

The alarming rise of early-onset colorectal cancer

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Background

Over the past 20 years of the Australian National Bowel Cancer Screening Program, there has been a reduction in Australia's overall rates of colorectal cancer. However, during this same period, there has been a steady rise in the incidence of early-onset colorectal cancer (EOCRC), presenting a new public health issue.

Objective

The aim of this study was to evaluate the literature regarding the rising incidence of EOCRC, highlight the importance of the recent reduction in screening age and document what might be done in a primary healthcare setting.

Discussion

The increasing incidence of EOCRC has been largely attributed to risk factors including a Western diet, obesity, tobacco use and alcohol intake, which contribute to microbiome dysgenesis and chronic inflammation from an early age. In response, the initial screening age for colorectal cancer was lowered to 45 years from July 2024 via an opt-in system; however, there is evidence to support a further reduction in screening age to 40 years.

COLORECTAL CANCER (CRC) is the fourth most common type of cancer and the second leading cause of death in Australia, with estimates of 15,367 diagnoses and 5307 deaths in Australia in 2023.¹ Over the past 20 years the incidence of CRC has started to trend down following the commencement of the National Bowel Cancer Screening Program (NBCSP), introduced in 2006, as demonstrated by the declining incidence since 2007 (Figure 1).²⁻⁶ Despite this, there has been a rising incidence of early-onset CRC (EOCRC) diagnosed in patients aged less than 50 years, as shown in Figure 2.

The increased incidence of EOCRC has previously been associated with a Western diet rich in processed meat, red meat, fast food and refined carbohydrates, as well as other factors, including obesity, smoking, increased alcohol intake and a sedentary lifestyle from a younger age.⁷ However, there is evidence that due to the aggressive and distal phenotypic characteristics of EOCRC, with its own distinct biology, further research is required to elucidate risk factors specific to EOCRC.⁸

The increasing incidence of EOCRC is a significant issue because this cohort is missed by the NBCSP. This results in younger patients being more likely to present with advanced disease, with one Australian study showing 81.9% of EOCRC being Stage III or IV.⁹

In response, the Australian screening guidelines have recently lowered the initial screening age in late 2023 to start at 45 years;¹⁰ however, there is evidence

for a further reduction and for biennial immunochemical faecal occult blood test (iFOBT) screening to start at age 40 years.^{11,12}

Aim

The aim of this study is to review the evidence for the increasing rates of EOCRC over the past 30 years, highlight the importance of the recent reduction in screening age and document what might be done in a primary healthcare setting.

The rise in young CRC

In Australia, there has been a rise in EOCRC over the past 30 years (Figure 1), with the percentage of EOCRC rising from 7.6% in 1992 to 11.1% in 2021.²⁻⁵ This trend is similarly demonstrated in the Bowel Cancer Outcome Registry (BCOR), which reports that there has been a gradual increase in the incidence of EOCRC, with the percentage of EOCRC peaking at 11.1% in 2021 (vs 5.8% in 2007).¹³ The majority of EOCRC consistently occurs between the ages of 40 and 49 years.²⁻⁵ Concerningly, the percentage of EOCRC cases occurring prior to age 40 years in Qld, NSW, Vic and Tas has been trending up, with 30% of EOCRC diagnosed prior to age 40 years in 1982–86 compared with 44% in 2017–21.²⁻⁵

Hereditary syndromes such as familial adenomatous polyposis, Lynch syndrome or other known germline mutations account for approximately 35% of EOCRC, compared with 10% of overall CRC.¹⁴ Despite younger

patients being more likely to develop CRC secondary to genetic mutation, there is no evidence of any increase in the prevalence of genetic conditions to account for the rise in EOCRC seen in the past 40 years.¹⁴ In Australia, individuals with a known or family history of a predisposing hereditary syndrome undergo early screening, which subsequently reduces the impact this group has on the rising incidence of EOCRC.

