Screening for bowel cancer

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The incidence of bowel (colorectal) cancer in Australia is high by world standards but death rates are comparatively low.[1] Some 12,000 new cases were diagnosed in 2000 and the lifetime risk of developing bowel cancer is one in 17 men and 1 in 26 women, making it the most common internal cancer.[1] Although it is the second leading cause of cancer death (after lung cancer) in Australia,[1] it is estimated that around a third of bowel cancer deaths could be avoided by population screening.

This article addresses screening for bowel cancer in the asymptomatic population, a process in which GPs have an important role. For people presenting with symptoms, diagnostic strategies are different, with primary reliance being placed on colonoscopy, particularly when symptoms present over the age of 40 to 45 years. Faecal occult blood (FOB) testing should not be used in the work-up of the symptomatic patient, especially if the history includes rectal bleeding.

Bowel Cancer Screening Pilot Program

The Federal Government has signalled a commitment to screening the Australian population for bowel cancer through the implementation of the Bowel Cancer Screening Pilot Program, which is designed to assess the feasibility, acceptability and cost effectiveness of nationwide screening for bowel cancer.[2] The program follows indisputable level 1 evidence (meta-analysis of randomised controlled trials) of reduction in mortality from bowel cancer through the simple measure of testing stool for occult blood followed, when positive, by colonoscopy with polypectomy when approriate and surgical management of detected cancers (Figures 1 and 2). It is the first such screening program managed for Australians at a federal level and in close cooperation with the States and Territories. Much maligned for its imperfect sensitivity and specificity and doubts about whether it will be adopted by Australians, the FOB testing approach

IN SUMMARY

- **Offering screening for bowel cancer to Australians over the age of 50 years at average risk is now of great importance, given the level 1 evidence of mortality reduction using faecal occult blood testing followed by appropriate management of detected cancers and adenomatous polyps.**
- **Logistics remain difficult, but possible on a user pays basis.**
- **A family history of bowel cancer is an important risk factor: ask about the family.**
- **Gene testing is available for appropriate families, and familial bowel cancer clinics are now established nationwide (contact the Cancer Helpline, telephone 13 11 20).**
- **Colonoscopy should be used judiciously in screening patients considered to be at moderate or high risk on the basis of their family history.**
- **Screening colonoscopy is not recommended for patients with only a single first degree relative over 55 years of age at diagnosis.**

has been successful in Europe and USA. Despite its limitations, the number of lives saved by this approach will be greater than those saved through the more established cancer screening programs (cervical cancer programs, for example), and with very comparable cost effectiveness. This is because bowel cancer is so common in Australia.

Many GPs will already be familiar with the pilot program, which commenced in late 2002 and early 2003 in south and west Adelaide, north-east Melbourne and Mackay, Queensland. In these regions, all people aged 55 to 74 years are being invited to participate. It is hoped the program will identify the logistic bottlenecks, resource issues and acceptability of participation in FOB testing.

GPs are pivotal to the success of the program, because the target population – who are approached directly from the national screening registry – are advised to see their doctor if the test is positive, they declare symptoms or they have a family history indicating risk for bowel cancer. In these cases, colonoscopy is the recommended follow up, to be arranged by the patient's GP.

