, including degree of relationship, number of diagnoses in relatives and the ages of diagnoses\*

Risk category by family history		Number of 1st degree relatives with CRC before age 55 years									
		0					1				
		0		1	2	3	0		1	2	0
Number of 2nd degree relatives with CRC before age 55 years		0	1	1	2	3	2	2	3	3	3
Number of 2nd degree relatives with CRC at age $\geq$ 55 years		1	1	1	2	3	2	3	3	3	3
0		2	1	2	3	3	3	3	3	3	3
1		3	2	2	3	3	3	3	3	3	3
2		4	2	3	3	3	3	3	3	3	3
0		0	1	2	3	3	2	3	3	3	3
1		1	2	3	3	3	3	3	3	3	3
2		2	3	3	3	3	3	3	3	3	3
0		0	2	3	3	3	3	3	3	3	3
1		1	3	3	3	3	3	3	3	3	3
CRC = colorectal cancer. * For example, a person with no first degree relatives with colorectal cancer and two second degree relatives with colorectal cancer diagnosed at age $\geq$ 55 years fits the criteria for risk category 1. A person with one first degree relative and two second degree relatives with colorectal cancer diagnosed at age $\geq$ 55 years fits the criteria for risk category 2. ♦											

CRC = colorectal cancer. \* For example, a person with no first degree relatives with colorectal cancer and two second degree relatives with colorectal cancer diagnosed at age  $\geq$  55 years fits the criteria for risk category 1. A person with one first degree relative and two second degree relatives with colorectal cancer diagnosed at age  $\geq$  55 years fits the criteria for risk category 2. ♦

### Ten-year colorectal cancer risk based on age and family history

For the 90% of the population who have no first degree relative with colorectal cancer, their 10-year risk of colorectal cancer (for males and females combined) is 0.25% (1/400) at age 40 years, and 0.9% at age 50 years. This is about the same as the risk for a 45-year-old at a twofold risk due to their family history, a 40-year-old at a fourfold risk, or a 35-year-old at an eightfold risk. That is, having a family history results in a specific 10-year risk of colorectal cancer being reached at a younger age (Box 4).

### Screening strategies for people with a family history of colorectal cancer

The guidelines recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 October 2017 under section 14A of the *National Health and Medical Research Council Act 1992*. Screening recommendations are based on the risk categories (Box 2) and on evidence for screening effectiveness at reducing risk, early detection and reduction of colorectal cancer mortality.

### Overview of evidence

Guidance in this section is based on the 2005 edition of the guidelines,<sup>13</sup> the systematic reviews performed for the section above on colorectal cancer risk according to family history, selected subsequent articles and international guidelines and the consensus of the guidelines authors. The NHMRC constituted the panel of national experts in colorectal cancer prevention, detection and treatment

which reviewed these guidelines. The panel met in person on two occasions and corresponded by email during the review process. Before releasing the guidelines, there was a public consultation period, during which all relevant professional bodies were invited to comment. Details about the review process and public consultation have been described,<sup>34</sup> and the NHMRC levels of evidence are available in the online Appendix.

### Recommendations

#### Category 1: people at near average risk

**Screening recommendation:** Immunochemical FOBT (iFOBT) every 2 years from age 50 to 74 years. For individuals with one first degree relative with colorectal cancer, biennial iFOBT from age 45 years should be considered (Box 5) (grade C).

**Justification:** For this category, the yield of clinically significant lesions at screening colonoscopy is low.<sup>30,35-38</sup>

Three level II randomised controlled trials reported colorectal cancer-specific mortality in guaiac FOBT (gFOBT) screening trials.<sup>39-41</sup> These trials collectively reported that screening for faecal occult blood reduced overall colorectal cancer-specific mortality on the basis of intention to screen by 15–33%. The 2012 update from the Nottingham trial reported a colorectal cancer-specific mortality reduction of 13% at about 20-year follow-up.<sup>42</sup>

Many countries around the world, including Australia, New Zealand, Canada and a number of European countries, have established national population-based colorectal cancer screening programs that use either gFOBT or iFOBT for screening. The FOBT is the preferred screening modality in those countries, based on the available evidence, their experience with other cancer screening programs, cost-effectiveness and the characteristics of their health systems.

An advantage of the FOBT is that the test kit can be posted in the mail to the participant, with collection of tiny samples at home and return of these samples by mail, and it is highly cost-effective.<sup>43</sup> The analysis of many brands of iFOBT is automated and some allow quantitative analysis of haemoglobin. In contrast, flexible sigmoidoscopy and colonoscopy are invasive procedures, requiring a highly trained workforce and special facilities. There are particular concerns about its acceptability and feasibility in the Australian setting as well as its cost-effectiveness.<sup>44</sup>

#### Category 2: people at moderately increased risk

**Screening recommendation:** Biennial iFOBT from age 40 to 49 years. Colonoscopy every 5 years from age 50 to 74 years (Box 5) (grade C).

**Justification:** There have been no trials for colorectal cancer prevention for this risk category. For people in this category, their risk of

## 4 Ten-year absolute risks of colorectal cancer (%) based on age and family history

Number of first degree relatives with colorectal cancer	Multiplication of population risk due to family history (RR)	Age (years)				
		30	35	40	45	50
0	0.9	0.07%	0.12%	0.25%	0.5%	0.9%
1	2	0.15%	0.29%	0.59%	1.1%	1.9%
2	3-6	0.30%	0.60%	1.2%	2.2%	3.8%
3+	7-10	0.60%	1.2%	2.4%	4.8%	7.6%

RR = relative risk (the risk of colorectal cancer relative to the average risk in the population). Estimates are based on the assumption that the RR is the same for all age groups. The unshaded cells represent risks less than 1%. The blue cells represent risks from about 1% to 3%. The orange cells represent risks about 4% or higher.