EOCRC has been documented to have different molecular properties than CRC that presents later in life, with a higher proportion of distal colonic or rectal tumours in EOCRC and aggressive variants associated with a poorer prognosis.⁸ Given this, there is still the potential for a rise in the prevalence of other, as yet to be documented, underlying germline mutations responsible for the rise in EOCRC. This has also prompted theories that EOCRC is, in fact, a separate cancer biology from that which is more commonly seen in the later stages of life.^{8,15} A diagnosis of EOCRC, especially in patients aged <35 years, should prompt referral for genetic screening to investigate for an underlying genetic predisposition.¹⁴

However, approximately 50% of cases of EOCRC have neither an attributable

genetic syndrome or familial predisposition to CRC and instead are sporadic in nature. This might be attributed to the dietary and lifestyle risk factors listed in Table 1.^{6,7,14-17} Increasing rates of EOCRC have been largely

ascribed to Western dietary changes over the past 40 years. This was demonstrated in South Korea, where there was a marked change in diet following the Korean War, with a significant increase in food, particularly

Table 1. Risk factors and protective factors for early onset colorectal cancer^{6,7,15-17}

Risk factors	Protective factors
• Diet – Processed meat – Red meat – High fat – Low-fibre diet – High glycaemic index/simple carbohydrate-rich food – Refined grains – High-sugar beverages • Alcohol • Tobacco • Sedentary lifestyle • Obesity – Specifically early life/adolescent obesity	• Diet – Whole grains – Fruits and vegetables – Folate-rich diet – Calcium – Dairy products – Vitamin D – Vitamin B6 – Magnesium intake – Fish – Garlic • Physical activity • Aspirin¹¹ – Guidelines recommend a low dose (100–300 mg/day) of aspirin for at least 2.5 years, commencing at age 50–70 years • Non-steroidal anti-inflammatory drugs

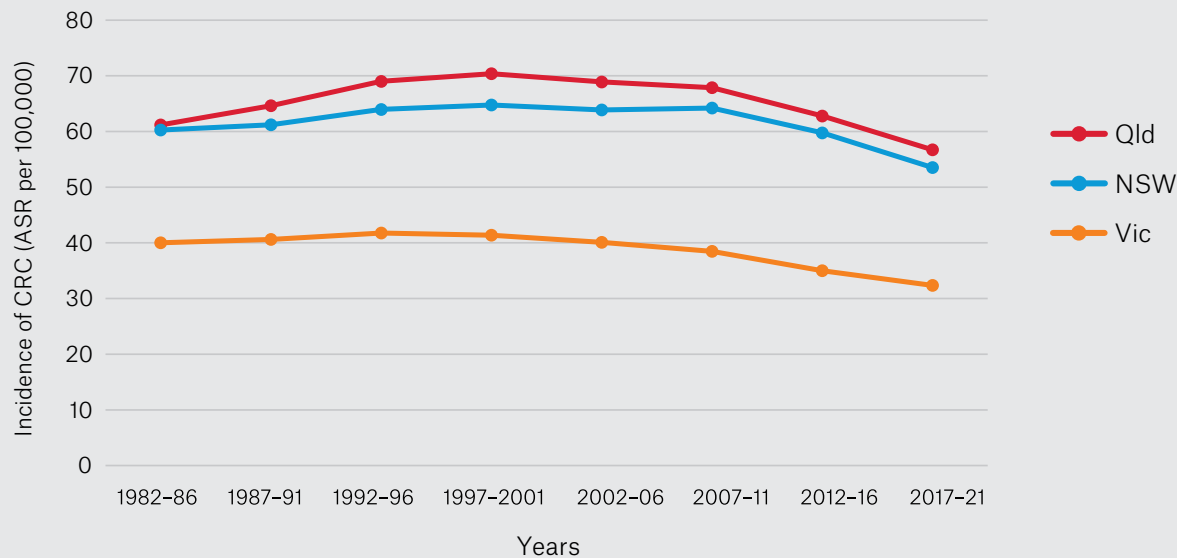


Figure 1. Incidence of colorectal cancer (CRC) from 1982 to 2021 in Queensland (Qld), New South Wales (NSW) and Victoria (Vic).²⁻⁴ ASR, age standardised rate.

