

Early Detection, Screening and Surveillance for

Bowel Cancer



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Foundation



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Established in 1990, the Digestive Health Foundation (DHF) is an educational body committed to promoting better health for all Australians by developing education and community health programs to improve awareness and understanding of digestive diseases.

Research and education into gastrointestinal disease are essential to prevent and ameliorate these conditions for all Australians. 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.

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INTRODUCTION

The fourth edition of this booklet is an update to alert health professionals to new information on the early detection, screening and surveillance of colorectal cancer. It builds on previous editions, to present a practical overview of current and evolving practice. The authors wish to acknowledge the DHF staff, scientists, physicians and surgeons that have contributed to earlier editions.

The DHF supports the recommendations of the Cancer Council of Australia on colorectal cancer screening, surveillance and detection.¹

Recommendations contained in this document may change as new information becomes available, particularly with respect to improved faecal detection techniques, epidemiological risk stratification, advances in colonoscopic practice and technology, computed tomographic colonography (CTC) and the promise of molecular and capsule endoscopic strategies.

COLORECTAL CANCER: THE PROBLEM

In Australia, colorectal cancer (CRC) is the second most frequently diagnosed internal malignancy and the second most common cause of cancer death (**Figure 1**).² In 2005, over 13,000 Australians were diagnosed with, and over 4000 Australians died from, CRC (**Figure 1**).^{1,2}

One in 17 Australian males and 1 in 26 Australian females will develop CRC.¹ These are sobering statistics for a cancer with well defined risk factors, originating from slowly progressive precursor lesions that are within reach of, and cured by, colonoscopic polypectomy.³

Furthermore, surgical resection of early stage CRC is associated with excellent long term survival (**Table 1**).⁴

Figure 1. Cancer specific deaths and diagnoses in Australia during 2005²

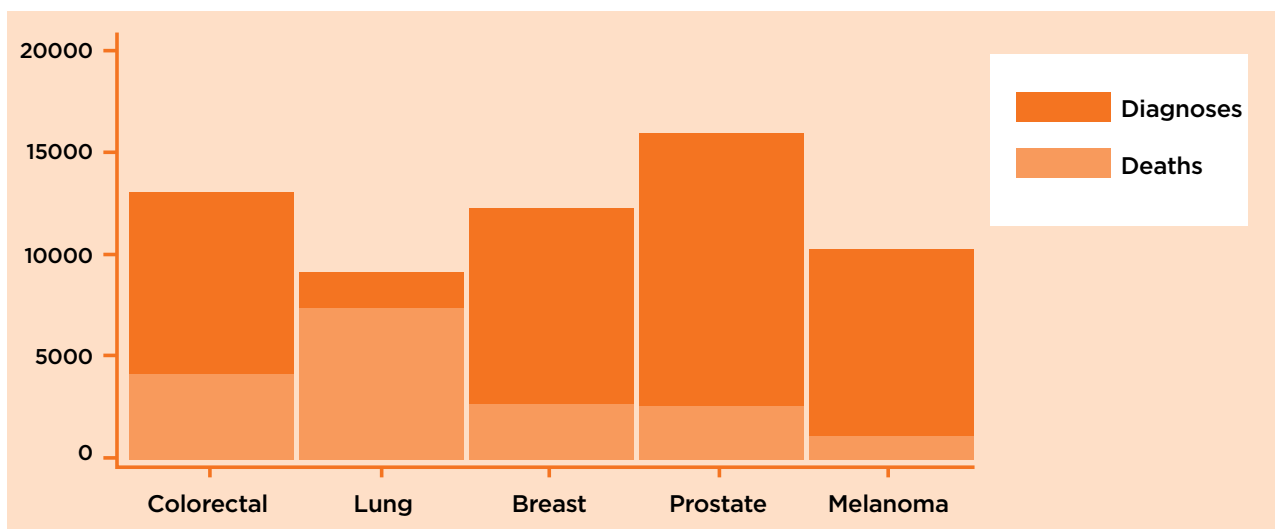


Table 1. Five-year survival by the American Joint Committee on Cancer system⁴

Stage	Definition	5-year survival
I	T1 or T2 N0 M0	93.2%
IIa	T3 N0 M0	84.7%
IIb	T4 N0 M0	72.2%
IIIa	T1 or T2 N1 M0	83.4%
IIIb	T3 or T4 N1 M0	64.1%
IIIc	Any T N2 M0	44.3%
IV	Any T or N M1	8.1%

T1 = tumour invades submucosa; T2 = tumour invades muscularis propria; T3 = tumour invades through the muscularis propria into the subserosa or into non-peritonealised pericolic tissues; T4 = tumour directly invades other organs or structures and/or perforates visceral peritoneum; N0 = no regional lymph node metastasis; N1 = metastasis to one to three regional lymph nodes; N2 = metastasis to four or more regional lymph nodes; M0 = no distant metastasis; M1 = distant metastasis.

In the context of CRC, screening tests may be applied to large, unselected populations, referred to as mass screening, such as in the Commonwealth Government's National Bowel Cancer Screening Program. Screening tests may also be offered by doctors to their patients when they consult for unrelated reasons, so called case finding. Furthermore, individuals with a known history of colorectal polyps and cancer can undergo careful monitoring, usually by colonoscopy, known as surveillance and those seeking medical attention for specific colorectal symptoms generally undergo a diagnostic procedure.⁵ It can be confusing, because while faecal occult blood testing is the only Australian mass screening initiative, colonoscopy may be used as a screening (case finding), surveillance and diagnostic tool. It is important to appreciate the differences between these clinical scenarios, in terms of patient risk of CRC.

