*Evidence-based Best Practice Guideline*

MAY 2004

# Surveillance and Management of Groups at Increased Risk of *Colorectal Cancer*

NEW ZEALAND GUIDELINES GROUP
Promoting Effective Health and Disability Services
www.nzgg.org.nz

Evidence-based Best Practice Guideline

# SURVEILLANCE AND MANAGEMENT OF GROUPS AT INCREASED RISK OF COLORECTAL CANCER

MAY 2004

NEW ZEALAND GUIDELINES GROUP
Promoting Effective Health and Disability Services

## ENDORSED BY:

College of Nurses Aotearoa NZ

The Royal New Zealand College of General Practitioners

The Royal Australasian College of Physicians New Zealand

New Zealand Nurses Organisation

The Royal Australian and New Zealand College of Radiologists New Zealand

RCPA The Royal College of Pathologists of Australasia

New Zealand Society of Gastroenterology Inc.

## SUPPORTED BY:

Royal Australasian College of Surgeons – New Zealand Branch

### *STATEMENT OF INTENT*

Evidence-based guidelines are produced to help health care practitioners and consumers make decisions about health care in specific clinical circumstances. Research has shown that if properly developed, communicated and implemented, guidelines can improve care. The advice on surveillance and management of groups at increased risk of colorectal cancer given in this guideline is based on epidemiological and other research evidence. While the guideline provides recommendations based on the latest available evidence, it is not intended to replace the health care practitioner's judgment in each individual case.

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# PURPOSE

The aim of this guideline is to provide evidence-based surveillance recommendations for individuals identified to be at increased risk of developing colorectal cancer. The guideline was developed as a companion document to the 1998 National Health Committee's working party report on *Population Screening for Colorectal Cancer.*

The guideline is intended for use by primary health care providers, and medical and surgical specialists, to facilitate consistency of advice and care for those individuals who are at increased risk of developing colorectal cancer by virtue of their personal history of colorectal disease or family history of colorectal cancer.

# ABOUT THE GUIDELINE



## FOREWORD

The New Zealand Guidelines Group Incorporated (NZGG) is a not-for-profit organisation established to promote effective health and disability services. Guidelines make a contribution to this aim by collating and summarising the latest international studies and advising on their application in the New Zealand setting. The guidelines consider the current availability of resources in the publicly funded health system to ensure that recommendations are realistic and to inform policy and planning – for example, to cope with an anticipated increase in referrals for colonoscopy.

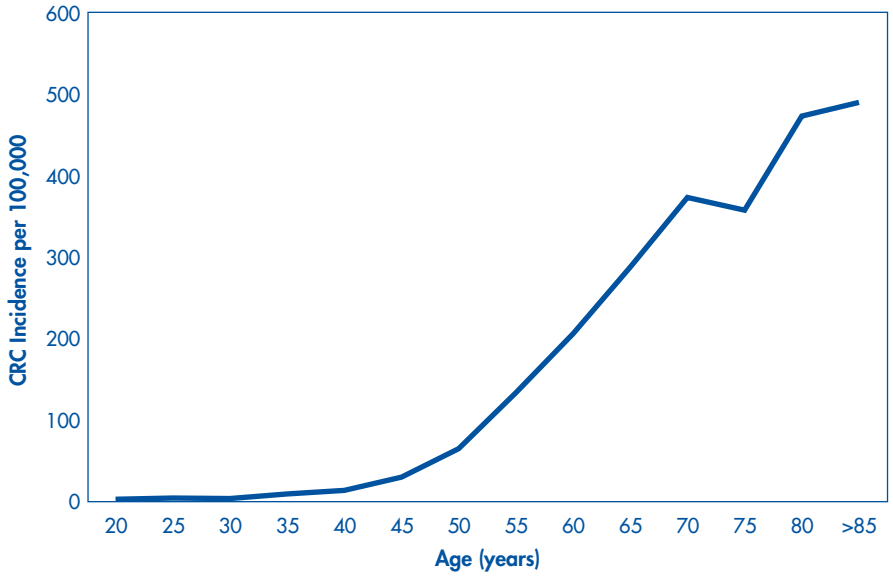
Specialists, general practitioners, individuals with colorectal cancer (CRC) and consumers are increasingly requesting information on risk assessment and surveillance advice for CRC. These guidelines will assist in meeting this need and in identifying the most appropriate use of limited colonoscopic resources.