processed wheat and meat products, being imported from the US.⁷ As a result, South Korea currently has one of the highest rates of EOCRC and overall rates of CRC in the world behind Australia and the US.⁸ This is in contrast with lower-income countries, including Chile, Uganda and India, who reported the lowest incidence of EOCRC during the same period.⁷ Unfortunately, with limited healthcare resources, under-reporting might occur in these countries.

An increasing obesity rate in countries such as Australia and the US is a risk factor that, particularly when present early in life, has been linked to the increasing incidence of EOCRC. A study by Ochs-Balcom et al in Utah in the US showed that being overweight or obese in addition to having two first-degree relatives with CRC was associated with a fourfold

increase in risk compared with the same family history and being in a healthy or underweight body mass index range, where the risk was double the risk of the average population.¹⁸

All the previously stated risk factors might increase the risk of bowel cancer through microbiome dysbiosis, a theorised process resulting in an altered balance of the bacteria that make up the microbiome. The result is an overgrowth of pathogenic bacteria paired with a reduction of protective bacteria that suppress the growth of pathogenic species.^{1,17,19,20}

This results in chronic inflammation of the colorectal epithelium secondary to the release of toxins and metabolic by-products such as acetaldehyde from pathogenic bacteria and increasing carcinogenesis.¹⁷ Other theorised risk factors for dysgenesis include the increasing use of antibiotics, altered

microbiome development with formula feeds for infants and operations, such as appendicectomies or cholecystectomies, which have been suggested to contribute to dysbiosis.¹⁹ Although there are links between these previously stated factors and alterations of the microbiome, there is no clear link to show how this might contribute to CRC. In addition, conditions such as inflammatory bowel disease contribute to the degree of dysbiosis and inflammation, significantly increasing carcinogenesis.¹⁷ Conversely, the protective factors in Table 1 have been associated with an increase in lower rates of CRC and are associated with an alteration in the gastrointestinal microbiome.^{17,21}

Although these risk factors are also present in the older population, it is believed that the increasing prevalence of these risk factors

