

CLINICAL UPDATE

Early Detection, Screening and Surveillance for

# Bowel Cancer

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## **Digestive Health Foundation**

**The Digestive Health Foundation (DHF) is an educational body committed to promoting better health for all Australians by promoting education and community health programs related to the digestive system.**

**The DHF is the educational arm of the Gastroenterological Society of Australia, the professional body representing the specialty of gastrointestinal and liver disease in Australia. Members of the Society are drawn from physicians, surgeons, scientists and other medical specialties with an interest in GI disorders.**

**Since its establishment in 1990 the DHF has been involved in the development of programs to improve community awareness and the understanding of digestive diseases.**

**Research and education into gastrointestinal disease are essential to contain the effects of these disorders on all Australians.**

**Guidelines for General Practitioners and patient leaflets are available on a range of topics related to GI disorders. Copies are available by contacting the Secretariat at the address below.**

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## Introduction

**The third edition of this booklet has been produced as an update to alert health professionals to new information published on the early detection, screening and surveillance for bowel cancer. It builds on the second edition, which was published by the Australian Gastroenterology Institute and the Australian Cancer Society in 1994.**

The authors of the third edition wish to acknowledge the firm foundation provided by the working party for the second edition:

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Dr Richard Mendelson (RACR)

Mr Lawrie Wright (ACS).

Compelling data from randomised controlled trials reaching level 1 evidence is now available to support screening for bowel cancer. In addition, there have been major advances in knowledge about the genetic basis of inherited predisposition to bowel cancer leading to availability of predictive genetic testing for many families.

These developments have been recognised by the Australian Health Technology & Advisory Committee (AHTAC), advising the Federal Minister of Health. The Digestive Health Foundation (DHF) supports the recommendations of the AHTAC Committee and has prepared this booklet to assist clinicians and health professionals as the Australian community develops and implements plans for the early detection, screening and surveillance for bowel cancer.

Nevertheless, recommendations contained in this document may change as more information becomes available, particularly with respect to improved faecal occult blood detection techniques and the benefits of endoscopic screening.

It should be recognised that many screening tests are less precise than the diagnostic tests used to investigate patients with symptoms. The objective of screening is to apply a test to people who are as yet asymptomatic, to classify them as being more likely or less likely to have that disease. To have maximal impact on disease morbidity and mortality in the community, the test needs to be acceptable to a substantial proportion of the population. A screening test therefore must be safe, relatively simple and preferably inexpensive. Those with positive screening tests should have follow-up diagnostic investigation.

## Bowel Cancer in Australia

### Incidence & Mortality

Bowel cancer is the most common internal malignancy affecting both men and women in Australia. The incidence begins to rise in the fifth decade, with a sharp and continuing increase from age 50 years.

Survival is stage-specific, with cancers confined to the bowel wall (Australian Clinico Pathological Stage [ACPS] A) having 87% five year survival, penetrating the bowel wall (ACPS B) 75%, involving lymph nodes (ACPS C) 40% and distant organs (ACPS D) 8%. (South Australian hospital-based registries 1987-1995). Overall, 5-year survival is 46%. Detection of the disease at an early pathological stage provides substantial improvement in survival for the individual and decreases mortality from the disease in the community.

The prognosis for bowel cancer patients is relatively good compared with that for some other cancers such as lung (where mortality is 87% of incidence rate) and stomach (81%).

There have been marginal increases in the incidence of bowel cancer among both males and females between 1990 and 1996, an annual average of 1.0% and 0.2% respectively (Figure 1). In 1997, incidence in males dropped slightly and in females there was a sharper rise. In comparison mortality rates have fallen slightly but steadily. This is encouraging.

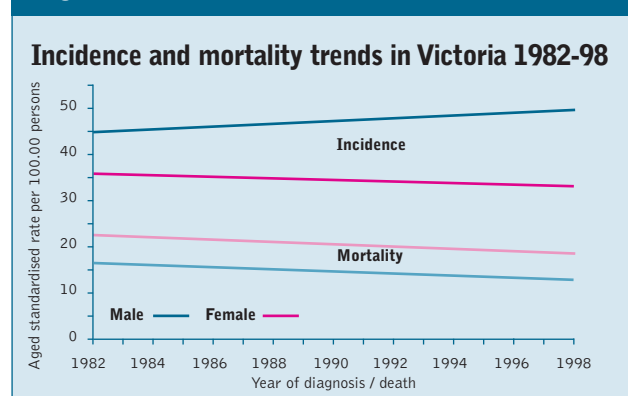
## Risk Assessment for Bowel Cancer

- Based on Anti-Cancer Council of Victoria (ACCV) data, the lifetime risk up to age 75 years for bowel cancer in Australia is 1 in 18 for men and 1 in 23 for women.
- The incidence of bowel cancer under 50 years of age is low. 7.6% of all bowel cancers occur in the first 5 decades.

Figures 2 & 3 (page 4) show the age specific incidence of bowel cancer for males and females. The sharp rise in incidence from age 50 years is evident.

It is useful to consider the chances of developing bowel cancer for males and females over succeeding 5, 10, 15 and 20 year intervals, as this can then be related to the duration of benefit of screening measures, and the complications of screening modalities.