The well established premise of CRC screening is that asymptomatic cancer has an earlier pathological stage than symptomatic disease and that earlier stage CRC has a better outcome.^{1,6} Colorectal cancer diagnosis, screening and surveillance saves lives.^{1,3,7,8} CRC screening is an excellent example of Australian policy makers, scientists, GPs, gastroenterologists and surgeons working together as GI cancer "preventionists"⁹ to improve digestive health in our community. But, as the numbers above plainly show, there is much work to do.

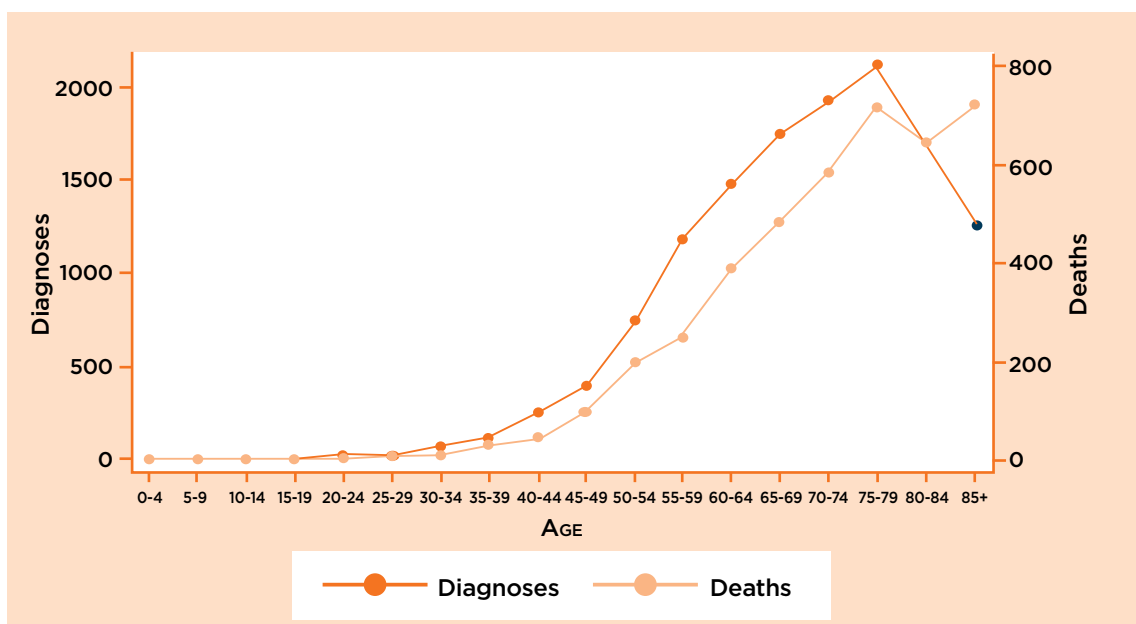
COLORECTAL CANCER: THE CAUSE

In Australia there is a dramatic increase in CRC diagnosis and death from the 5th decade (**Figure 2**).^{1,2,10} Colorectal cancer is a biologically heterogeneous condition, with at least 3 major carcinogenesis pathways. Each separate pathway is characterised by specific molecular signatures, unique pathological precursors and differing natural histories.¹¹

Approximately 5% of CRC can be attributed to high risk, genetically defined cancer syndromes such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC) and MUTYH-associated polyposis.¹² The remaining cases reflect a combination of low penetrant genetic and environmental influences. The best way to reduce one's risk of dying from CRC is to adopt a healthy lifestyle including regular exercise and a diet low in fat and high in vegetables (particularly cruciferous vegetables, such as cabbage, broccoli, cauliflower) and dietary fibre, particularly unprocessed wheat bran.¹³

One should avoid smoking and excess alcohol and, very importantly, participate in individual-specific CRC screening.

Figure 2. Colorectal cancer: age-specific diagnoses and deaths in Australia during 2005²



COLORECTAL CANCER: THE PRECURSOR

Colorectal cancers develop from precursor lesions, polyps. There are two chief types of colorectal polyps, which are readily distinguished by histopathology. Adenomas are the main type of colorectal polyp. The majority of CRCs develop from adenomas, but only 1 in 20 sporadic adenomas ever develop in to cancer.¹¹ ¹⁴ It is now recognised, however, that certain hyperplastic or “serrated” polyps similarly give rise to cancer, particularly proximal colonic cancers.¹⁵ The current consensus is to manage these proximal serrated polyps as one would adenomas,¹⁴ i.e. they require complete excision and subsequent colonoscopic surveillance, with the colonoscopic interval determined by size and number (see **table 3**). In contrast, diminutive, hyperplastic polyps of the rectosigmoid rarely, if ever, develop into cancer.¹⁴ These polyps are still ideally removed (to distinguish from adenomas), but do not require colonoscopic surveillance (see below).¹⁴

On the basis of the patient’s responses to these questions, they can be stratified into one of three CRC risk groups (Table 2)¹

COLORECTAL CANCER: THE RISK

Average risk CRC screening is designed for asymptomatic patients without a significant personal or family history of significant colorectal disease. These individuals are at risk of CRC by virtue of their age alone.¹

Practically, a patient’s clinical risk of CRC is determined by three factors:¹

- 1. Age**
- 2. Previous or current colorectal symptoms or disease**
- 3. Family history**

The first issue is to establish whether there are any circumstances demanding colonoscopic investigation, such as rectal bleeding (including occult bleeding), iron deficiency anaemia, previous colorectal neoplasia, chronic colitis etc. If there are any such factors one should plan appropriate endoscopic investigations or surveillance (discussed below).