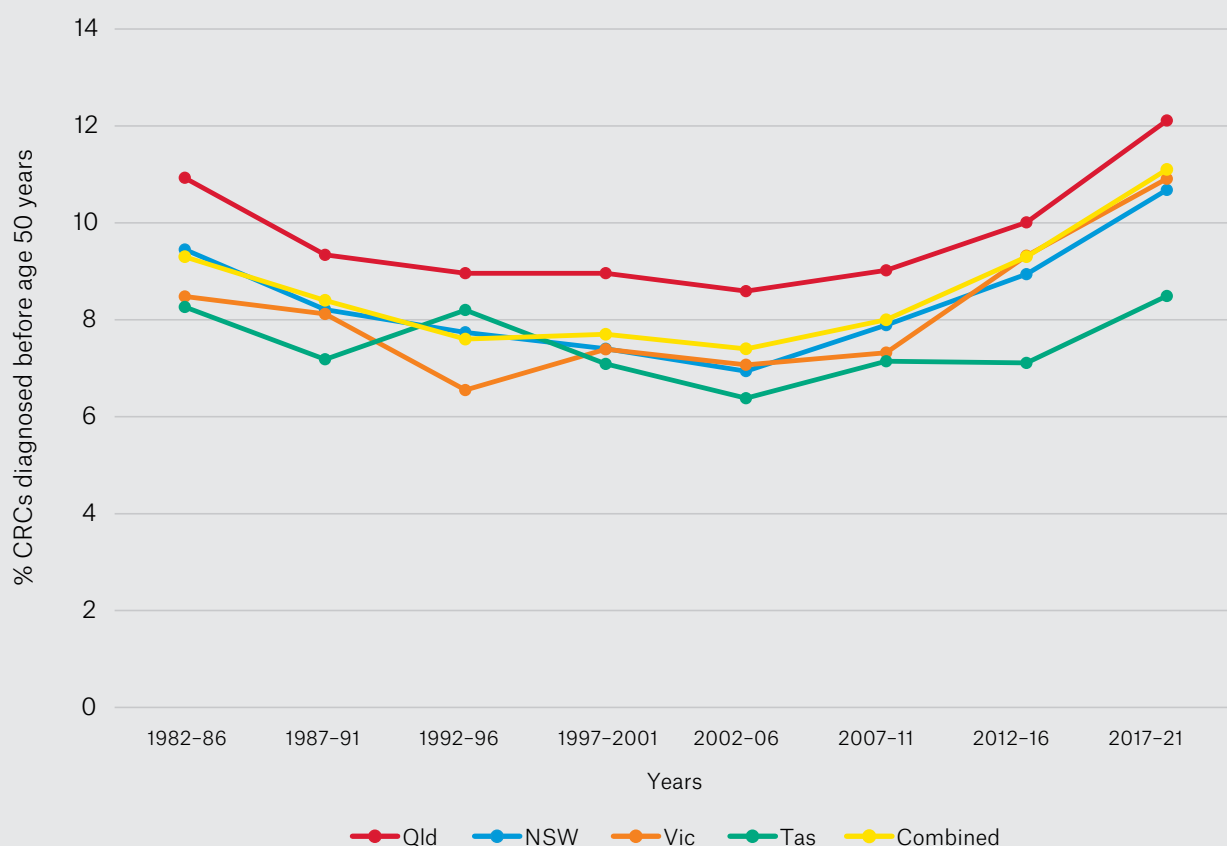


Figure 2. Proportion of colorectal cancers (CRC) diagnosed prior to 50 years of age between 1980 and 2021 as a percentage of total CRC diagnoses in Queensland (Qld), New South Wales (NSW), Victoria (Vic) and Tasmania (Tas).²⁻⁴

See Appendices 1-5 (available online only) for data used. Other states have been excluded due to lack of public access to cancer registries.

from a young age is a factor driving EO CRC.²⁰ Further research is needed to understand and support these theories and to quantify the burden of different risk factors towards the development of EO CRC.

Australian NBSCP

The decreasing incidence of CRC in Australia is largely attributed to the NBCSP, which, via iFOBT, promotes the early detection and management of precancerous lesions.⁶ Table 2 provides a summary of the Australian CRC screening guidelines as of November 2023, including the reduction of iFOBT screening age to 45 years. However, at this stage, iFOBT screening kits are only issued via online request or telephone (1800 627 701) for people aged 45–49 years from July 2024. This, combined with patient attitudes that CRC typically affects the older population, is likely to result in poor uptake.²²

The guidelines now also provide the option for practitioners to refer patients without symptoms of CRC for two-yearly iFOBT

from the age of 40 years via a Medicare-subsidised referral. However, the results of these tests are not centrally stored as a part of the NBCSP.¹⁰ Therefore, this system places the onus on the individual practitioner to have the conversation early with patients to discuss the benefits and risks of early screening and to encourage patients to participate in iFOBT screening from the age of 40 years. This includes discussing potential psychological and physical harms associated with screening, particularly the risks associated with colonoscopy following a positive iFOBT.¹⁰ This is significant when starting screening from age 40 years due to the increased risk of lifetime colonoscopy adverse events.¹⁰

Screening kits might be accessed by patients and general practitioners using the link below or via the in-built link in general practice software: www.health.gov.au/our-work/national-bowel-cancer-screening-program/about-the-national-bowel-cancer-screening-program/lowered-eligible-age.