**Figure 1. Bowel Cancer**



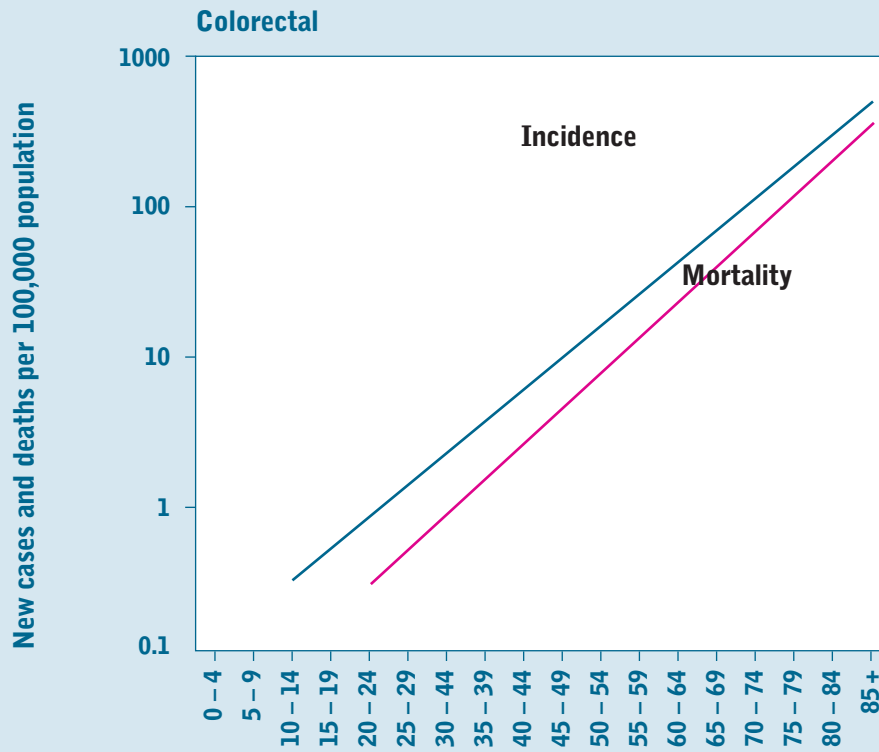
Source: Anti-Cancer Council of Victoria Epidemiology Centre. Nov 2000

**Table 1. Leading Cancer Deaths in Australia 1996**

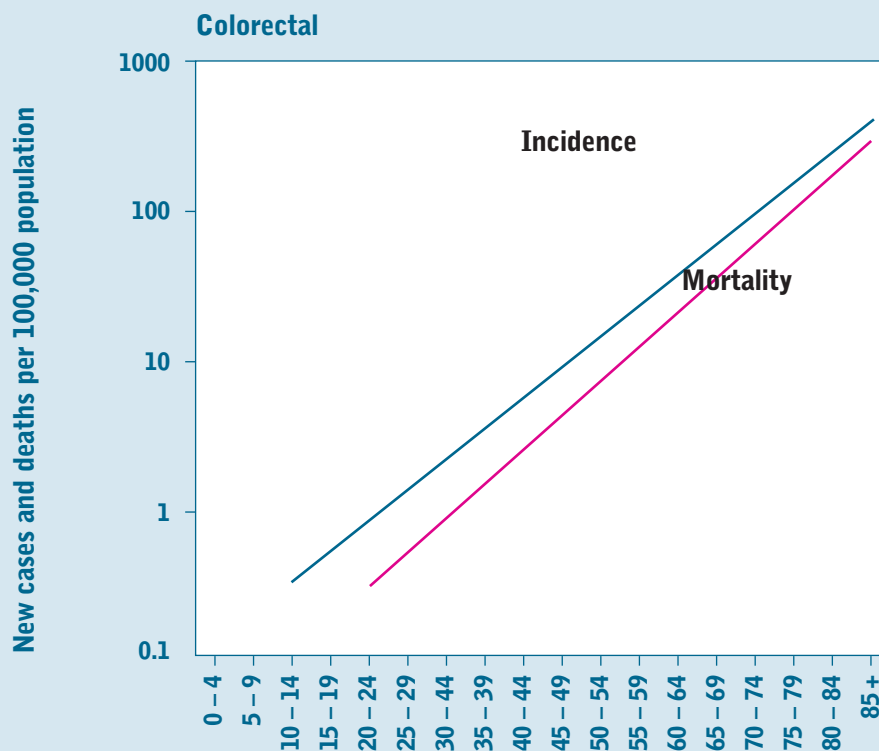
<b>Bowel cancer is the second commonest cause of cancer death in Australia</b>		
<b>MALES</b> Cancer Deaths	<b>FEMALES</b> Cancer Deaths	<b>PERSONS</b> Cancer Deaths
Lung 4,743	Breast 2,619	Lung 6,764
Prostate 2,644	Bowel 2,132	Bowel 4,606
Bowel 2,474	Lung 2,021	Breast 2,640
		Prostate 2,644

## Figure 2 & 3. Age-specific bowel cancer incidence rates

### Figure 2: Age-specific incidence and mortality rates - males



### Figure 3: Age-specific incidence and mortality rates - females



**Table 2. ACCV****Average risk of bowel cancer by age (Victorian data)**

On average, 1 in 18 males and 1 in 23 females will develop bowel cancer by the age of 75 years.

The table below shows the risk of bowel cancer of the next 5, 10, 15 or 20 years for people of different ages.

<b>If a person is aged</b>	<b>Risk in the next 5 years*</b>	<b>10 years</b>	<b>15 years</b>	<b>20 years</b>
30	1 in 7,000	1 in 2,000	1 in 700	1 in 350
40	1 in 1,200	1 in 400	1 in 200	1 in 90
50	1 in 300	1 in 100	1 in 50	1 in 30
60	1 in 100	1 in 50	1 in 30	1 in 20
70	1 in 65	1 in 30	1 in 20	1 in 15
80	1 in 50	1 in 25		

\* In people with affected relatives, risk is increased.

**How to use this table**

People with a family history will have a higher risk, depending on the extent and other characteristics of their family history. For example:

- A 50 year-old woman with no family history of bowel cancer is at about average risk – as shown on the table, her chance of developing bowel cancer is about 1 in 300 over the next 5 years, and 1 in 30 over the next 20 years.
- If her father was diagnosed with bowel cancer at age 68 (that is, 55 years or older), her risk approximately doubles, to 1 in 150 and 1 in 15 respectively.
- If her grandmother as well as her father had bowel cancer, or if her father was diagnosed at age 48, her risk is 'moderately increased', at three to six times average – that is, between 1 in 100 and 1 in 50 over the next 5 years; and between 1 in 10 and 1 in 5 over the next 20 years.