If an individual is asymptomatic and free of colorectal disease then one must determine their family history of CRC, by asking “Have any of your blood relatives been diagnosed with cancers or colorectal polyps?” If yes, then clarify the “who”, “what”, “when” and “how many”:

WHO	<ul style="list-style-type: none"> • First-degree: parents, siblings, children • Second-degree: grandparents, grandchildren, aunts, uncles, nieces, nephews • Important to differentiate maternal and paternal sides of the family
WHAT	The type of primary cancer?
WHEN	How old when the cancer was diagnosed?
HOW MANY	Are there any patients with multiple cancers or multiple colorectal polyps?

Table 2. Family CRC risk categories¹

<p>Category 1 Those at or slightly above average age-specific risk</p>	<p>This includes patients with no family history up to those with one affected first-degree relative diagnosed ≥ 55 years. Whilst patients with one affected first-degree relative (≥ 55 years) have up to twice the average risk of CRC, this is not sufficient to warrant more intensive screening.</p>
<p>Category 2 Those at moderately increased risk, a relative risk of approximately 3 to 6-fold</p>	<p>Patients with one first-degree relative diagnosed with CRC < 55 years, or two first- or second-degree relatives (on the same side of the family) diagnosed with CRC at any age.</p>
<p>Category 3 Those at potentially high risk</p> <p>(these criteria also serve as a guide for clinical genetics referral, Appendix A)</p>	<ul style="list-style-type: none"> • One first-degree and ≥ 2 first- or second-degree relatives with CRC on the same side of the family, or • One first-degree and ≥ 1 first- or second-degree relatives with CRC on the same side of family in the context of: <ul style="list-style-type: none"> o multiple CRCs in one individual o CRC < 50 years o the presence of other HNPCC-related cancers, which includes gastric, small intestinal, endometrial, ovarian, ureter, renal pelvis, biliary tract, pancreas and brain • Relatives diagnosed with an autosomal dominant inherited CRC syndrome, such as HNPCC or familial adenomatous polyposis (FAP) • Siblings of patients with MUTYH-associated polyposis (an autosomal recessive condition)

COLORECTAL CANCER: THE RESPONSE

The DHF strongly endorses the role of GPs in CRC screening programs. GPs have a critical role in case finding, individual tailoring of strategies, compliance with screening and follow up.

Once a patient's age, symptoms (or lack of symptoms), past medical and family history are established, the appropriate management follows (Table 4).

Symptoms

The most common initial symptoms of CRC are no symptoms. There are, however, several important warning signs, which necessitate diagnostic testing. After careful history and examination, patients with rectal bleeding, iron deficiency anaemia or other concerning colorectal symptoms should proceed to a definitive diagnostic investigation, often colonoscopy.

Personal history of colorectal disease

Patients with a personal history of colorectal cancer, adenomas or hyperplastic polyps (excluding diminutive, rectosigmoid hyperplastic polyps), undergo colonoscopic surveillance, rather than screening.

Chronic colitis

In chronic ulcerative colitis and Crohn's colitis, surveillance is recommended after at least 8 years of pancolitis or 12 to 15 years of left sided colitis.³ Surveillance colonoscopy is recommended every 1 to 2 years and should include multiple mucosal biopsies to assess for dysplasia. Chromoendoscopy with targeted biopsies is more sensitive for detecting dysplasia, and should be considered standard of care where experience is available. Without the assistance of chromoendoscopy, studies suggest that 32 biopsies should be taken to ensure a 90% chance of detecting occult mucosal dysplasia. This has led to the

recommendation that quadrant biopsies should be taken every 10cm along the colorectum.¹⁶ In addition, isolated polyps should be excised and multiple biopsies should be taken from plaque-like lesions or areas of mucosal irregularity. Flat dysplasia, if confirmed by a second experienced pathologist, should be considered an indication for colectomy especially if it is high-grade or diffuse. Localised dysplasia may be able to be managed with endoscopic mucosal resection in expert hands.

Following curatively resected CRC

Surveillance after a curative resection of CRC is performed in collaboration with the treating colorectal surgeon and often medical oncologist. Depending on the exact resection, the follow up may vary, but in general, the schedule is designed to detect both synchronous and metachronous cancers. Synchronous disease is excluded by performing a full colonoscopy at the time of diagnosis or within 3-6 months following surgery, if a full colonoscopy was not performed pre-operatively. A second colonoscopy at 12 months is often performed, as a second check.³ Thereafter a colonoscopy is often scheduled every 3 to 5 years to exclude metachronous cancers.³ More frequent sigmoidoscopic examination may be performed to exclude local recurrence after anterior resection of rectal and distal sigmoid cancers. Additional blood tests (CEA 3-6 monthly) and imaging (CT) periodically may be added to colonoscopy.¹⁷

Following completely excised colorectal polyps

Initial colonoscopy should provide a careful assessment of the entire colorectal mucosa with attention to quality indicators of practice. Bowel preparation is a critical aspect of quality colonoscopy. Where possible, all colorectal polyps should be completely removed and sent away for pathological assessment.

To plan post-polypectomy surveillance, one must begin with a good quality, complete colonoscopy (from rectum to caecum). Thus, if required, a baseline colonoscopy may need to be repeated in cases of poor bowel preparation (immediate rescheduling), possible incomplete excision of a large polyp (often at 3 months) or the presence of multiple adenomas (>10) to ensure complete clearance (usually within 12 months).

In the absence of other risk factors, there are two main recommended surveillance intervals (**Table 3**). If the follow up colonoscopy is negative, surveillance is still recommended every 5 years, reflecting the heightened risk of CRC in patients with a personal history of colorectal polyps.

Table 3. Colonoscopic post-polypectomy surveillance guidelines

Interval	Findings from an adequate baseline colonoscopy
5 years	If <3 polyps (excluding diminutive rectosigmoid hyperplastic polyps) provided that all polyps are "simple" as defined by dimensions (≤ 10 mm) and histopathology (no high-grade dysplasia or villous change).
3 years	If 3 or more polyps (excluding diminutive rectosigmoid hyperplastic polyps) or if one or more polyps is "advanced" as characterised by dimensions (>10mm) and/or histopathology (presence of high-grade dysplasia or villous change).