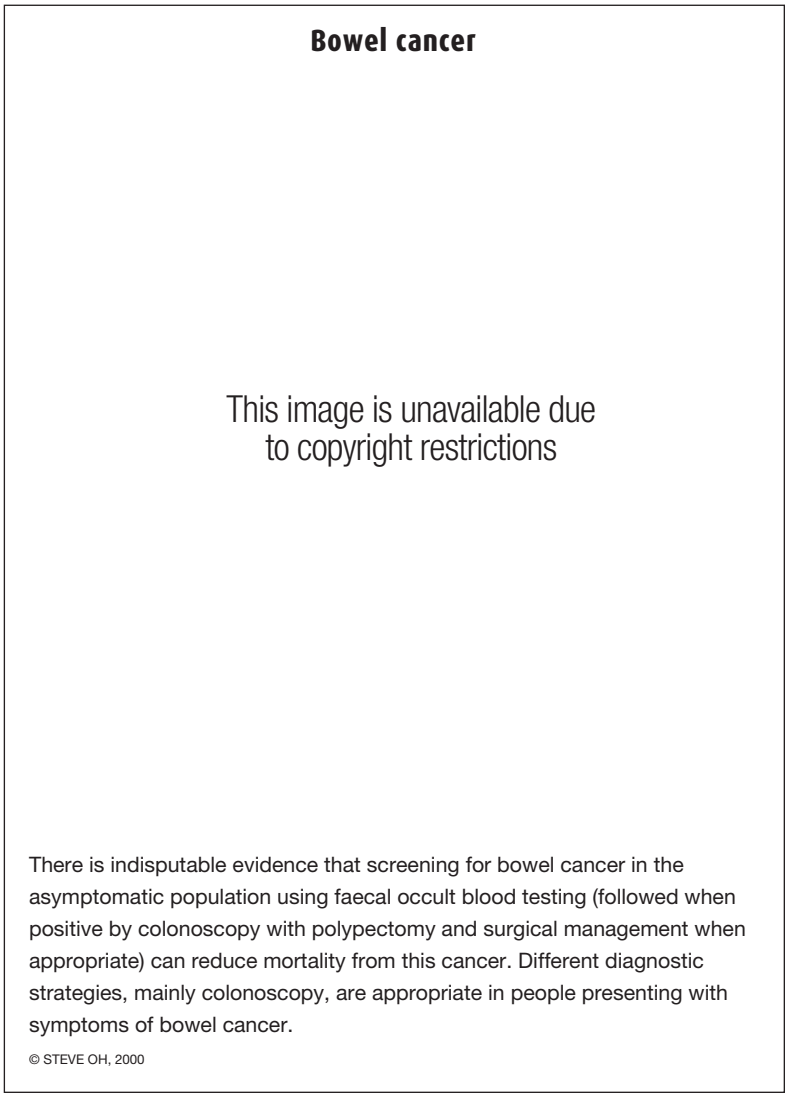
The quality of the colonoscopy service is an important part of the program. Colonoscopies are not without risk, and the program could be severely jeopardised if adverse events occur at this stage. To minimise this, GPs should ensure their preferred colonoscopy provider practises through a State or Territory licensed centre, and has his or her training recognised by the Conjoint Committee of the RACS, RACP and Gastroenterological Society of Australia, or is of equivalent standard judged independently (see the box on page 18). The risk–benefit ratio needs to be an order of magnitude safer when invasive modalities are applied to screening well-people, most of whom will not have a cancer.

The pilot program will not be completed until late in 2005, and results will be presented in terms of staged cancer diagnoses and adenomas removed. Participation rates in the separate regions are being closely monitored, and already site-specific variation is apparent, from which lessons will be learned.

FOB testing outside the pilot program

What should GPs do outside the pilot programs? This is a contentious issue that has been troubling State and Territory cancer councils. The time to advise and act seems to be well overdue. Over 4400 Australians die from bowel cancer each year, and up to 1000 of these could be saved by FOB screening, even if there is only 50% participation. In the view of many, there is an ethical imperative to act for the benefit of all Australians, not just those in the pilot regions. However, access to quality controlled (clinically tested) FOB tests is restricted because the Medicare rebate only applies for symptomatic patients, notably those with iron deficiency anaemia. This item is long outmoded in common clinical practice even in this situation, and the requirement for both guaiac and immunochemical testing is quite inappropriate in screening.

Bowel cancer



There is indisputable evidence that screening for bowel cancer in the asymptomatic population using faecal occult blood testing (followed when positive by colonoscopy with polypectomy and surgical management when appropriate) can reduce mortality from this cancer. Different diagnostic strategies, mainly colonoscopy, are appropriate in people presenting with symptoms of bowel cancer.

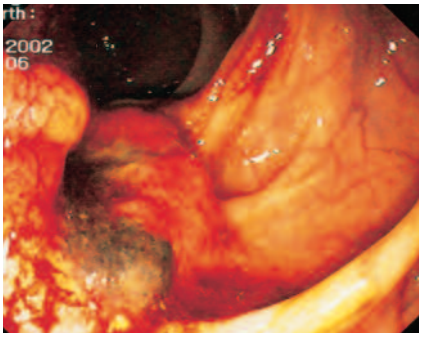


Figure 1. Invasive colorectal cancer as seen at colonoscopy.