Source for risks: Ten-year risks were calculated using annual colorectal cancer incidence rates for males and females combined for the year 2000 from the Australian Institute of Health and Welfare.<sup>32</sup> For relative risks, please see references 17,19,21,22-30,33 ◆

colorectal cancer is as high at age 40 years as that of the average population at age 50 years, which is about 1% (Box 4). Accordingly, a screening recommendation based on disease risk would justifiably consider biennial screening with iFOBT (the same recommendation as for risk category 1) from age 40 to 49 years, as appropriate.

By age 50 years, their risk is about 4% (3.8%), which is about four times the risk of the average population. In the context of population screening, based on the risk of adverse events for colonoscopy,<sup>45,46</sup> we would expect 0.75% of individuals undergoing the procedure to have a bleed or perforation, and 0.01% to die after two colonoscopies over a 10-year period. Therefore, the risk of colorectal cancer at age 50 years is five times the risk of an adverse event, and 40 times the risk of death from the procedure used to screen for it. There have been no studies conducted to determine the utility of beginning screening 10 years before the earliest diagnosis in the family, which was a recommendation in the 2005 guidelines and, therefore, it is not included in these guidelines.

### Category 3: people at high risk

**Screening recommendation:** Biennial iFOBT from age 35 to 44 years. Colonoscopy every 5 years from age 45 to 74 years (Box 5) (grade C).

**Justification:** There have been no trials for colorectal cancer prevention for this category of risk. The risk for some people with three (or more) relatives with colorectal cancer may be difficult to categorise, especially if all cases of colorectal cancer 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 extracolonic cancers associated with Lynch syndrome.<sup>47</sup> If there is uncertainty about their

mutation status, these patients should be referred to a family cancer clinic, where they can be assessed for Lynch and other genetic syndromes.

For people in this category, who are not known or suspected as having a genetic syndrome, their risk of colorectal cancer is as high at age 35 years as that of the average population at age 50 years. Accordingly, biennial iFOBT screening from age 35 years is appropriate. By age 45 years, their 10-year colorectal cancer risk ranges from about above 4%, which is sufficiently high to warrant screening by colonoscopy every 5 years.

### Summary and recommendations

Since 2005, when the previous guidelines were published, the National Bowel Cancer Screening Program has been implementing a phased roll-out. By 2019, it will offer all Australians aged 50–74 years free biennial iFOBT screening. The revised guidelines recommend that all people in category 1 avail themselves of this screening program, which will be sufficient given their risk of colorectal cancer.

These guidelines differ from the previous ones<sup>13</sup> in a number of ways. There have been some changes in the family history inclusion criteria for categories 1 and 2 (eg, having one first and one second degree relative diagnosed with colorectal cancer after the age of 55 years now meets category 1 criteria). The genetic syndromes have been removed from category 3 and, as a consequence, colonoscopy screening for category 3 is now every 5 years. For categories 2 and 3, screening is now recommended to begin with iFOBT before age 50 years and transitioning to colonoscopy at a later age. Given potential delays in transitioning to colonoscopy due to service availability,

## 5 Recommended screening by family history category and age

Number of first degree relatives with colorectal cancer	Age (years)						
	30–34	35–39	40–44	45–49	50–54	50–74	75+
Category 1: people at near average risk*	No screening	No screening	No screening	No screening	iFOBT every 2 years	iFOBT every 2 years	No screening
Category 2: people at moderately increased risk	No screening	No screening	iFOBT every 2 years	iFOBT every 2 years	Colonoscopy every 5 years	Colonoscopy every 5 years	No screening
Category 3: people at high risk	No screening	iFOBT every 2 years	iFOBT every 2 years	Colonoscopy every 5 years	Colonoscopy every 5 years	Colonoscopy every 5 years	No screening

iFOBT = immunochemical faecal occult blood test. \* For people with one first degree relative with colorectal cancer, biennial iFOBT from age 45 years should be considered. ◆

participation in the iFOBT screening offered by the National Bowel Cancer Screening should be recommended until colonoscopy can be arranged.

The optimal age to stop screening is not known. Health economic research is needed to determine whether the benefits of iFOBT screening or colonoscopy screening beyond age 74 years outweigh the inherent risks.

Only a small number of studies examined the performance of colorectal cancer screening before age 50 years. Guidance presented here is based on the few studies that provide sensitivity estimates for colorectal cancer for individuals aged under 50 years which are similar to sensitivity estimates for people aged 50 years and over.<sup>48,49</sup>

Health economic research within varying national cost contexts 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.

In summary, the 2017 guidelines<sup>2</sup> recommend screening modalities based on risk according to age and family history. iFOBT screening is recommended for the majority of Australians, with modest or no family history, from age 50 years. Depending on the strength of the family history, it is recommended to start iFOBT screening from age 35 or 45 years (ie, up to 15 years younger) before transitioning to colonoscopy after 10 years.

**Acknowledgements:** Mark Jenkins has a Research Fellowship from the NHMRC.

**Competing interests:** Albert Chetcuti and Laura Wuellner are employed by Cancer Council Australia to assist in the preparation of these guidelines – Cancer Council Australia received financial support from both Cancer Council Australia and the Australian Government Department of Health. Mark Jenkins, Jon Emery, Finlay Macrae and James St. John received travel support from Cancer Council Australia to attend meetings for development of the guidelines. Mark Jenkins, Jon Emery, Finlay Macrae and James St. John are members of the Clinical Advisory Group of the National Bowel Cancer Screening Program and received travel support and sitting fees.

**Provenance:** Not commissioned; externally peer reviewed. ■

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