Family history

In asymptomatic patients, without any significant history of colorectal disease (chronic colitis, polyps, CRC), the appropriate CRC screening strategy (**Table 4**) is determined by their age and family history (risk categories from **Table 2**).¹

High risk (Category 3) family history and specific CRC syndromes Familial Adenomatous Polyposis (FAP)

FAP is an autosomal dominant syndrome, characterised by adenomatous polyposis (>100 colorectal adenomas). The adenomas are usually evident by late teenage years and, in the absence of prophylactic colectomy, CRC occurs in essentially all cases by the age of 50 years.^{12, 18} FAP arises due to a pathogenic mutation in the tumour suppressor gene, Adenomatous Polyposis Coli (APC). Interestingly, the site of mutation within APC influences the resultant clinical phenotype both in terms of associated extra-colonic features as well as colorectal disease severity.¹⁸

Generally, mutations within the central region of the APC gene are associated with a higher colorectal burden >1000 adenomas, whilst mutations at the 5' or 3' ends of the gene result in a milder phenotype, so-called attenuated FAP (AFAP). AFAP is characterised by <100 colorectal adenomas, and the development of CRC is delayed by approximately 15 years compared to classical FAP.¹⁸

APC gene mutation testing, conducted through clinical genetics services (in some states known as Family Cancer Clinics), should be considered for patients that satisfy the colorectal criteria for classical FAP (>100 adenomas) or AFAP (**Table 5**), and in the first degree relatives (sibling, parents, children) of those with an informative APC mutation. Genetic testing of relatives is only valuable when a pathogenic mutation is demonstrated in an affected relative.

Table 4. CRC screening on the basis of family history

Category 1 At or slightly above average risk	These patients should be offered faecal occult blood testing (FOBT) using a sensitive immunochemical test (faecal immunochemical test, FIT) from 50 years of age. ⁸ The commonwealth government is offering FIT kits free of charge to Australians turning 50, 55 or 65 years of age between January 2008 and December 2010. It is very important that negative tests are repeated every two years and positive tests are followed by colonoscopy. FOBT screening is ideally a program not a one off test.
Category 2 Those at moderately increased risk	These patients should be screened by 5-yearly colonoscopy from 50 years of age, or 10 years earlier than the youngest relative diagnosed with CRC.
Category 3 At potentially high risk	Management must address both the patient and the family and the clinical genetics team is essential. If an informative mutation is discovered in an affected relative it can be used to guide management, see below.

APC mutations are discovered in about 85% of Australian patients with classical FAP.¹² In families without an informative mutation, clinical screening by flexible sigmoidoscopy takes the place of genetic testing. Full colonoscopy, however, is preferred to flexible sigmoidoscopy in some centres.¹⁹ Screening and surveillance with annual flexible sigmoidoscopy or colonoscopy should begin at 12 to 15 years or from the time of diagnosis.¹² Chromoendoscopy and narrow band imaging endoscopy both enhance the detection of small adenomas and are likely to be helpful in characterising the phenotype.¹² Once polyposis is confirmed a referral should be made to the colorectal surgical team to plan an elective resection, usually a total colectomy with ileorectal anastomosis or a restorative proctocolectomy with pouch formation.¹² The usual timing of these procedures is in the late teenage years or early adulthood. Any residual rectal mucosa requires lifelong surveillance. Upper gastrointestinal malignancies, particularly gastric (antral) and ampullary adenocarcinoma are important extra-colonic manifestations of FAP. Thus, annual upper gastrointestinal endoscopy alternating with side viewing duodenoscopy is advisable following the development of colorectal disease.¹²

MUTYH-associated polyposis (MAP)

MAP is an autosomal recessive cause of multiple colorectal adenomas and cancer. Its phenotype is similar to AFAP, although more severe colorectal disease (>100 adenomas) can occur.^{20, 21} Its endoscopic surveillance and surgical management is similar to AFAP, above.¹ MUTYH is a DNA glycosylase which helps to repair mispaired bases that develop following oxidative DNA damage, and thus protects against mutations in important CRC genes such as APC and KRAS.^{18, 21} The MUTYH missense mutations Y165C and G382D both impair the enzymatic activity of MUTYH, and together account for about 80% of mutant alleles in northern European populations.¹⁸ Biallelic mutations in MUTYH confer a 93-fold increased risk of CRC, with almost complete penetrance by 60 years of age.^{22, 23}

Biallelic MUTYH mutations appear to be particularly common in patients diagnosed with 15-100 colorectal adenomas without APC mutation,²⁰ but may occur with a much more attenuated phenotype.²⁴ MAP is also associated with extracolonic manifestations including duodenal polyposis.¹⁸

In patients satisfying the colorectal criteria for at least AFAP, but without evidence of dominant inheritance, MUTYH testing should occur in concert with APC. In the setting of dominant inheritance, however, MUTYH should only be performed once APC mutation is excluded. Patients with confirmed biallelic MUTYH mutations should be managed as for AFAP, with annual or biennial colonoscopic and upper gastrointestinal surveillance, until colectomy is necessitated on the basis of colorectal adenoma burden.¹² Given that MAP is a recessive disorder, genetic testing is applied to siblings, and carrier status of spouse and children is occasionally offered following genetic counseling.²⁵ The ideal management of patients identified with only one MUTYH mutation, however, is still evolving. These individuals are likely to have a modest increase in CRC risk, perhaps a twofold increase.²⁶ One reasonable approach is to offer carriers 5 yearly colonoscopy from the age of 50 years, to reflect their "moderately increased risk". For patients with monoallelic MUTYH mutation identified because of multiple colorectal adenomas, it is appropriate for the clinical phenotype to guide surveillance.¹²