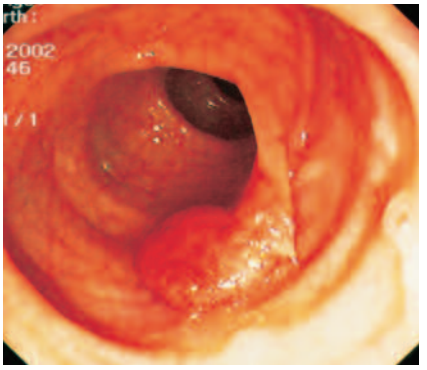


Figure 2. Stalked polyps in colon.

A guaiac test (e.g. Hemoccult) requires testing on three separate bowel motion samples and also dietary restriction of red meat and certain fresh vegetables to avoid false positive results from the myoglobin and other peroxidase activity present when these foods are taken in generous portions. Immunochemical tests (e.g. !nform and Magstream Hem-Sp), however, have been shown to give good results on a two-test strategy and do not require dietary restrictions. In addition, collection techniques have improved; for example, the !nform test uses a brush technique with minimal faecal contact, and the Magstream Hem-Sp test uses a technique that dips a device into the faecal sample and also has minimal stool contact.

For average risk people, FOB testing should be done annually from the age of 50 years. A program of screening is important, not just a one-off test, and annual screening is more effective and leads to greater mortality reduction than biennial testing.

The !nform and Magstream Hem-Sp tests were selected in the Commonwealth's tender process for the pilot program. Almost all the other commercially available immunochemical tests have not been tested for their sensitivity and specificity for detection of adenomas or cancers in symptomatic or asymptomatic populations. Indeed, many have bad or unknown performance characteristics in clinical use in bowel cancer screening although they may appear satisfactory *in vitro*.

Accessing a reliable test can be difficult. One test that can be accessed anywhere in Australia is the !nform test (telephone 1800 556575). Office based testing with the three stool sample Hemoccult kit is acceptable, but experience in interpreting the test card is necessary. We await the marketing of alternative tests with proven performance characteristics and equivalent convenience.

Although Medicare does not cover FOB testing in asymptomatic populations outside the pilot program, its provision is important to enable an option for bowel cancer mortality reduction for Australians choosing to protect themselves in this way.

Selecting a colonoscopy provider

- Is the centre accredited by the Australian Council of Health Care Standards or its equivalent?
- Do the colonoscopists have their training recognised by the Conjoint Committee of the RACS, RACP and Gastroenterological Society of Australia?
- Is there proof of processing for the disinfection practices used in the centre?
- Do the centre and its colonoscopists have data on complication and miss rates?
- What are the average withdrawal times practised by the colonoscopists (it has been shown that quick withdrawal is associated with missing lesions)?
- Are there adequate processes for handling consent, anticoagulated patients, those on aspirin and those with heart prostheses?

All of the above have been included as quality assurance indicators in the national Bowel Cancer Screening Pilot Program; they are just as relevant outside that program.

Other bowel cancer screening options

There are, of course, other technologies that can be applied to bowel cancer screening. The US Agency for Health Care Policy recommends offering screening options and encourages physicians and patients to decide together which is the best approach for them, based on an informed discussion about the advantages and disadvantages of each approach.

Flexible sigmoidoscopy

Flexible sigmoidoscopy is one option. The flexible sigmoidoscope covers the regions of the bowel where 70% of cancers occur (the rectum and distal colon) but cannot reach the more proximal colon. No sedation is required and an enema on the day is all the preparation needed. The UK is investing in flexible sigmoidoscopy as a bowel cancer screen, with prospective trials in progress to test efficacy and feasibility. We know now that people presenting with bowel cancer are half as likely to have had a flexible sigmoidoscopy in the previous 10 years than a control group without cancer, suggesting a protection that extends for this length of time. Current Australian (NHMRC) and US guidelines recommend consideration of flexible sigmoidoscopy every five years.[3]