Should the screening age be reduced to 40 years?

The latest release of the NBCSP addresses the decision not to reduce the screening age to 40 years due to the increase in lifetime colonoscopy-related adverse events outweighing the benefits, including reductions in incidence and mortality rates.¹¹ Specifically, it has been estimated that by lowering the screening age to start at 40 or 45 years, there would be a 1–19% increase in lifetime colonoscopy-related adverse events compared to the previous guidelines, which recommended screening people aged 50–74 years. The reduction in CRC incidence, however, favoured starting at age 40 years with a predicted reduction in incidence of 5–8% compared to 3–5% when screening from 45 years (based on 40–60% participation).¹¹ The latest guidelines acknowledge the screening down to age 40 years was a cost-effective strategy.¹¹

The benefits of screening down to age 40 years were also demonstrated by modelling conducted using Canada’s population, which

Table 2. Australian Bowel Cancer Screening guideline based on family history summary²⁴

	Average risk	Above-average risk (less than double)	High risk (risk between 2- and 4-fold higher than average)	Very high risk (risk between 2- and 20-fold higher than average)
Criteria	No first- or second-degree family history of CRC	One first-degree relative diagnosed with CRC at age 60 years or older	One first-degree relative diagnosed before the age of 60 years OR Two first-degree relatives diagnosed at any age OR One first-degree relative and one or more second-degree relatives diagnosed at any age	Two first-degree relatives AND one second-degree relative with CRC, with at least one diagnosed before the age of 50 years OR Three or more first-degree relatives diagnosed at any age OR Two first-degree relatives AND two or more second-degree relatives diagnosed at any age
Screening tool	Population screening cohort - Age 45–74 years: Biennial iFOBT home screening test (screening kits for those aged 45–49 years must be requested online) - Age 40–44 years: Biennial iFOBT provided via a Medicare-subsidised referral following discussion of benefits and risks (screening outcome not stored centrally by the NBCSP)		Colonoscopy should be offered every 5 years starting at 10 years younger than the earliest age of diagnosis of CRC in a first-degree relative or at age 50 years, whichever is earlier, to age 74 years	Colonoscopy should be offered every 5 years starting at 10 years younger than the earliest age of diagnosis of CRC in a first-degree relative or at age 40 years, whichever is earlier, to age 74 years Recommend referral for genetic testing of underlying risk factors

Exclusion criteria: symptomatic OR previously confirmed gene associated with a high-risk familial syndrome OR family history of familial adenomatous polyposis OR first- or second-degree relative diagnosed with Lynch syndrome and one family member diagnosed with CRC prior to age 50 years OR single first-degree relative diagnosed with multiple CRCs.

CRC, colorectal cancer; iFOBT, immunochemical faecal occult blood test; NBCSP, National Bowel Cancer Screening Program.

showed an improvement in quality-adjusted life-years, CRC incidence, mortality and an overall reduction in healthcare costs when screening from the age of 40 years compared with starting at 45 and 50 years.¹² Specifically, based on the Canadian population in 1973–92, screening from age 45 years would result in 12,188 fewer cases of CRC and 5261 fewer CRC deaths at an additional cost of \$298 million CAD but a saving for overall CRC management of \$719 million CAD.¹³ In comparison, screening from 40 years would result in 18,135 fewer cases of CRC and 7988 fewer CRC deaths at an additional cost of \$649 million CAD and a saving for overall CRC management of \$1.1 billion CAD.¹³

Interestingly, Austria is one of the few countries that currently commences screening with faecal-based screening at age 40 years, and is one of the few Western countries that does not have a rising incidence of EOCRC.^{7,23}

EOCRC and primary healthcare

Currently, the iFOBT participation rate is 40.9%, which is an area for improvement.²⁴ It is important to be encouraging all patients to participate in the NBCSCP from the age of 45 years and hopefully increase overall participation and maximise the benefits of the program. A barrier to this is that the current system requires patients to order iFOBT kits online. To help overcome this, general practices can order iFOBT kits in bulk to provide to their patients. In addition to this, significant benefit might be gained by offering screening to patients from the age of 40 years after they have been made aware of the benefits and harms of screening. An important development in this area would be the inclusion of a reminder or prompt in general practice software to remind clinicians to discuss CRC screening with patients from the age 40 years and to encourage participation in the NBCSCP.