Several conventional non-steroidal anti-inflammatory drugs, aspirin and COX2-selective inhibitor agents exert an adenoma attenuation effect in both sporadic adenoma and FAP.²⁷⁻³⁰ But, these chemopreventative agents do not absolutely prevent cancer and their benefits beyond standard colonoscopic surveillance programs alone in FAP, AFAP and MAP are uncertain. Nevertheless, thoughtful use of chemopreventative agents, particularly in the context of clinical trials, may prove of some benefit.¹⁹

Table 5. Genetic testing guidelines for patients with multiple colorectal adenomas

Consider genetic testing if:

Local criteria vary, but reasonable guidelines include:

the detection of at least 20 colorectal adenomas (can be metachronous)

or

≥5 adenomas in patients <60 years, with a personal history of, or a first- or second-degree relative with, CRC or adenoma with high-grade dysplasia also before 60 years.

Refer to clinical genetics service:

If there is an autosomal dominant history of colorectal neoplasia then genetic testing will begin with APC. If no suggestive family history then APC and MUTYH testing will be performed concomitantly.

APC testing can be stopped

if biallelic MUTYH mutations are discovered.

If an informative mutation is discovered in:

APC – genetic testing for this mutation should be offered to all first degree relatives following genetic counseling.

MUTYH – genetic testing should be offered to the siblings, and possibly to spouse and children to clarify carrier status, again in the context of genetic counseling.

If no informative mutations are found then:

First degree relatives of patient with AFAP or FAP – should undergo colonoscopic or flexible sigmoidoscopic screening, respectively, as described in the text. If no colorectal adenomas have developed by age 35 years, then annual surveillance can be extended out to every 3 years, and if still no adenomas by 55 years, then return to population based screening.¹²

Hyperplastic polyposis syndrome (HPS)

HPS is a CRC-syndrome characterised by multiple, large hyperplastic polyps. The WHO criteria for HPS are:

1. At least 5 hyperplastic polyps, proximal to the sigmoid colon, of which at least 2 are >1cm in diameter
2. Any number of hyperplastic polyps proximal to the sigmoid colon in a first degree relative of a patient with HPS
3. >30 hyperplastic polyps throughout the colon.

In a recent series of HPS, the median age of diagnosis was 44 years and although 50% of patients had a first degree relative with CRC only a minority had a family history of HPS, per se.³¹ No germline mutation has yet been identified for this syndrome. Whilst management strategies are still evolving, a reasonable approach includes annual to biennial colonoscopy depending on the polyp burden, with surgical resection guided by patient factors such as preference, polyp burden, age and comorbidities. Colonoscopic screening of first degree relatives is advisable from 40 years of age or 10 years younger than the earliest diagnosis in the family.¹⁴

Hereditary Non-polyposis Colorectal Cancer (HNPCC, Lynch syndrome)

Hereditary non-polyposis CRC (also known as Lynch syndrome) is an autosomal dominant cancer syndrome, inherited by a mutation in one of four genes involved in DNA mismatch repair (MMR), MLH1, MSH2, MSH6 or PMS2.³² The MMR system is one of the cell's "quality assurance" mechanisms checking all newly synthesised DNA against the template strand. Patients with HNPCC begin life with one faulty copy (from their affected parent) and one functioning copy (from their unaffected parent) in all somatic cells.

If the "good" copy of the gene stops working through silencing, genomic loss or mutation, the MMR system fails. This ultimately produces a population of mutated and mutable cells from which cancers can develop.³²

Several clinicopathological criteria have been developed to identify patients and families that are at higher risk of HNPCC. These criteria help to identify tumours for further molecular testing (**Table 6**).^{1, 33-35}

HNPCC mutation positive patients should undergo annual colonoscopic surveillance from 25 years or 5 years earlier than their youngest affected relative. Families without an informative mutation but who still fulfil the Amsterdam criteria (the 3-2-1 rule: **three** relatives affected over **two** generations, with one being a first-degree relative of another two, and at least **one** of the cancers occurred before 50 years of age) are usually managed the same, although colonoscopy is often scheduled for every other year. Mutation negative members of an HNPCC-family with an informative mutation are only at average risk for CRC and should be managed accordingly (category 1). The cancer risk in HNPCC is not confined to the colorectum (see footnote to **Table 6** above).

Extracolonic screening by intermittent gastroscopy, annual urinary cytology and in women transvaginal ultrasound (plus CA-125 in post-menopausal women) is a reasonable approach.

Families meeting the Amsterdam criteria but with no evidence of mismatch repair deficiency (type x families) have a lower risk, and first degree relatives can be offered surveillance colonoscopy every 3 to 5 years; women do not need HNPCC-protocol gynaecological screening in type x families.

Table 6. The Revised Bethesda Guidelines for further testing of colorectal tumours, such as immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 and microsatellite instability³⁵

Tumours from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours,* regardless of age.
3. Colorectal cancer with the MSI-H** histology*** diagnosed in a patient who is less than 60 years of age.
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age.

*HNPCC-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain tumours, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome and carcinoma of the small bowel.

**MSI-H refers to changes in two or more of the five National Cancer Institute-recommended microsatellite markers.

***Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

COLORECTAL CANCER SCREENING: THE OPTIONS

Diagnostic and screening tests are applied to different populations. The discussion above is largely restricted to colonoscopy and FOBT. In Australia, the faecal immunochemical test (FIT) a type of faecal occult blood test has become the preferred population-based test for CRC screening. It must be acknowledged, however, that a range of tests are offered, for the purpose of average risk CRC screening.