## BACKGROUND TO THE GUIDELINE

### Colorectal Cancer in New Zealand

Colorectal cancer is an important cause of morbidity and mortality. In New Zealand, the lifetime risk of developing this condition is 5.9% by the age of 75 years. It is the second most common cancer registered for both men and women. Each year between about 2000 and 2500 New Zealanders (2075 in 1992, 2069 in 1993, 2476 in 1994, 2403 in 1995, 2434 in 1996) will be diagnosed with CRC and about 1000 will die as a result of CRC. The age-specific incidence of CRC in New Zealand is shown graphically in Figure 1 and reported in Table 1. Table 2 shows the risk of development of CRC in the New Zealand population from one given age to another.

*Figure 1: Age-specific incidence of CRC in New Zealand, 1998*




Source: New Zealand Health Information Service. Cancer: New Registrations and Deaths 1998. Wellington: Ministry of Health; 2002.

*Table 1: Age-specific CRC incidence in New Zealand, 1998*

| Age group (years) | Colorectal cancer registrations | Rate per 100,000 | Risk during 5-year period (%) | Cumulative risk to end of 5-year period (%) |
|---|---|---|---|---|
| **0 – 24** | 1 | 0.1 | <0.1 | <0.1 |
| **25 – 29** | 8 | 2.8 | <0.1 | <0.1 |
| **30 – 34** | 7 | 2.4 | <0.1 | <0.1 |
| **35 – 39** | 26 | 8.4 | <0.1 | 0.1 |
| **40 – 44** | 38 | 13.7 | 0.1 | 0.1 |
| **45 – 49** | 73 | 29.1 | 0.1 | 0.3 |
| **50 – 54** | 140 | 64.4 | 0.3 | 0.6 |
| **55 – 59** | 233 | 133.2 | 0.7 | 1.3 |
| **60 – 64** | 288 | 205.4 | 1.0 | 2.3 |
| **65 – 69** | 380 | 287.1 | 1.4 | 3.7 |
| **70 – 74** | 438 | 372.4 | 1.9 | 5.6 |
| **75 – 79** | 319 | 356.6 | 1.8 | 7.4 |
| **80 – 84** | 272 | 471.1 | 2.4 | 9.7 |
| **>85** | 210 | 488.0 | 2.4 | 12.2 |

Source: New Zealand Health Information Service. Cancer: New Registrations and Deaths 1998. Wellington: Ministry of Health; 2002.

*Table 2: Risk of CRC for the New Zealand population from one given age to another, 1998*

| Risk (%) of CRC to age | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Current age** | **29** | **34** | **39** | **44** | **49** | **54** | **59** | **64** | **69** | **74** | **79** | **84** |
| **25** | <0.1 | <0.1 | 0.1 | 0.1 | 0.3 | 0.6 | 1.3 | 2.3 | 3.7 | 5.6 | 7.4 | 9.7 |
| **30** | | <0.1 | 0.1 | 0.1 | 0.3 | 0.6 | 1.3 | 2.3 | 3.7 | 5.6 | 7.4 | 9.7 |
| **35** | | | <0.1 | 0.1 | 0.3 | 0.6 | 1.2 | 2.3 | 3.7 | 5.6 | 7.4 | 9.7 |
| **40** | | | | 0.1 | 0.2 | 0.5 | 1.2 | 2.2 | 3.7 | 5.5 | 7.3 | 9.7 |
| **45** | | | | | 0.1 | 0.5 | 1.1 | 2.2 | 3.6 | 5.5 | 7.2 | 9.6 |
| **50** | | | | | | 0.3 | 1.0 | 2.0 | 3.5 | 5.3 | 7.1 | 9.5 |
| **55** | | | | | | | 0.7 | 1.7 | 3.1 | 5.0 | 6.8 | 9.1 |
| **60** | | | | | | | | 1.0 | 2.5 | 4.3 | 6.1 | 8.5 |
| **65** | | | | | | | | | 1.4 | 3.3 | 5.1 | 7.4 |
| **70** | | | | | | | | | | 1.9 | 3.6 | 6.0 |
| **75** | | | | | | | | | | | 1.8 | 4.1 |
| **80** | | | | | | | | | | | | 2.4 |

Source: New Zealand Health Information Service. Cancer: New Registrations and Deaths 1998. Wellington: Ministry of Health; 2002.