Colonoscopy

Colonoscopy is the most accurate examination of the bowel, and many physicians consider it should be an option. Indeed, it is covered under US Medicare reimbursement as a screen in average risk individuals. Cost–benefit analyses indicate it is a competitive option on a 10-yearly basis. However, there are no randomised controlled trials of screening with colonoscopy and, therefore, no empirical evidence of benefit over cost. Some case–control studies do show reduction of bowel cancer risk with colonoscopy, in much the same way as with flexible sigmoidoscopy. The cost of colonoscopy includes complications – typically quoted as a one in 500 chance of postpolypectomy haemorrhage requiring transfusion, and a one in 1500 chance of perforation. The ultimate analysis is dependent on randomised prospective trials in average risk populations, but these have not yet been done. Other quality control issues concerning colonoscopy have been discussed earlier (see box on page 18).

Double contrast barium enema is included in this discussion only to dismiss it in the context of screening. It is now outmoded, carries a radiation risk and has inferior sensitivity and specificity.

Virtual colonoscopy

Virtual colonoscopy (or CT colonography) is rapidly emerging as another option. The cost of virtual colonoscopy is already less than that of conventional colonoscopy, and the technique is undoubtedly safer due to its noninvasive nature. Infection risks and disinfection costs are eliminated but radiation exposure must be considered, which at 4 to 5 mSv is not trivial in the screening setting. The risk of dying from exposure to this amount of radiation is equivalent to the risks of travelling 200,000 km by air or 20,000 km by car, or smoking five to 10 packets of cigarettes in a lifetime. In Perth, virtual colonoscopy has been tested for average risk screening in people randomly selected from the electoral roll, with encouraging participation and acceptance.

The technology is improving quickly, but already has excellent sensitivity for polyps over 9 mm in diameter and good sensitivity for polyps 5 to 9 mm in diameter, which is far better than FOB testing. MRI colonography is on the horizon and promises equivalent accuracy without radiation exposure. Costs will decrease with technological development and greater availability.

Approach to screening

A practical approach to screening for bowel cancer is given in the flow chart on page 20. Patients recognised as being at above average risk should be offered tailored surveillance. Risk factors are a personal history of bowel cancer or adenomas, or inflammatory bowel disease (not considered here), or a family history of bowel cancer or adenomas.

High risk patients

The patients at highest risk group are those in families with familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer syndrome (HNPCC). FAP is characterised by many (hundreds to thousands) of adenomatous polyps, and hence is easy to recognise. Cancer development is inevitable if colectomy is not performed. Management is straightforward, but should include a multidisciplinary approach with mutational analysis of the APC gene in an affected family member, experienced genetic counselling for predictive testing in as yet unaffected family members, expert surveillance including sideviewing duodenoscopy, and surgical expertise including ileo-anal pouch reconstruction where appropriate.

HNPCC is more difficult to detect and depends on the family history. A golden rule in prevention of bowel cancer is, 'Ask about the family'. HNPCC is defined on pedigree grounds by the 3, 2, 1 rule: three first degree relatives affected over two generations, with one under age 50 years. Such a family history should prompt a referral to a familial cancer clinic (telephone the Cancer Helpline, 13 11 20, for contact details) to investigate the possibility of a germline mutation in one of the mismatch repair genes (MMR; mutations in these genes are responsible for the condition). Once a MMR gene mutation is identified in an affected family member, other family members in the extended pedigree can be offered predictive testing to see if they too carry the family-specific mutation. If they do, intensive surveillance is in order – annual colonoscopy and gynaecological screening to allow early detection and treatment, targeting particularly their 80% risk of bowel cancer and 40 to 60% risk of endometrial or ovarian cancer.