Considering the evidence that EOCRC is a biologically distinct variant, modifiable risk factors, present from an early age, should be targeted in an attempt to reduce its incidence. It is therefore important as a public health measure to raise awareness of the modifiable risk factors and protective factors shown in Table 1 from a young age.²⁰

Primary prevention in this area warrants further public health campaigns to increase awareness that CRC is a disease that also affects young people. Bowel Cancer Australia launched a campaign in May 2024 titled 'Australia's deadliest cancer for people aged 25–44', highlighting some individuals' encounters with EOCRC and the lifelong effects, such as young people living with stomas (which is more likely in distal colonic and rectal cancers).²⁵

Approximately 75% of people diagnosed with CRC initially present with symptoms that require investigation, with younger patients being even more likely to present symptomatic.^{26,27} High clinical suspicion is key in the context of EOCRC to take steps to reduce the rates of Stage III/IV diagnosis. EOCRC presents with the same set of symptoms as CRC, including rectal bleeding, abdominal pain, altered bowel habits, low-calibre stool, unintentional weight loss and iron deficiency anaemia.¹⁶ The main clinical difference found in EOCRC is the increased proportion of distal or rectal malignancy.⁷ Therefore, clinicians must have suspicion of obstructive symptoms, rectal pain, tenesmus and altered stool calibre that should trigger prompt further investigation. A list of screening tools and investigations to consider is presented in Table 3, as well as novel DNA-based tests that are currently undergoing clinical trials for the continued improvement in CRC screening and investigation.²⁸

Currently, guidelines recommend consideration of low-dose aspirin chemoprophylaxis from the age of 50 years for patients with no significant family history for at least 2.5 years if no contraindications are present.¹¹ High-risk patients should start low-dose aspirin when they reach colonoscopy screening age.¹¹

Conclusion

Despite the success of Australia's NBCSP achieving an overall reduction in the rates of CRC, the rise of EOCRC has presented a challenge over the past 30 years. Pressingly, this cohort of patients has, until recently, largely missed out on population screening and, combined with evidence that EOCRC is a biologically unique disease, they are more likely to present with advanced disease,

which carries a worse prognosis. In response, the screening age has been lowered to 45 years, but at this stage screening is only available upon request. There is, however, evidence to support a further reduction in screening age to start at 40 years. A multimodal approach is required to raise awareness of the rising incidence in EOCRC, the modifiable risk factors for developing EOCRC and the importance of participating in screening.

Key points

- Over the past 20 years, there has been a steady rise in the incidence of EOCRC in Australia.
- There is evidence that EOCRC is a biologically distinct form of CRC.
- The increasing incidence of EOCRC is attributed to a Western diet and microbiome dysgenesis.
- The Australian Government responded in 2023 by lowering the screening age for CRC to 45 years.
- New guidelines also allow for early referral for CRC screening in patients down to the age of 40 years.