## Working Party on Population Screening

In late 1996, a reduction in CRC mortality was demonstrated as a result of screening for CRC with faecal occult blood tests (FOBTs) in two population-based randomised controlled trials: in Nottingham, England and Funen, Denmark. In response to this, the National Health Committee convened an independent working party to:

- review the evidence for benefits and risks associated with the introduction of population screening for CRC
- identify the economic and resource implications of introducing a CRC screening programme and its likely acceptability
- report to the National Health Committee on issues surrounding population screening for CRC and make recommendations on the introduction of a screening programme in New Zealand or other actions that should be taken to reduce deaths from CRC in New Zealand.

Members of the working party were nominated by relevant medical colleges and societies and the Cancer Society of New Zealand Inc. (CSNZ), and included consumer and Maori representatives. The working party adopted an evidence-based approach, critically evaluating the literature on the benefits, risks and adverse effects of screening for CRC using a variety of screening modalities. The working party met on several occasions over an 18-month period and published its recommendations in a comprehensive report in November 1998. The report of the working party was endorsed by the National Health Committee and circulated to the majority of medical practitioners.

The working party advised that:

- given the modest potential benefit, the considerable commitment of health sector resources and the small but real potential for harm, population-based screening for CRC with FOBTs is not recommended in New Zealand

- population-based screening for CRC with other modalities, such as flexible sigmoidoscopy, colonoscopy or double-contrast barium enema, is also not recommended as there is not yet evidence of benefit from randomised controlled trials that screening with any of these modalities produces a reduction in CRC mortality
- these decisions should be reviewed as evidence of benefit from new FOBTs and other screening modalities becomes available
- CRC is recognised as an important cause of morbidity and mortality and it is recommended that New Zealand participates in international research in this area
- wider consultation and further consideration should be undertaken to develop appropriate advice on surveillance for groups identified to be at increased risk of CRC.



## Developing Advice on Surveillance for Groups at Increased Risk of CRC

To address the last recommendation, a subcommittee of the original National Health Committee working party was constituted in 1999, under the auspices of the NZGG to develop a guideline outlining recommendations for the surveillance and management of groups identified to be at increased risk of developing CRC. The subcommittee comprised medical and surgical specialists, a general practitioner, an epidemiologist, and consumer and CSNZ representatives. The subcommittee met over an 18-month period, and used an evidence-based approach to review the relevant literature.

# GUIDELINE DEVELOPMENT PROCESS

In establishing the present guidelines the subcommittee took an independent approach. The key issues and questions to be addressed were agreed at the outset. Individual sub-committee members then performed a comprehensive literature review of the four major increased risk groups for CRC identified in this guideline.

1. Family history of CRC
2. Personal history of CRC
3. Colorectal adenoma
4. Inflammatory bowel disease



The individual sub-committee members then reviewed the evidence using the same evidence grading system as was used in the 1996 working party report. This is described in detail on page xii. The evidence in each area was then presented and over several meetings between April 1999 and late 2001 the sub-committee developed the recommendations made in this guideline. Each recommendation represents a consensus decision by the sub-committee. The chapters of the guideline were drafted by individuals and an editor employed to work with the Chairperson to bring the chapters and recommendations into a single document.

In developing these recommendations, consistency with evidence-based guidelines within Australasia was seen as desirable, where possible. In this regard the value of the resource base provided by the Australian National Health and Medical Research Council (NHMRC) clinical practice guidelines on The Prevention, Early Detection and Management of Colorectal Cancer (1999) and on Familial Aspects of Cancer (2000) in preparing this guideline is acknowledged. In some sections, after reviewing the evidence, the recommendations in the New Zealand guideline mirror those in the Australian guideline.

Successful implementation of clinical practice guidelines requires endorsement and support from the appropriate specialist, general practitioner and consumer groups. To facilitate this, the initial draft document was circulated for expert comment to the appropriate colleges and societies and others in December 2001. This guideline includes revisions made in response to both returned comments and significant medical literature published subsequently. Reviewers were asked to appraise the draft using the AGREE Instrument. Suggestions and comments were incorporated into the final draft. The final draft was sent out for endorsement in April 2004.