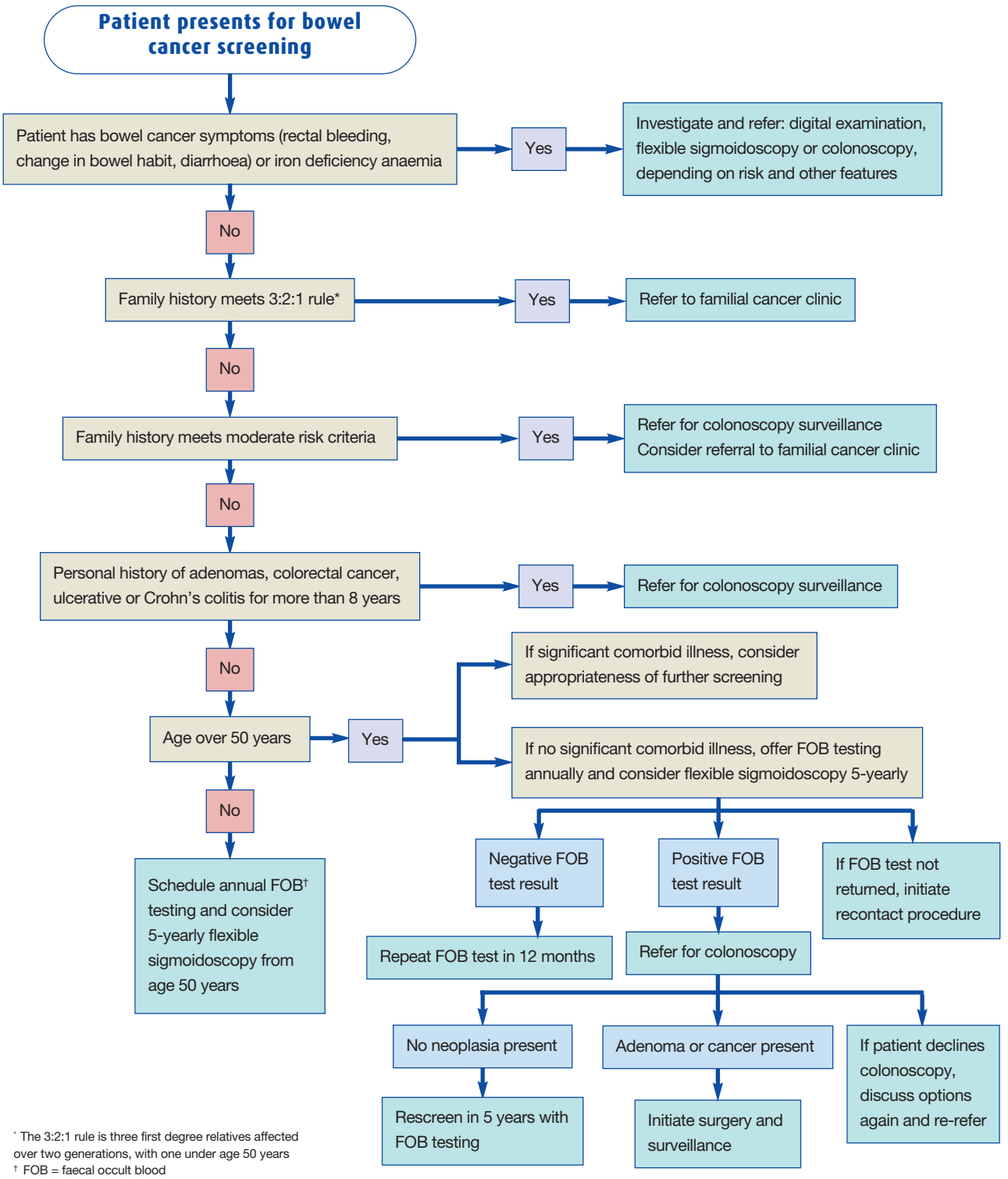
Cancers develop at a young age in these families as they are primed from birth with one faulty allele of their vital mismatch repair machinery. Surveillance should start at 25 years of age or five years younger than the youngest affected person in the family. If a family member does not carry the family mutation then surveillance can be relaxed to that appropriate for average risk, which is an enormous benefit for the individual and the healthcare system. Multidisciplinary referral is also needed, including to a familial bowel cancer clinic.

Moderate risk patients

Less dense family histories also need colonoscopy screening, though less frequently. A first degree relative diagnosed under the age of 55 years (the US guidelines make this 60 years) defines a risk four to six times the average, and colonoscopy should be offered five-yearly. However, if the single affected first degree relative is over 55 years at diagnosis, then NHMRC guidelines suggest reversion to average risk screening as the relative risk is only just above average (about 1.8).[3] This recommendation is controversial in some circles in Australia, but is upheld by all State and Territory cancer councils.

continued

Screening for bowel cancer – a practical approach



* The 3:2:1 rule is three first degree relatives affected over two generations, with one under age 50 years

† FOB = faecal occult blood

If there are two first degree relatives or one first degree and one second degree relative on the same side of the family diagnosed at any age, then colonoscopy every five years is recommended. In any instance, the starting age for colonoscopy screening in moderate risk patients is 50 years (40 in the US guidelines) or 10 years less than the earliest age of onset in the family, as empirical evidence from relatives under 50 years outside these recommendations reveals a low adenoma yield.