Although the scientific knowledge base supporting screening is the same for both mass screening and case finding, there are some relevant differences between these groups. Firstly, case finding involves an individual doctor providing an opinion for an individual patient. That opinion may take into account parameters other than the scientific knowledge base including patient anxiety, minor symptoms, the individual's risk of screening and an unwillingness (patient or doctor) to accept suboptimal sensitivity even in the face of higher procedural risks. 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.

Even though FOBT is the evidenced-based strategy for CRC-screening in average risk populations, it is appropriate to discuss the options with self-selected individuals to reach an informed decision on the CRC-screening modality of choice.

There are a large number of possible "CRC screening tests", including digital rectal examination, double contrast barium enema, molecular faecal and serum assays as well as emerging, and very exciting, capsule technology. The most effective, acceptable and readily available choices in Australia, however, fit into 3 main categories:

1. Stool based:

- a. Guaiac-based FOBT (gFOBT) (e.g. Hemoccult II and Hemoccult SENZA): guaiac tests are based on the pseudoperoxidase activity of haem. gFOBTs require dietary restrictions prior to testing and are not entirely specific for colorectal bleeding.
- b. Faecal immunochemical tests (FIT): immunochemical tests that utilise antibodies to human haemoglobin. Dietary restrictions are not necessary and these tests are more specific for colorectal bleeding. Many of the FIT kits also have had their sampling protocols optimised, which has translated into enhanced participation.⁸ FIT technology now includes quantitative analysis, enabling greater flexibility.⁸ gFOBT and FIT generally require multiple sampling of 2 to 3 stools per test.

Whilst, only gFOBT kits are proven to reduce CRC-specific mortality in randomised controlled trials, it is well established that the FIT constitutes a more sensitive, specific and acceptable assay.³ The estimated sensitivity of one-time testing for CRC using gFOBT is approximately 35-67% vs. 65-90% for FIT.^{3, 36, 37} FIT has become the standard of care in CRC screening in Australia.⁸ The specificity for neoplasia overall (cancers and adenomas) ranges from 90-98% for gFOBT and 95% for FIT, depending again on the exact test and cut offs used.⁸ The sensitivity of either FIT or gFOBT for advanced adenomas on one-time testing, however, is more modest (27%).³⁶ FOBT-screening programs have shown a slight reduction in the incidence of CRC.³⁸ If CRC prevention is the new goal of CRC screening,³ rather than simply reducing CRC specific mortality, then advanced adenomas need to be more reliably detected either through new technologies or a greater reliance on structural examinations, such as colonoscopy.³

2. Endoscopic:

- a. Colonoscopy: This is the current gold-standard test for the diagnosis of CRC. Following a good bowel preparation, careful colonoscopy is potentially able to inspect the entire mucosal surface of the colorectum. At the same session, any polyps can usually be excised and retrieved, providing a complete diagnostic and therapeutic procedure. Cost, capacity, compliance, complications, convenience and lack of controlled trial evidence remain barriers to promoting colonoscopy as a primary, average-risk screening tool. Furthermore colonoscopy is an imperfect gold standard.³ Bowel preparation, careful technique and time are imperative in maintaining high quality colonoscopy. The colonoscopy miss rate for large adenomas (>10 mm) has been reported at 6-12% and the miss rate for cancers may be as high as 5%.³ The higher proportion of right sided interval cancers in patients after complete colonoscopy, suggests that the miss rate may be even higher for proximal sessile polyps.³⁹ These estimates, however, are likely to be operator dependent, highlighting the need for rigorous quality assurance of colonoscopy performance. In Australia, colonoscopy is recommended only for higher risk individuals, identified by symptoms, a positive FOBT, strong family history or previous colorectal disease (as described above).
- b. Flexible sigmoidoscopy: Flexible sigmoidoscopy screening involves endoscopic inspection of the distal colorectum, usually to the splenic flexure. Any distal adenomatous polyps serve as a trigger to perform full colonoscopy. Flexible sigmoidoscopy screening is often performed unsedated using limited bowel preparation. Compared to colonoscopy, flexible sigmoidoscopy detects 60% to 70% of advanced neoplasia.³ However, this figure varies with age because proximal neoplasia is more common in patients older than 65 years, especially in women.³ Flexible sigmoidoscopy screening every 5 years is endorsed in our national guidelines as an optional addition to annual or biennial FOBT-based screening guidelines in the