**Risk Categories****Average Risk**

Persons who are aged 50 years or more, and have no symptoms of bowel cancer and no special risk factors, are classified as being at average risk for developing bowel cancer. At age 50 years, the chance of developing symptomatic bowel cancer over the next 5 years is about 1 in 300. At age 60, the chance of developing symptomatic bowel cancer over the next 5 years is about 1 in 100.<sup>2</sup>

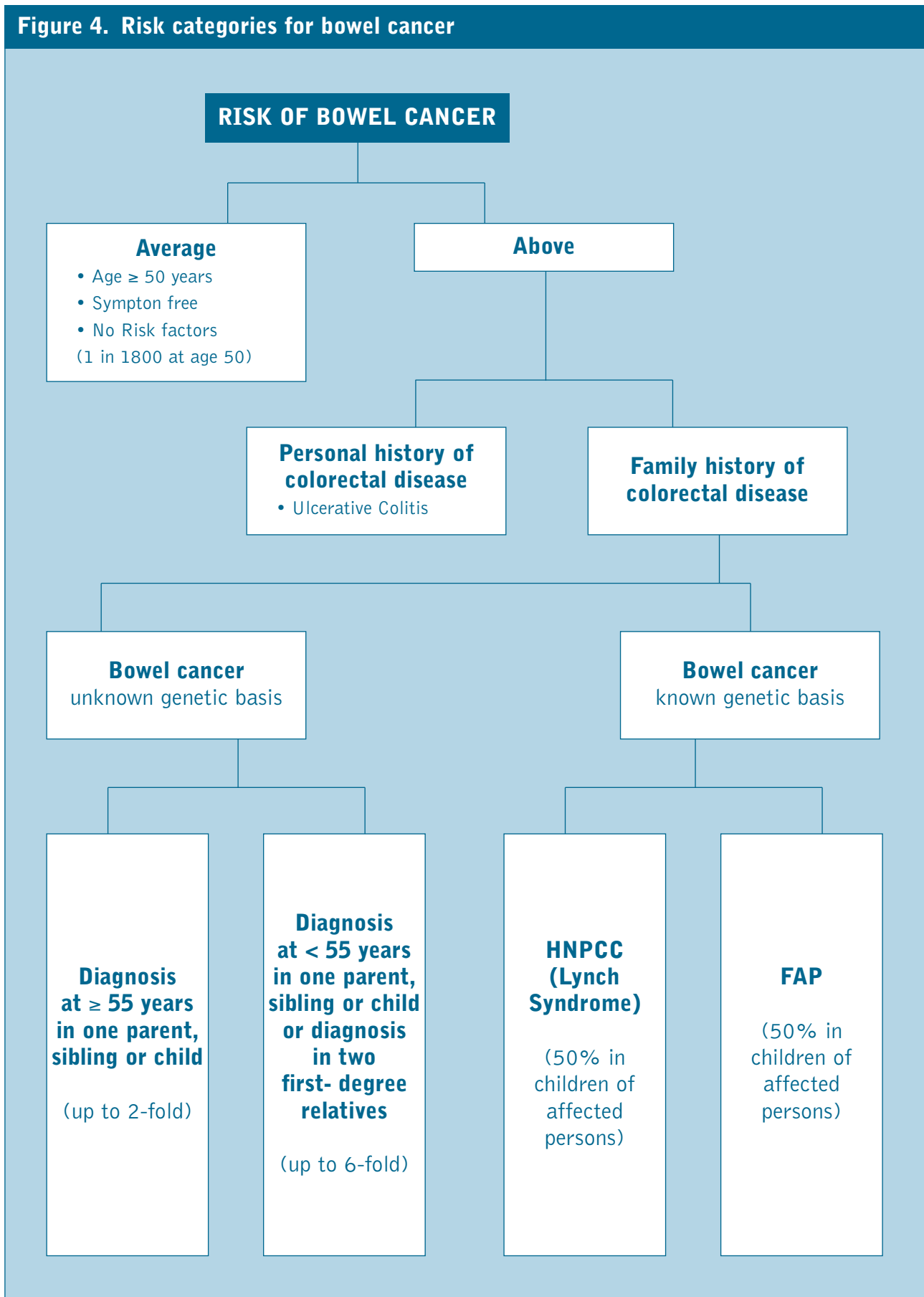
**Above Average Risk****Personal History**

A person who has extensive and longstanding ulcerative colitis or (less substantially) Crohn's disease involving the colon and most people who have had colorectal tumours removed,<sup>4,5</sup> are at above average risk for bowel cancer.

**Family History (Figure 4)**

Individuals with a family history of bowel cancer have an above average risk of developing bowel cancer.<sup>6</sup> Several studies have shown relatives of patients with adenomas, especially large ones, carry the same increased risk though the data is not as

**Figure 4. Risk categories for bowel cancer**



strong for risk to relatives of patients with adenomas as it is for relatives of patients with cancers.

- **Risk - Slightly above average: two-fold increase**

One first-degree relative diagnosed with bowel cancer at age 55 years or older - this applies to approximately 8-10% of middle-aged people in Australia.

- **Risk - Moderately increased: three to six-fold increase**

One first-degree relative diagnosed with bowel cancer at age less than 55 years or two or more first-degree relatives on the same side of the family diagnosed with bowel cancer at any age.

- **Risk - Potentially high:**

- **Familial adenomatous polyposis**

Familial adenomatous polyposis (FAP) is an autosomal dominant disease that is caused by a mutation in the APC gene on chromosome 5.<sup>7,8</sup> The children of affected individuals have a 50% chance of developing FAP. If untreated, affected individuals develop multiple adenomatous polyps and, subsequently, bowel cancer.<sup>9</sup> Atypical forms of FAP are now being recognised with specific mutations in the APC gene. These families have fewer and more proximal distribution of adenomas, even with complete rectosigmoid sparing. Cancer incidence, however, remains very high. Predictive DNA testing is available in families where a mutation has been characterised.

- **Hereditary non-polyposis colorectal cancer (Lynch syndrome)**

Hereditary non-polyposis colorectal cancer (HNPCC)<sup>10</sup> is an autosomal dominant disease that is characterised by early age of onset of bowel cancer, multiple bowel cancers in an individual, a higher-than-usual incidence of right-sided colon cancers, microsatellite instability in the cancers (repetitive sequences of tumour DNA not seen in the patient's "normal" DNA), and a "Crohnoid" reaction in the tumours with tumour-infiltrating lymphocytes. The children of affected individuals have a 50% chance of inheriting the syndrome-

causing mutation. Multiple polyposis is not a feature of this syndrome. The diagnosis also should be suspected on the basis of pathological findings and microsatellite instability in tumours in young patients, with or without a family history of bowel cancer. In many families HNPCC is associated with cancer of the endometrium and other organs.<sup>10</sup>

HNPCC is diagnosed if the family history meets the "Amsterdam criteria" (see table 3) or where a mismatch repair gene mutation has been identified in constitutional (germline) DNA. Lymphocytes are the usual constitutional cells tested due to their accessibility. Mismatch repair is the cellular DNA "maintenance" system, which identifies, excises and corrects mistakes made during DNA copying during cell division. Mutations causing mismatch repair deficiency are seen in the genes hMLH1, hMSH2, hMSH6 or rarely, PMS2 and TGFbRII. Mutations in these genes lead to failure of mismatch repair and increase substantially the likelihood that a cell will collect a series of mutations affording uncontrolled growth.