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Table 3. Screening tests and further investigations

Test/investigation	Indication	Benefits	Risks/drawbacks	Efficacy
Guaiac faecal occult blood test (gFOBT) ²⁹	• Predecessor to iFOBT • No longer used in Australia	• Cheap • Non-invasive • Home test	• Requires multiple samples • Risk of false positives due to factors such as consumption of red meat	Colorectal cancer: • Sensitivity: 25–55% • Specificity: 91–96% Precancerous lesions: • Sensitivity: 12–20% • Specificity: 92–96%
Immunochemical faecal occult blood test (iFOBT) ²⁹	• Biennial screening from age 45 years (or 40 years with private referral) in asymptomatic patients (ie absence of frank bleeding)	• Cheap • Non-invasive • Home test	• Need for prompt colonoscopy following positive test • More expensive than gFOBT	Colorectal cancer: • Sensitivity: 57–88% • Specificity: 91–98% Precancerous lesions: • Sensitivity: 27–40% • Specificity: 90–98%
Full blood count plus iron studies	• Iron deficient anaemia raises clinical suspicion	• Perioperative optimisation	• Negative result does not exclude CRC • Further investigation required with colonoscopy	Not applicable
Carcinoembryonic antigen ³⁰	• Not indicated for screening or diagnosis	• Surveillance for recurrence following surgical resection	• High rates of false positives and false negatives	Detection of CRC in asymptomatic patients: • Sensitivity: 36% • Specificity: 87%
CT scans ³¹	• Typically indicated for staging or other clinical concern suggestive of a symptomatic lesion (eg obstruction, perforation)	• Non-invasive • Minimal risk • Relatively cheap and accessible	• Poor ability to assess intraluminal lesions • No application in screening and prevention of precancerous lesions	• CRC detection sensitivity: 72% • Detection of polyps >10 mm sensitivity: 14.5%
Flexible sigmoidoscopy ³²	• Not used for screening in Australia due to low cost–benefit ratio • Commonly used in the US for screening	• Examination of distal colon • Limited bowel preparation • Faster examination • Ability to remove precancerous polyps in distal bowel	• Need subsequent colonoscopy if polyps detected • Invasive • Patient discomfort • High cost and requirement for skilled team, equipment and facility	Screening for precancerous lesions: • Sensitivity: 58–75%
Colonoscopy ³³	• Positive iFOBT • Family history • Symptomatic patient • Iron deficiency anaemia • Gold standard for investigation and prevention	• Examination of entire colon • Removal of polyps	• Bowel preparation • Risk of perforation • Broad range of sensitivity and specificity due to operator variation	• Sensitivity for adenomas >6 mm: 73–98% • Specificity: 89–91%
CT or MR colonography ³⁴	• Incomplete colonoscopy or colonoscopy contraindicated	• Less invasive • Minimal risks	• No ability to manage precancerous lesions, biopsy or tattoo lesions • Still requires bowel preparation • Limited availability in some areas	Detection of adenomas >6 mm or CRC: • Sensitivity: 88–92% • Specificity: 52–91%

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Table 3. Screening tests and further investigations (cont'd)

Test/investigation	Indication	Benefits	Risks/drawbacks	Efficacy
Pill Cam or capsule endoscopy ³⁵	Less evidence and uncertain indication for screening of large bowel pathology	Non-invasive	- No ability to manage precancerous lesions - Still requires bowel preparation	Detection of CRC: - Sensitivity: 79–89% - Specificity: 64–97%
Next-generation multitarget stool DNA test ³⁵ (not yet available)	Potential next step for CRC screening	Better sensitivity without any reduction in specificity compared with iFOBT	- Limited to no availability in Australia - Expensive novel test	Colorectal cancer: - Sensitivity: 94% - Specificity: 91% Precancerous lesions: - Sensitivity: 43% - Specificity: 93%
Faecal-based microbe detection ³⁵ (not yet available)	- Opportunity to be future screening tool - Detection of high-risk bacteria in the microbiome	Potential option to be used alongside other screening tools for risk stratification	- Poor availability - Expensive novel test	Early studies investigating detection of precancerous lesions: - Sensitivity: 71% - Specificity: 76%
Serum tumour DNA testing ³⁵ (not yet available)	- Multiple tests in clinical development/trial phase - Blood tests for surveillance of CRC-specific biomarkers	Future screening option	Not available	Limited data

CRC, colorectal cancer; CT, computed tomography; MR, magnetic resonance.

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