Successful implementation of guidelines also requires adequate availability of information for all involved and adequate provision of health care resources. We hope to ensure the former but, given the anticipated increase in referrals for colonoscopy as a result of these guidelines, a commitment by health care funders is necessary to ensure the latter. Discussion with the appropriate providers about the impact of these guidelines on colonoscopic referrals has already begun and strategies for managing this should be in place prior to publication of these guidelines.

This guideline does not address service delivery issues, such as the way in which services should meet the needs of Maori. These areas will be addressed in the guideline update in 2007.

# GUIDELINE DEVELOPMENT TEAM

The Guideline Development Team was commissioned by the NZGG and funded by the Ministry of Health to develop a guideline outlining recommendations for the surveillance and management of groups at increased risk of CRC. A multidisciplinary team was convened with members representing stakeholder professional and consumer groups.



## Guideline Subcommittee Members

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## Declarations of Competing Interests
There were no competing interests declared for this guideline.

# CONSULTATION
The initial draft of these guidelines was circulated for expert comment to the appropriate colleges, societies and others in December 2001. The subcommittee is grateful to the following for their comments:

- Associate Professor Ingrid Winship, Northern Regional Genetic Service, Auckland City Hospital and University of Auckland, Auckland
- Associate Professor John McCall, Surgeon, Auckland City Hospital; Department of Surgery, University of Auckland, Auckland
- Associate Professor Mark Lane, President, New Zealand Gastroenterology Society; Gastroenterology Department, Auckland City Hospital and University of Auckland, Auckland
- Dr Alexa Kydd, Central Regional Genetic Service, Wellington Hospital, Wellington
- Dr Brian Cox, Chair, New Zealand Cancer Control Group; Director, Hugh Adams Cancer Epidemiology Unit, Dunedin School of Medicine, University of Otago, Dunedin
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# EVIDENCE-GRADING SYSTEM USED FOR THESE GUIDELINES

To maintain consistency, the evidence-grading hierarchy used by the initial 1998 National Health Committee working party was continued by the subcommittee. This is outlined in Table 3.

*Table 3: Evidence-grading hierarchy*

| Description | Comments | Grade of Evidence |
|---|---|---|
| Randomised controlled trials | Randomised controlled trials can control for various forms of bias associated with screening | 1 |
| Non-randomised controlled trials | Randomisation is needed to minimise bias and confounding | 2 |
| Non-randomised historical cohort studies<br><br>Case-control and other population studies | Compares current outcomes due to intervention with previous outcomes, which may permit inappropriate groups to be compared | 3 |
| Case series | Data are derived from a group of unselected individuals, and are limited in value | 4 |
| Expert (consensus) opinion | Not evidence *per se*, but may have value where evidence is not likely to be or become available | 5 |

# SUMMARY AND RECOMMENDATIONS



## KEY MESSAGES

- The risk of developing colorectal cancer (CRC) for the average New Zealander is 0.6% by the age of 55 years and 5.6% by the age of 75 years.
- Individuals with a personal history of CRC, colorectal adenomas and inflammatory bowel disease are at increased risk of developing CRC.
- A family history of CRC may increase an individual's lifetime risk of developing this disease. The number of affected first-degree relatives and the age at which they were diagnosed with CRC determine this risk.
- Offer colonoscopy every 5 years from the age of 50 years (or from an age 10 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). to individuals at moderately increased risk of developing CRC on the basis of a family history of CRC. Individuals with a moderate increase in risk are those with:
  - one first-degree relative with CRC diagnosed before the age of 55 years, OR
  - two first-degree relatives on the same side of the family with CRC diagnosed at any age.
- Individuals offered colonoscopy should be informed that it is an invasive procedure and generally safe, but is not totally without risk.
- Where an inherited bowel cancer syndrome is suspected (high-risk individuals), refer to a genetic specialist, family cancer clinic or familial bowel cancer registry and a bowel cancer specialist to plan appropriate surveillance and management.
- Individuals or families with hereditary CRC syndromes should be offered referral to a familial bowel cancer registry.
- Individuals who have undergone resection of CRC with curative intent should have specialist follow-up over the time period in which the majority of cancer recurrences occur. Individuals free of recurrent CRC for 3 to 5 years should be referred for regular colonoscopy surveillance.
- Individuals who have had high-risk colorectal adenomas identified require continued colonoscopic surveillance. This group includes those initially identified with multiple (>3), large (>10 mm), severely dysplastic or villous adenomas and those with a significant family history of CRC.
- Individuals with longstanding (8 – 10 years duration) extensive inflammatory bowel disease should be referred for regular colonoscopic surveillance.
- Surveillance colonoscopy should be performed in well individuals by experienced operators with acceptable completion rates to the caecum.