At present, the efficiency of detection of mutations in HNPCC families meeting Amsterdam criteria is 45%. DNA testing is available in most Australian states.

**Table 3. Modified Amsterdam Criteria for Diagnoses of HNPCC**

- Three or more relatives with verified colorectal or certain other syndrome-associated cancers
- One related to the other two in first degree (see below)
- At least 2 successive generations affected
- At least one individual affected under 50 years
- FAP excluded
- For the purposes of classification, the other syndrome-associated cancers are cancer of the endometrium, small bowel, renal pelvis and ureter.

## Aspects of Early Detection in Clinical Practice (case finding)

### History

Thoroughly assess the degree of risk for each person.

### Family history

Always take a family history for bowel and other cancers. Determine the closeness of the relationship of any relatives who have had bowel cancer, the degree of certainty about the diagnoses of cancer and its primary site, and the ages of affected relatives at the time of diagnosis. Verify diagnoses of cancer from clinical or pathology records and other reliable sources wherever possible.

### Age

Recognise that the risk of adenoma and bowel cancer increases with age (Fig. 2 and 3 page ?).

### Symptoms

#### Ask about:

- rectal bleeding - new onset rectal bleeding in persons over the age of 40 years is the most common and most important symptom of early stage bowel cancer and needs investigation;<sup>14</sup>
- persistent changes in bowel habit or the onset of abdominal pain;
- symptoms of anaemia.

### Previous removal of polyps or cancers

Previous removal of an adenomatous polyp (except for a small, ie. <10 mm diameter, rectosigmoid tubular adenoma) or bowel cancer places a person at above average risk. Hyperplastic (metaplastic) polyps are non-neoplastic and are not a marker of cancer risk. Except in the context of multiple large hyperplastic polyps (especially if right sided) (hyperplastic polyposis syndrome), follow-up is not required.

### Chronic inflammatory bowel disease

Longstanding and extensive ulcerative colitis, or to a lesser extent Crohn's colitis also places a person at above average risk.

### Physical Examination

- Abdominal examination checking for a palpable mass or hepatomegaly is usually normal.

- Digital rectal examination will detect about 20% of rectal cancers and 5% of all bowel cancers.

### Investigations

Table 5 summarises the screening procedures for bowel cancer.

Sensitivity and specificity are important measures of test performance. Sensitivity refers to the proportion of tests that are positive (abnormal) in people with the disease in question. In the present context, it can be expressed as sensitivity for cancer alone, for cancer and large adenomas, or for cancers and adenomas of any size. Specificity refers to the proportion of tests that are negative (ie. normal) in healthy people without the disease in question (ie. without bowel cancer or adenoma).

### Faecal occult blood tests (FOBT)

Two main types of faecal occult blood tests are available - guaiac tests and immunochemical tests:

- guaiac tests are based on the pseudoperoxidase activity of haem
- immunochemical tests utilise antibodies to human haemoglobin.

In screening programs, a person who has a positive FOBT has a 30% to 45% chance of having an adenoma and a 3% to 5% chance of bowel cancer. Traditional guaiac tests (e.g. Hemocult) will detect about 50% of asymptomatic bowel cancer.<sup>15-18</sup> (see Table 4 page ?). Detection in a program of annual testing is about 75%.

Attention to detail in performing FOBT is important in order to secure high performance:

- sample three stools annually;
- participants should be given test cards to prepare at home, not specimen containers.
- use the more sensitive guaiac tests (e.g. Hemocult®Sensa®) or immunochemical tests with acceptable performance characteristics (eg, HemSp® Hemolex®);
- dietary restrictions are highly desirable for guaiac tests (no beef, no lamb);
- development of tests in a laboratory with an appropriate FOBT quality assurance program;

- any positive test should be followed up with colonoscopy.
- test systems designed to facilitate collection of samples should be considered (eg Inform®) to enhance compliance and participation rates.

When dietary restrictions are followed (see Appendix 8), a test such as Hemocult® is highly specific – 98% to 99% of healthy subjects will be FOBT negative.<sup>15-17</sup> This means false positive results are uncommon (1-2%).

The newer guaiac tests (e.g. Hemocult® SENSE®) and immunochemical tests (specific for human haemoglobin eg. Inform®, HemSp®, Hemolex®) are more sensitive than the earlier guaiac tests such as Hemocult®. Their specificity of 95% to 98% is slightly lower than that of the earlier guaiac tests, that is, false positive tests are more common.

Attention to detail in performing FOBT is important in order to secure high performance:

- sample three stools annually;
- participants should be given test cards to prepare at home, not specimen containers.

**A POSITIVE FOBT, WHETHER POSITIVE on one sample or on multiple samples, must be investigated by colonoscopy, or by flexible sigmoidoscopy and double contrast barium enema if colonoscopy is not available**

### Sigmoidoscopy

- Flexible sigmoidoscopy has a higher diagnostic sensitivity than rigid sigmoidoscopy as more colon is examined. However, the equipment is more expensive to purchase and maintain, and disinfection of the instrument requires special expertise and care.

Flexible endoscopy should be performed in quality-controlled centres (state licensed or public hospital).

### Double contrast barium enema

Barium enema is less sensitive for bowel polyps and cancer than colonoscopy and involves exposure to ionising radiation, a factor which should be

considered in young patients, especially those entering long-term surveillance. Biopsy and polypectomy cannot be performed during the procedure. Flat lesions are difficult to detect. Any suspicious lesion must be investigated by colonoscopy.