These families should also be considered for referral to a familial cancer clinic. Pre-genetic tests such as microsatellite instability testing (microsatellite instability is the molecular hallmark of an MMR gene mutation) are done through these clinics on archived tumours seeking evidence of a MMR mutation, thereby potentially raising the family into the high risk group. A more common strategy nowadays is to test tumours for lack of expression of each of the MMR genes by immunohistochemistry. This not only indicates MMR deficiency (as does microsatellite instability testing) but also signals which particular MMR gene is mutated.

In the case of a relative being diagnosed with an adenoma (no cancer), the advice to first degree relatives is also controversial. Case–control studies indicate the risk to the relatives is much the same as if the index case had cancer. However, there are many fewer of these epidemiological studies than studies of relatives of cancer patients, and so we are less certain of the risks. The US Guidelines recommend screening relatives of patients with adenomas if diagnosed under 60 years; that is, they do not differentiate whether the single affected relative in the family has an adenoma or a cancer. Australian guidelines do not recommend screening relatives of patients with adenomas and no cancer. It should be remembered that 40 to 60% of men aged over 50 years have adenomas in the bowel at autopsy.

Patients with a personal history

The recommended intensity of screening in patients with a personal history of adenoma or cancer is now being reduced in guidelines worldwide. A randomised controlled trial has shown no benefit from annual compared with three-yearly colonoscopy in adenoma follow up. Therefore, unless there is doubt about the adequacy of removal at the initial colonoscopy (which should be uncommon in competent hands), there is rarely any justification for follow up colonoscopy any more frequently than three-yearly. Where there are only small tubular adenomas in the distal colon, the risk is not above average, and guidelines for follow up are stretched to five-yearly or more. This is quite a large group of patients in the total burden of adenoma patients. Patients with common hyperplastic polyps (unless multiple and large) are at no increased risk and do not need any follow up.

The place of colonoscopy in the follow up of cancer patients is also limited. There is slender evidence of benefit from colonoscopy in the detection of operable recurrences, and surveillance of metachronous (subsequent second primary) cancers is recommended in current guidelines only every three years.

Conclusion

In practice, what can be done for Australians? If your practice happens to fall in the pilot program territory, then it is important to facilitate the program and act on a positive result. Outside the pilot program, there is no Medicare reimbursement for average risk screening and yet there are strong reasons to offer screening. The !nform test is the only adequately tested facility currently offering a complete and accessible FOB testing service, although the Hemoccult test is acceptable if done in the surgery.

Colonoscopy definitely has a role in screening moderate and higher risk patients. An important message is to ask about the family history of bowel cancer to define the population in need of colonoscopy. Colonoscopy services are readily available, but their quality should be questioned by the referring GP. Medicare rebates are available for surveillance colonoscopy of above average risk patients and for those at average risk found to have a positive FOB test result since the latter raises the chance of bowel cancer some 40-fold. An important discriminator of risk is the age of onset of cancer in the affected relative – under 55 years affords a risk warranting colonoscopy whereas a single affected relative over 55 years does not, according to the current Australian guidelines.

Many Australians are touched by bowel cancer in their lives and are asking their GPs what they can do to protect themselves from the disease. It is, after all, Australia's second leading cause of cancer death and we do have the means at our disposal to drop this statistic considerably, as well as a concerned Government. This is one area where the medical profession should be thoroughly backing the Government's efforts in public health. MT

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3. NHMRC. Guidelines for the prevention, early detection and management of colorectal cancer. Commonwealth of Australia: Canberra; 2000.

A list of further reading is available on request to the editorial office.

DECLARATION OF INTEREST: Professor Macrae is on the scientific advisory committee of Enterix and is a member of the quality assurance task workgroup of the Bowel Cancer Screening Pilot Program.

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Further reading

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3. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. Gastroenterology 2003; 124: 544-560.