# RECOMMENDATIONS

| CATEGORY 1: INDIVIDUALS WITH A SLIGHT INCREASE IN RISK OF CRC DUE TO FAMILY HISTORY (UP TO 2-FOLD COMPARED WITH THE GENERAL POPULATION)<br>• One first-degree relative with CRC diagnosed over the age of 55 years | |
|---|---|
| No specific surveillance recommendations are made for this group at this time given the slight increase in risk, the uncertainty regarding the age at which this additional risk is expressed and the concern regarding the appropriateness of colonoscopy as a surveillance procedure in this group. | 5 |
| Prompt investigation of lower bowel symptoms is advised. | 5 |
| Individuals requesting information should be fully informed regarding their absolute risk of developing CRC and advised of the reasons for this recommendation. | 5 |

| CATEGORY 2: INDIVIDUALS WITH A MODERATE INCREASE IN RISK OF CRC (3- TO 6-FOLD COMPARED WITH THE GENERAL POPULATION)<br>• One first-degree relative with CRC diagnosed under the age of 55 years<br>• Two first-degree relatives on the same side of the family with CRC diagnosed at any age | |
|---|---|
| Offer colonoscopy every 5 years from the age of 50 years (or from an age 10 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). | 3 |
| Fully inform individuals in category 2 about their risk of developing CRC and the reason for this recommendation. | 5 |
| Individuals in category 2 should be informed that colonoscopy is generally a safe procedure, but it is an invasive procedure with some rare but recognised risks. | 5 |

| CATEGORY 3: INDIVIDUALS WITH A POTENTIALLY HIGH (50%) RISK OF CRC<br>• A family history of familial adenomatous polyposis, hereditary non-polyposis colorectal cancer or other familial CRC syndromes<br>• One first-degree relative plus two or more first- or second-degree relatives, all on the same side of the family, with a diagnosis of CRC, at any age<br>• Two first-degree relatives, or one first-degree relative plus one or more second-degree relatives, all on the same side of the family, with a diagnosis of CRC and one such relative<br>– was diagnosed with CRC under the age of 55 years, or<br>– developed multiple bowel cancers, or<br>– developed an extracolonic tumour suggestive of hereditary non-polyposis colorectal cancer (ie, endometrial, ovarian, stomach, small bowel, upper renal tract, pancreas or brain)<br>• At least one first- or second-degree family member diagnosed with CRC in association with multiple bowel polyps<br>• A personal history or one first-degree relative with CRC diagnosed under the age of 50, particularly where colorectal tumour immunohistochemistry has revealed loss of protein expression for one of the mismatch repair genes (hMLH1 or hMSH2). | |
|---|---|
| Refer to:<br>• a genetic specialist/family cancer clinic or familial bowel cancer registry for further risk assessment and possible genetic testing (for contact details see Appendix B)<br>• a bowel cancer specialist to plan appropriate surveillance and management. | 5 |

## RECOMMENDATIONS: FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is an autosomal-dominant inherited disease characterised by the presence of multiple small adenomas (>100) throughout the colon and rectum. These polyps develop in the early-to-midteens. The median age at diagnosis for CRC in untreated affected individuals is 40 years.