Sigmoidoscopy (preferably flexible) should always supplement radiological examination, as rectosigmoid tumours cannot be confidently excluded without sigmoidoscopy. In the presence of severe diverticular disease or overlapping colon loops, barium enema may fail to detect neoplasms, particularly those in the rectosigmoid area.

Barium enema is less costly and more readily available than colonoscopy.

### Colonoscopy

Colonoscopy is the most accurate procedure for detecting early stage bowel cancer and adenomatous polyps - a biopsy or polypectomy can be performed during the examination. However the procedure is expensive and carries a small risk. (see below).

If total examination of the colon is impossible, a double contrast barium enema (or virtual colonoscopy if available) should be performed to examine the colon beyond the reach of the colonoscope.

Issues of quality control, disinfection are also mandatory for colonoscopy.

### Blood Tests

Carcino-embryonic antigen (CEA) and other immunobiological tests are not suitable for the early diagnosis of bowel cancer.

### New Imaging Methods

Virtual colonoscopy (reconstruction by computer manipulation of a “colonoscopic view” of the large bowel from high resolution CT images performed after bowel preparation) is being rapidly developed and evaluated for its sensitivity, specificity and cost-benefit in bowel cancer and polyp detection.

## Recommendations for Screening and Surveillance

### Average Risk

Persons aged between 50 and 75 years, who have no symptoms of bowel cancer and no special risk factors

There is now unequivocal (Level 1) evidence of a 15-33% reduction in mortality from bowel cancer in three large-scale randomised trials of screening using faecal occult blood testing. For those who actually performed the test mortality reduction was estimated to be 40%. The trials used Hemocult II but better performance could be expected from the currently available Hemocult® Sensa® and some immunochemical tests with defined performance criteria.

In the trials, testing was performed either annually or biennially; overall results favoured annual testing.

Screening by flexible sigmoidoscopy is supported by (Level 3) evidence of mortality reduction from case-control studies. Flexible sigmoidoscopy should be considered for individuals at average and especially, slightly above average risk. Until randomised controlled trials show benefit, no firm recommendation can be given yet for population screening by sigmoidoscopy. Randomised controlled trial data will be available in about five years. The risks and benefits should be explained. Risks of perforation from diagnostic flexible sigmoidoscopy are not well defined in the literature, but are likely to be low. Risk of transmissible infection by the instrument necessitates performance in quality controlled settings.

Persons older than 75 years of age should be offered screening if life expectancy of that individual is expected to be long and follow up by colonoscopy is acceptable if the test is positive, but population approaches to this age group are not recommended. Individuals under 50 years should not be offered screening in the absence of symptoms or special risk factors.

### Recommendations

Average risk individuals from age 50 years should be counselled to engage in a screening program for bowel cancer with the following characteristics:

- A history focussing on symptoms, family and personal risk factors for bowel cancer and general health status. Bowel symptoms developing during a screening program should be rigorously evaluated regardless of screening test results.
- Advice on the concept, performance and risks of screening modalities for bowel cancer, including the levels of evidence for the different modalities (FOBT level 1; flexible sigmoidoscopy level 3; colonoscopy level 3).

### FOBT

- Annually;

### And consider

- Flexible Sigmoidoscopy. Performed every 5 years;
- Colonoscopy

In the absence of evidence from randomised controlled trials, its relatively high cost and definable risk, population screening by colonoscopy for average risk individuals is not recommended.

Discussion of risk versus benefit for an individual seeking advice is appropriate. Risks with screening colonoscopy are perforation 1 in 3,000, and serious bleeding 1 in 1,200 (Mandel JS New Eng J Med 1993 328 1365-71. Serious complications occurred in 0.3% of Lieberman's study of colonoscopic screening in 3121 asymptomatic veterans. Lieberman DA et al New Eng J Med 2000; 343:162-168.). Estimated mortality is 1 in 10,000. These should be balanced against age related bowel cancer risks. Table 4 informs the debate on this.

The NHMRC Guidelines on prevention, early detection and management of colorectal cancer (ref) includes the statement:

**“THE ISSUE OF OCCASIONAL COLONOSCOPY for example at the age of 55, as a ‘once only’ screening process is controversial and not yet proven either in terms of effect on mortality or from the perspective of cost effectiveness. A way of directing limited endoscopic resources to those more likely to benefit is through FOBT”.**

**Table 4. Comparative estimates of once off colonoscopy versus flexible sigmoidoscopy plus annual FOBT versus annual FOBT alone in 50-year-old average risk person over a 5-year period**

Screening Modality	Risk of CRC in next 5 years				Risk of Procedures		Significant Neoplasia		Mortality Reduction	Cost
	without screening									
	Incidence	Mortality	Morbidity <sup>e</sup>	Mortality	Sensitivity	Specificity				
<b>Colonoscopy</b>	1:300	1:600	1:300 to 1:2,000	1:10,000	95%	99%			~ 80%	\$1000
<b>Flexible Sig.<sup>a</sup> &amp; Annual FOBT +</b>	1:300	1:600	1:1,500 to 1:10,000	1:50,000	80% <sup>b, c</sup>	98%			>30%	\$687 <sup>d</sup>
<b>Annual FOBT Alone<sup>f</sup></b>	1:300	1:600	1:3,000 to 1:100,000	1:50,000	75% <sup>b</sup>	98%			15-30%	\$130 <sup>d</sup>

**a)** Based on 20% of flexible sigmoidoscopes requiring colonoscopy for polypectomy and full evaluation.  
**b)** Based on 50% sensitivity for significant neoplasia in first screen, 20% in subsequent screens.  
**c)** Based on 70% of advanced adenomas found at flexible sigmoidoscopy & associated follow up colonoscopy, 25% of remainder found on FOBT and another 20% of remainder at later FOBTs.  
**d)** Costs include those of colonoscopy in follow up of positive findings.  
**e)** Estimates derived from Mandel & Liebermann. (See above)  
**f)** Based on 2% positivity rate in FOBT screening.

The DHF recognises that this is a controversial issue: on present evidence, the DHF supports screening based on faecal occult blood testing as the primary screening approach but with special attention paid to higher risk categories.