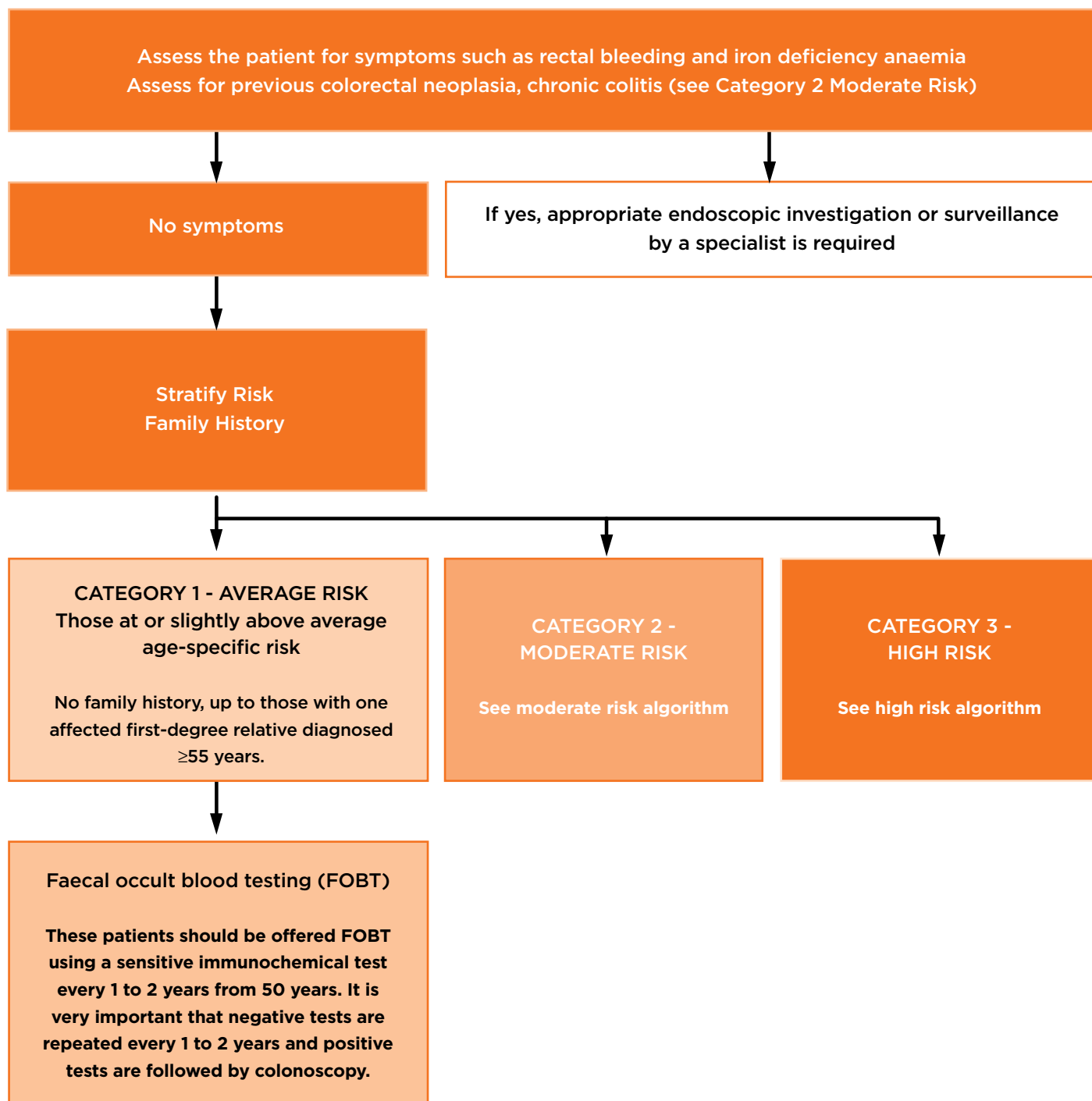
average risk population from 50 years of age. It must be acknowledged, however, that flexible sigmoidoscopy is a less frequently utilised aspect of average risk screening.

3. CT colonography (CTC):

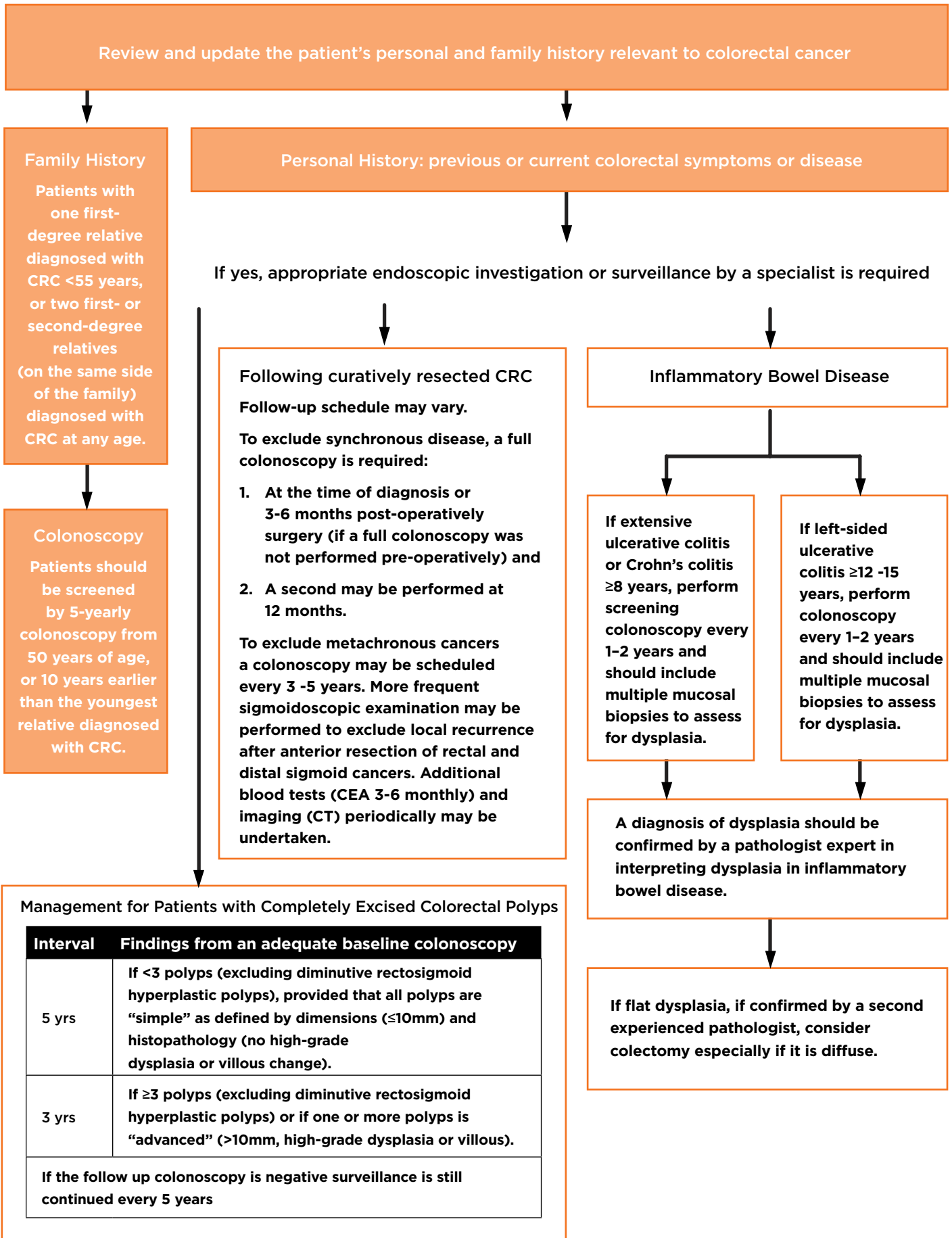
CTC promises to be a valuable alternative in CRC screening. CTC may have a sensitivity of up to 90% for detecting neoplasia 10mm or more in diameter, which is comparable to colonoscopy, although some earlier studies suggested lower sensitivities.^{40,41} The sensitivity of CTC for detecting smaller lesions, however, is more modest. In a recent series, the sensitivity for adenomas 5mm or more fell to 65%.⁴⁰ The finite risk of adenocarcinoma even in these small polyps must be addressed when counseling patients about the risks and benefits of CTC. Other limitations of CTC include the radiation dose, the necessity for a standard cathartic bowel preparation and, of course, CTC is a non-therapeutic strategy. There is also the issue of identifying extra-colonic abnormalities. The cost-effectiveness of CTC in CRC-screening depends on the polyp-dimension thresholds used for triggering colonoscopy.⁴¹ In the future, particularly if a less demanding bowel preparation is realised, it is likely that CTC will be introduced into case finding CRC screening algorithms.⁴¹