| | |
|---|---|
| **Genetic testing**<br>Offer referral to a genetic service for consideration of genetic testing within the context of appropriate counselling to:<br>• individuals with a clinical diagnosis of FAP<br>• all at-risk family members if a family-specific genetic mutation has been identified<br>at the age when sigmoidoscopic surveillance would normally begin. | 5 |
| **Bowel surveillance**<br>Sigmoidoscopy 1- to 2-yearly from the age of 12 to15 years is recommended for asymptomatic individuals with an identified disease-causing FAP mutation and for all at-risk members of families with FAP if genetic testing is not available or is non-informative.<br>Individuals found to have colorectal adenomas should be referred to a bowel cancer specialist.<br>Increase the interval for sigmoidoscopic surveillance to 3-yearly at 35 years if previous examinations have been normal. Consider cessation at 55 years.<br>If attenuated FAP is suspected colonoscopy is advised. Depending on the family history this may begin as late as 18 years and continue beyond 55 years. | 3 |
| **Prophylactic colectomy**<br>Prophylactic colectomy comprises total colectomy and ileo-rectal anastomosis or restorative proctocolectomy procedures. The choice of procedure is influenced by the rectal polyp burden and the individual's preference.<br>Offer to individuals with an established diagnosis of FAP.<br>The timing of surgery is individualised but is usually performed by the late teenage years.<br>Following colectomy and ileo-rectal anastomosis, annual surveillance of the rectum by sigmoidoscopy with removal and destruction of polyps is advised until restorative proctectomy with ileo-anal pouch construction is performed. This surgery should be considered in all such individuals at age 45 to 50 years because of the increasing risk of rectal cancer.<br>Proctectomy should be performed at an earlier age if polyps are not adequately controlled or CRC develops. | 3 |
| **Surveillance of upper gastrointestinal tract**<br>There are no published data demonstrating a reduction in mortality from duodenal cancer as a consequence of upper gastrointestinal surveillance.<br>Gastroduodenoscopy to detect duodenal adenomas at 1- to 3-yearly intervals from 30 to 35 years of age is commonly advised, as most advanced duodenal adenomas develop after the age of 40 years.<br>The Spigelman Criteria may be used to guide surveillance interval.<br>Pancreaticoduodenectomy should be considered in those with advanced but benign disease (Spigelman Stage IV). | 3 |

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

1 Randomised controlled trials
2 Non-randomised controlled trials
3 Non-randomised historical cohort studies
4 Case series
5 Expert (consensus) opinion

## RECOMMENDATIONS: HEREDITARY NON-POLYPOSIS COLORECTAL CANCER

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal-dominant inherited condition characterised by the development of CRC at a mean age of 45 years, and was previously known as Lynch Syndrome.

| | |
|---|---|
| **Genetic testing**<br>Offer referral to a genetic service for consideration of genetic testing, within the context of appropriate counselling, to all at-risk members of families with HNPCC, at the age when colonoscopic surveillance would normally begin. | 5 |
| **Bowel surveillance**<br>Colonoscopy is recommended 2-yearly from the age of 25 years (or from an age 5 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). Consider annual colonoscopy in known mutation carriers. | 3 |
| **Surgery**<br>Colectomy with ileo-rectal anastomosis is advised once cancer develops in known mutation carriers or at-risk members of families with HNPCC.<br>Annual surveillance sigmoidoscopy of any residual large bowel should be performed. | 5 |
| **Prophylactic surgery**<br>Prophylactic subtotal colectomy should be discussed with individuals who are known mutation carriers and have recurrent adenomas with a high degree of dysplasia or a villous growth pattern.<br>Prophylactic colorectal surgery in known mutation carriers without any colorectal pathology (ie, negative colonoscopies) is not indicated because 10 to 20% of such individuals will not develop CRC in their lifetime.<br>Consider prophylactic surgery in known mutation carriers who are not willing or are unable to undergo periodic surveillance colonoscopy. | 5 |
| **Extracolonic surveillance**<br>Surveillance for at-risk members of families with HNPCC or known mutation carriers takes into account the pattern of cancers occurring in particular families and the gene location of the disease-causing mutation, if known.<br>**Surveillance for endometrial cancer**<br>This is the most common extracolonic malignancy. Surveillance with annual transvaginal ultrasound (+/- endometrial aspiration biopsy) is usually advised for:<br>• known mutation carriers<br>• at-risk members of families with HNPCC as determined by the Amsterdam Criteria if there is a family history of uterine cancer and/or genetic testing is non-informative.<br>The efficacy of these surveillance tools remains uncertain in premenopausal younger women. | 5 |

## RECOMMENDATION: HAMARTOMATOUS POLYPOSIS SYNDROMES

| | |
|---|---|
| Individuals with hamartomatous polyps of the large or small bowel, or those with a first-degree relative known to have multiple polyps alone or associated with CRC should be referred to the appropriate bowel and genetic specialists. | 5 |