## Recommendations for Population Screening versus Case-Finding in Average Risk Situations

Although the scientific knowledge base supporting screening is the same with respect to recommendations for population screening versus case-finding (the patient presenting for advice on screening), there are differences. Firstly, the contract is for an opinion from the doctor in consultation, with respect to the individual patient. That opinion may take into account parameters other than the scientific knowledge base including level of patient anxiety, minor symptoms, estimation of risk of screening in that particular patient, and an unwillingness (patient or doctor) to accept suboptimal sensitivity for that patient even in the face of higher interventional risk. In addition, the effectiveness of screening is critically dependent on participation. The participation of individuals already seeking advice is much higher than that in mass

screening, so advice to undertake screening has higher cost effectiveness in these populations. Although level 1 or 2 evidence is not available for anything other than faecal occult blood testing for average risk populations, it is appropriate to discuss the evidence available with self-selected individuals and reach an informed decision on long term surveillance planning for that individual.

It is important to point out to the motivated person that the surveillance process has some risk and is not perfect. Giving advice on primary prevention by diet is also advisable and ultimately, benefit will be achieved by both.

## Implementation of Population Screening

Pilot programs of faecal occult blood testing should be instituted to define the optimal approach to the Australian community in order to have high participation rates. It is important that the benefits of screening should be extended to all Australians, and not only those spontaneously seeking medical advice. Population screening should be introduced on the basis of the results of those pilot programs. In pilot programmes, and when introduced nationally, family doctors should be closely

involved in bowel cancer screening programmes. Selection of individuals for screening is relatively complex; it requires

- identification of symptomatic patients who need full diagnostic investigation.
- Exclusion of individuals for whom screening would be inappropriate (eg the elderly and frail and those under 50 years).
- If screening for bowel cancer is to be introduced, it should be performed systematically through family doctors, with quality control for FOBT, and with adequate linkage to follow-up investigation and management. Pilot projects are needed to assess how this may be best achieved and it is recommended that the electoral lists should also be used for identification of the target populations and for access to non-compliers in GP initiated programmes.

Provision of a comprehensive program of flexible sigmoidoscopy screening in Australia has major resource and logistic implications. In general, endoscopy centres and services are at present poorly prepared and equipped to handle large numbers of subjects presenting for screening: preceding enema preparation, personnel, instruments, disinfection requirements all require substantial planning and modification to meet the needs of such a program.

## Above Average Risk

### Personal history of colorectal disease

#### 1A Previous bowel cancer or adenomas

##### Recommendations:

- Most patients who have had curative surgery for bowel cancer or removal of advanced colorectal adenomatous polyps should enter an endoscopic surveillance program for detection of metachronous (new primary) lesions.
- In general, colonoscopy is recommended every 3-5 years. In persons with resections for cancers of the rectum and distal sigmoid colon, inspection of the anastomosis at more frequent intervals to detect local recurrence may be

advisable, although evidence for benefit is questionable. More frequent examinations may be required in patients with a large sessile adenoma, malignant polyps multiple adenomas, or when other special factors are present.

Patients who had just one small tubular adenoma require less frequent colonoscopy or no colonoscopic surveillance at all.<sup>5</sup> Five yearly is a reasonable strategy in these patients. Most other patients with adenomas could be scheduled for 3-yearly surveillance.

#### 1B Chronic Inflammatory Bowel Disease

Studies addressing mortality reduction by surveillance in ulcerative colitis are not published. In some British studies, downstaging (to earlier stage) was evident in screen-detected cancers in ulcerative colitis compared with control groups. Recommendations are therefore based on level 3 evidence, principally related to risk of colorectal cancer rather than benefit of surveillance.

- In ulcerative colitis, surveillance is based on regular colonoscopy with examination of multiple mucosal biopsies for the presence of dysplasia.<sup>3</sup> Random biopsies should be taken at intervals throughout the colon. Multiple biopsies should be taken from plaque-like lesions or areas of mucosal irregularity. Detailed studies of operative specimens indicate that 32 biopsies need to be taken to ensure a 90% chance of detecting dysplasia where not macroscopically visible. If there is no evidence of dysplasia, patients should be encouraged to have repeat surveillance colonoscopy every 2 years.
- In patients with total or extensive ulcerative colitis, the program of surveillance should be started eight years after onset of symptoms.
- In patients whose disease does not extend proximal to the splenic flexure, the value of surveillance colonoscopy is less certain. In some centres, surveillance is offered to patients 12-15 years after onset of symptoms.
- Cancer risk is not increased when ulcerative colitis is confined to the rectum. Surveillance colonoscopy is not recommended for these patients. No clear evidence is available for risk of patients with procto-sigmoiditis.

- Recommendations for surveillance colonoscopy cannot be given for Crohn's colitis because of the lack of information about the degree of risk and the value of such programs. However, where macroscopic disease mimics ulcerative colitis, surveillance is prudent.

## Above Average Risk

### 2. Family history of bowel cancer - uncertain genetic basis

The following recommendations are based on the degree of risk, not on evaluation of outcomes. A reported family history of bowel cancer should be verified wherever possible, as many people cannot give precise information about cancer, particularly the site of a primary cancer, in their relatives.

2A. One first-degree relative (parent, sibling or child) with bowel cancer diagnosed at age 55 years or older (risk: two-fold)

Recommendations: same as average risk

- Recommend FOBT annually from age 50 years (up to 75 years).
- Offer sigmoidoscopy (preferably flexible), every 5 years from age 50 years (up to 75 years).
- The DHF recognizes this recommendation is controversial and there is a continuum of risk between this group of relatives and those with higher risk. Nevertheless there are no case control or cohort studies of screening evaluating the benefits of endoscopic screening in this group. Several audits of colonoscopic surveillance for this subgroup have revealed a low yield of significant lesions.<sup>23</sup> It will be important to fully audit future surveillance programs whatever protocol is followed. At present, the DHF does not recommend colonoscopy in this group and supports similar advice from the Australian Health & Technology Advisory Committee, the NHMRC and the Australian Cancer Society. For self-selected individual (casefinding) screenees should be appraised of the slender risk versus benefit ratio involved, particularly for individuals under 65 years of age. (see page 14?)

Individuals with only second or third degree relatives with bowel cancer have a 1.25 to 1.5 risk increase. Average risk screening applies.