COLORECTAL CANCER SCREENING: THE ALGORITHMS

Colorectal Cancer Screening Recommendation for Individuals at Average Risk (asymptomatic patients age 50 years or older)



Colorectal Cancer Screening Recommendation for Individuals at Moderate Risk



Colorectal Cancer Screening Recommendation for Individuals at High Risk



APPENDIX A

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 counseling 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.

Family Cancer Clinics are well placed to engage in clinical research efforts to identify new genes predisposing to cancer, screening methodologies, and psychosocial science. Many families appreciate these opportunities.

APPENDIX B

Contact Information for Familial Cancer Clinics

AUSTRALIA

ACT

Genetics Clinic
Canberra Hospital
Telephone (02) 6244 4042
Telephone (02) 6244 2133

New South Wales

Department of Clinical Genetics and Hereditary Cancer
Liverpool Hospital
Telephone (02) 9828 4665

Hereditary Cancer Centre
Prince of Wales Hospital
Telephone (02) 9382 2577

Family Cancer Service
Royal North Shore Hospital
Telephone (02) 9926 6502

Hereditary Cancer Clinic
St George Hospital
Telephone (02) 9113 3815

Family Cancer Centre
St Vincent's Hospital
Telephone (02) 8382 3395

Familial Cancer Service
Westmead Hospital
Telephone (02) 9845 6947

OUTREACH SERVICES:

Bathurst Community Health Centre
Telephone (02) 5339 5677

Broken Hill Health Service
Telephone (02) 4985 3100

Coffs Harbour Genetic Counselling Service
Telephone (02) 6656 7806

Dubbo Community Health Centre
Telephone (02) 6885 8999

Gosford Child and Family Health Centre
Telephone (02) 4328 7994

Goulburn Genetic Counselling Service
Telephone (02) 4827 3951

Lismore Base Hospital
Telephone (02) 6620 2967

Newcastle Hunter Family Cancer Service
Telephone (02) 4985 3100

Port Macquarie Health campus
Telephone (02) 6588 2783

Tamworth Community Health Service
Telephone (02) 6767 8151

Taree Child and Family Health Service
Telephone (02) 5592 9703

Wagga Wagga Community Health service
Telephone (02) 6938 6443

Woollongong Hospital
Telephone (02) 422 5576

Queensland

Genetic Health Queensland
Royal Children's Hospital
Telephone (07) 3636 1686

South Australia

Familial Cancer Unit
South Australia Pathology
Women's and Children's Hospital
Telephone (08) 8161 6995

Tasmania

Clinical Genetic Clinics
Royal Hobart Hospital
Launceston General Hospital
North West Regional Hospital
Outreach services available
Telephone (03) 6222 8296
www.dhhs.tas.gov.au

Victoria

Genetic Health Services Victoria
Royal Children's Hospital
Telephone (metro) (03) 8341 6201
Telephone (non-metro) (03) 8341 6224
www.genetichealthvic.net.au

The Peter MacCallum Familial Cancer
Centre
Telephone (03) 9656 1199
Email FamilialCancer@petermac.unimelb.edu.au
www.petermac.org

The Royal Melbourne Hospital Familial
Cancer Centre
Royal Melbourne Hospital
Telephone (03) 9342 7151
Email familycancer@mh.org.au
www.mh.org.au/RMHGenetics

The MMC Familial Cancer Centre
Monash Medical Centre
Telephone (03) 9594 2026

For further information contact the cancer
information and support service on
CanHELP 131120
www.cancervic.org.au/familycancer

Western Australia

Genetic Services of WA
King Edward Memorial Hospital
Telephone (08) 9340 1525

NEW ZEALAND

Northern Regional Genetic Services
Auckland Hospital
Telephone (09) 307 4949 - ext 5530
Freephone: 0800 476 123

Central Regional Genetic Services
Wellington Hospital
Telephone (04) 385 5310
Freephone: 0508 364 436

Southern Regional Genetic Services
Christchurch Hospital
Telephone (03) 379 1898
Freephone: 0508 364 436

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