2B. One first-degree relative with bowel cancer diagnosed under the age of 55 years, or two or more first-degree relatives on the same side of the family with bowel cancer at any age (risk: three – six fold)

Recommendations:

- Offer colonoscopy every 5 years starting at age 50 years, or at an age 10 years younger than the age of the earliest diagnosis of bowel cancer in the family (whichever comes first). If colonoscopy is unavailable, then offer flexible sigmoidoscopy and double contrast barium enema.
- Consider offering FOBT annually in the intervening years.

## Above Average Risk

### 3. Family history of bowel cancer - known genetic basis

3A. Familial adenomatous polyposis (risk: 50% chance of developing familial polyposis for children of affected persons)

Genetic testing for familial adenomatous polyposis (FAP) is highly specific and sensitive.

Recommendations:

- Families with FAP should be referred to centres supported by genetic counselling, and DNA diagnostic laboratories and FAP registries. In the 85% of FAP families where a mutation in the PC gene is characterised, at risk first-degree relatives should be offered predictive testing of the APC gene which will be 100% accurate (given accurate information on paternity and specimen collection). Endoscopic screening for polyposis is not needed in family members testing negative for the family-specific APC mutation, (refer to NH&MRC familial cancer guidelines) Predictive testing should be offered from teenage years.

- Individuals who test positive for the family-specific APC mutation, or all at risk first-degree relatives where no APC mutation has been characterised, should have annual or biennial (every 2 years) sigmoidoscopy from 12-15 years, the exact age depending on maturity, to 30-35 years and less frequently to 55 years of age. Colonoscopic screening should be considered if attenuated FAP is suggested in the pedigree, and surveillance continued beyond 55 years.
- Contact registries for assistance with follow-up. (see appendix B).

### 3B. Hereditary non-polyposis colorectal cancer (HNPCC-Lynch syndrome) (risk: 40-50% chance of developing bowel cancer for children of affected persons)

Genetic testing for HNPCC is now available in Australia.

#### Recommendations:

- Refer members of families with suspected HNPCC (see table) to centres supported by access to microsatellite instability MSI testing and/or immunohistochemistry of the mismatch repair gene product, DNA diagnostic laboratories, genetic counselling and registry support. Mutational analysis for the genes responsible for HNPCC is now available in most States. Predictive testing cannot be offered unless a family-specific mutation has been identified in an affected family member.
- Offer colonoscopy from age 25 years or 5 years younger than the age of the earliest cancer in the family (whichever comes first). The frequency should be annual in known mutation carriers, and biennial (every 2 years) for at risk first-degree members of families where the mutation is not characterised.
- Annual gynaecological screening with transvaginal ultrasound for ovarian screening and endometrial sampling should be recommended for premenopausal female gene carriers and at risk women in families where no mutation has been found. For postmenopausal women, transvaginal ultrasound evaluating endometrial thickness and ovarian pathology, and possibly serum CA 125 is recommended.

Prophylactic colonic resection and/or gynaecology surgery should be discussed with mutation carriers. Colonic surgery should be generally a colectomy with ileorectal anastomosis to provide protection from metachronous cancer and simplify surveillance.

- Individuals with tumours and/or family histories suggestive but not diagnostic of HNPCC should have MSI testing of their tumours performed with a view to referral for DNA testing, if positive.

**Table 5. Characteristics of individuals and families raising suggestion of HNPCC**

<b>Individuals</b>	<b>Families</b>
<p>Bowel cancer diagnosed &lt;45 years Right-sided bowel cancer, if young</p> <p>Synchronous bowel cancers</p> <p>Metachronous bowel cancers</p> <p>Endometrial, stomach, ovarian, small bowel, renal pelvis, ureter, brain or biliary cancers occurring in the same individual</p> <p>Tumour infiltrating lymphocytes or Crohnoid reaction in tumour</p> <p>Signet ring or mucinous undifferentiated bowel cancer</p> <p>Microsatellite instability</p>	<p>Three relatives affected with bowel, endometrial, small bowel, renal pelvis and/or ureteric cancers in pedigree, one related to the other two in first degree</p>

Individuals or families with one or especially several of these characteristics should be referred to multi-disciplinary centres, services including clinical, genetic counselling, molecular genetic and registry services. (see appendix)

**Table 4. Features of screening procedures for bowel cancer**

PROCEDURE	PERCENTAGE OF ASYMPTOMATIC BOWEL CANCER & LARGE ADENOMAS DETECTED	COST *†	COMPLIANCE	ADVANTAGES	DISADVANTAGES
FOBT	40% to 80%	\$3 to \$25	50% to 70% (first screen) 80% (rescreen)	Inexpensive	Low sensitivity; requires colonoscopy if positive
Rigid sigmoidoscopy	20% to 30%	\$60	20% (rescreen)	Inexpensive	Low sensitivity; requires colonoscopy if positive
Flexible Sigmoidoscopy	50% to 65%	\$87 + Hospital charges \$300-\$580	12-30%	High cost (equipment maintenance) Relatively simple day procedure; requires no sedation	Requires enema; requires followup colonoscopy or radiology if possible
Double contrast barium enema	85% to 95%	\$108	Uncertain	Cost (least expensive of highly sensitive techniques)	Requires vigorous bowel preparation Recto-sigmoid lesions may be missed, particularly if coexisting diverticular disease is present Radiation exposure
Colonoscopy	95% to 99%	\$260 + Hospital charges \$300 to \$710 Anaesthetic fees \$80-\$150	Uncertain	High sensitivity; biopsies and polypectomy are possible	High cost (equipment, operation, maintenance); requires sedation, vigorous bowel preparation; possible complications

\*Equipment maintenance, day care costs and time off work add considerable to the cost of colonoscopy. Sigmoidoscopy and colonoscopy may be associated with significant extra costs for histopathological and flexible sigmoidoscopy services and specialist consultations (eg. anaesthetists). These estimates are based on screening programs and long-term follow-up. †Australian dollars (2000)

## Appendix A

### Organisation of bowel cancer screening in Australia

The DHF considers that family doctors should be closely involved in bowel cancer screening programs

Selection of individuals for screening is relatively complex; it requires.

- identification of symptomatic patients who need diagnostic investigation;
- identification of subjects with above-average risk who require special screening protocols;
- assessment of likely compliance with follow-up investigations.

Organisations offering screening tests should specifically address the following issues in their programmes.

- Patients with symptomatic bowel cancer or adenomatous polyps should not be included. They may seek inclusion in that type of program, and be falsely reassured by a negative result.
- People for whom screening is inappropriate, such as those below 50 years of age or those whose general health is poor should be excluded from the program. People in above-average risk groups should be identified for more intensive screening.
- Screening for bowel cancer should be performed systematically, through family doctors, with quality control for FOBT, and with adequate linkage to follow-up investigation and management. Pilot projects are needed to assess how this may be best achieved and the role of electoral lists for identification of the target population akin to approaches taken for breast and cervical cancer.

## Appendix B

### Correct administration of faecal occult blood tests

#### Dietary requirements

- Patients must modify their diets for guaiac tests,<sup>24</sup> but not for the immunochemical tests. The modifications are straightforward.
- Patients should avoid the following foods, vitamins and drugs that can affect the guaiac test;
  - red meat (beef, lamb)
  - vitamin C supplements, which can produce false-negative results
  - aspirin or anti-inflammatory drugs, which can produce low grade gastric bleeding
- Patients should commence the modified diet three days before they take faecal samples and continue the diet through the testing period.

#### Sampling stools

Several precautions are necessary because haem and haemoglobin degrade in moist faeces and because haemoglobin may be leached out of stools by toilet bowl water.

- Sample the stool from a normally- passed bowel action; avoid contamination with water (eg. use a paper pad on top of the water in the bowl)
- Sample from the surface or where you think blood might be present
- Prepare a thin smear (which will dry readily) on the specimen card
- Follow manufacturers' instructions if you use other types of test kit - such test kits should stabilise the haem or haemoglobin
- Sample at least three stools - bleeding may be intermittent

The Inform test (Enterix (Australia) Pty Ltd) requires a sample collected by brushing the surface of a stool specimen passed into the toilet bowl with the fine brush supplied, minimising preparations required and contact with the stool.

### Reading results

FOBTs are perceived as being simple, but inexperienced readers may miss faintly positive results.<sup>25</sup>

- Read guaiac tests in a good light
- Report as positive any blue colour, no matter how transient

## Appendix C

### Role of multidisciplinary familial cancer clinics

Multi-disciplinary clinics perform a wide range of important functions beyond those reasonably achievable by most medical practitioners, including:

- ascertainment of families, construction of extended pedigrees;
- verification of diagnoses through death and cancer registers;
- collection of blood and tissue samples where appropriate throughout the pedigree;
- maintenance of a confidential database on behalf of the family and future generations;
- liaison with other relevant health professionals and registers within state, interstate and international;
- educational support and counselling;
- identification of at-risk members;
- coordination and planning mutational analyses where appropriate;
- genetic counselling before and after predictive DNA testing;
- documentation of follow-up in the extended family.

Expert clinical genetic counselling is important to ensure the best psychological outcomes and the correct interpretation of results given the associated clinical uncertainties, penetrance, variable sensitivity (never 100%) of mutational analysis using different techniques, harmless polymorphisms masquerading as pathogenic mutations, and limited development of functional tests of gene alterations. Furthermore, the absence of a mutation identifiable in a family must be considered with extreme caution in families with suspicious pedigrees given the possibilities of mutations being present which are inaccessible to current mutational analytic techniques, or on yet to be discovered genes.

## Contact information for FAP registers

### New South Wales

The Registrar  
NSW Familial Adenomatous Polyposis Register Board  
NSW State Cancer Council  
PO Box 572  
Kings Cross NSW 2011  
Telephone (02) 9334 1900

The Registrar  
The NSW & ACT Hereditary  
Cancer Register  
Locked Bag 1  
Kings Cross  
NSW 1340  
Telephone (02) 9334 1807

### Queensland

The Registrar  
Queensland Familial Adenomatous Polyposis Register  
Bancroft Centre  
300 Herston Road,  
Herston QLD 4029  
Telephone (07) 362 0251

The Coordinator  
Queensland Bowel Cancer Family Registry  
Queensland Clinical Genetics Service  
Royal Children's Hospital  
Bramston Terrace  
Herston, QLD 4029

### South Australia

The Registrar  
South Australia Familial Adenomatous Polyposis  
Register  
P.O. Box 929  
Hospital  
Unley SA 5061  
Telephone (08) 8291 411

HNPCC  
Familial Cancer Unit  
Women's and Children's  
North Adelaide SA 5006

### Victoria

The Registrar  
ESSO Familial Polyposis Register for Victoria  
100 Drummond Street  
Carlton  
VIC 3053  
Telephone (03) 9635 5176

Familial Cancer Centre  
Peter MacCallum Cancer Institute  
St Andrews Place  
East Melbourne  
Telephone (03) 9656 1199

Familial Bowel Cancer Clinic  
The Royal Melbourne Hospital  
Post Office  
Royal Melbourne Hospital  
VIC 3050  
Telephone (03) 9342 7151

Clinical Genetics  
Level 2  
Monash Medical Centre  
246 Clayton Rd  
Clayton  
VIC 3168  
Telephone (03) 9594 2026

CanHELP 131120  
(National Number)

### Western Australia

The Registrar  
Familial Polyposis Registry  
334 Rokeby Road,  
Subiaco  
WA 6008  
Telephone (08) 9346 2448

Genetic Services of WA  
King Edward Memorial Hospital  
374 Bagot Road  
Subiaco  
WA 6008

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## Further Reading

- Australian Health & Technology Advisory Committee. ***Colorectal Cancer Screening*** December 1997 Commonwealth Department of Health & Family Services
- National Health & Medical Research Council: ***Guidelines for the prevention, early detection and management of colorectal cancer.*** December 1999 National Health & Medical Research Council Commonwealth Department of Health & Family Services

## Guideline Application Statement

This document has been prepared by the Digestive Health Foundation of the Gastroenterological Society of Australia and every care has been taken in its compilation. The booklet is intended to be used as a guide only and not as an authoritative statement of every conceivable step or circumstance which may or could relate to the management of bowel cancer.

Practitioners should use this document as an aid in relation to early detection of bowel cancer and not as a complete or authoritative statement.

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A summary of this information entitled: ***Screening for bowel cancer a summary for general practitioners*** is also available from the Digestive Health Foundation.





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