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

1 Randomised controlled trials
2 Non-randomised controlled trials
3 Non-randomised historical cohort studies
4 Case series
5 Expert (consensus) opinion

| RECOMMENDATION: HYPERPLASTIC POLYPOSIS SYNDROME | |
|---|---|
| Individuals identified to have hyperplastic polyps beyond the rectosigmoid junction with risk features should be referred to the appropriate bowel and genetic specialists.<br>Risk features include:<br>• unusual numbers (>20)<br>• unusual size (≥10 mm)<br>• location in the proximal colon<br>• presence of high-grade dysplasia<br>• coincidental adenomas<br>• a first-degree relative with high-risk hyperplastic polyps<br>• a first-degree relative with CRC. | 5 |



| RECOMMENDATIONS: FAMILIAL BOWEL CANCER REGISTRIES | |
|---|---|
| There is a need for a national registry in New Zealand.<br>Familial bowel cancer registries facilitate:<br>• the diagnosis of hereditary CRC<br>• the maintenance of a confidential family database<br>• coordination of cancer surveillance<br>• multidisciplinary clinical management<br>• education for both families and medical practitioners. | 5 |
| Individuals or families with hereditary CRC syndromes should be offered referral to a familiar bowel cancer registry as coordination of cancer surveillance by registries in familial colorectal syndromes is associated with a reduction in cancer incidence (see Appendix B). | 3 |
| A working party is advised to review guidelines for the functioning of a national registry, particularly with regard to informed consent and confidentiality of registry information. | 5 |

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL CANCER | |
|---|---|
| Follow-up after resection of CRC with curative intent is recommended as it allows practitioners to monitor treatment outcome and is consistent with the preference of individuals with CRC. | 5 |
| All such individuals should have specialist follow-up over the time period in which the majority of recurrences (local or metastatic) are most likely to occur (3 – 5 years).<br>Follow-up should be appropriate to the clinical context. In deciding on intensity and duration of follow-up, age and comorbid conditions should be considered.<br>Follow-up should occur in conjunction with, and subsequently be continued by, the individual's general practitioner. | 5 |
| Individuals free of recurrent CRC for 3 to 5 years should be entered into a colonoscopy surveillance programme.<br>Colonoscopy should be performed at 3- to 5-yearly intervals. | 5 |
| All individuals with CRC should be informed of the uncertain efficacy of follow-up with regard to survival benefit. | 5 |

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL ADENOMA* | | | |
|---|---|---|---|
| **Factor** | **Assessed risk** | **First surveillance colonoscopy** | |
| Adenoma size ≥10 mm | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| ≥3 adenomas | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| Villous lesions and/or severe dysplasia | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| Adenomas with no high-risk features and: | | | 3 |
| • significant family history of CRC | High: continued surveillance | At 3 years | |
| • no family history of CRC | Low: consider discontinuing surveillance if subsequent surveillance colonoscopy normal. | At 5 – 6 years | |

*Presumes complete excision of previous adenomas.

†Shorter interval may be appropriate if multiple high-risk features at index procedure.

## RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

### ULCERATIVE COLITIS

**Initial surveillance colonoscopy** — 3

After 8 to 10 years, individuals with ulcerative colitis (UC) should undergo colonoscopy with serial biopsies (as detailed below) to define disease extent, both macroscopic and microscopic.

All those with significant disease extending proximal to the sigmoid colon should be enrolled in a surveillance programme.

**Surveillance colonoscopy** — 3

Colonoscopy is recommended 2-yearly for individuals with UC after 10 years' disease duration. At colonoscopy, 2 to 3 biopsies should be taken from each of 10 sites (caecum, proximal and distal ascending colon, proximal and distal transverse colon, proximal and distal descending colon, proximal and distal sigmoid colon and rectum). Additional biopsies should be taken from any mass lesions, but not from pseudopolyps.

Individuals with UC should be informed regarding:

- the rationale for surveillance colonoscopy and its limitations in detecting CRC
- the failure of studies to establish beyond doubt the value of surveillance in this situation.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE (CONTINUED) | |
|---|---|
| **Management of surveillance-detected dysplasia**<br>If high-grade dysplasia (HGD) is present on biopsy (and confirmed on histological review), the individual should be referred for colectomy.<br>If low-grade dysplasia (LGD) is found in the absence of significant inflammation:<br>• shorten the surveillance interval to 1 year<br>• refer for surgical review.<br>If LGD is found in the presence of active inflammation, it is advisable to repeat the colonoscopy after anti-inflammatory therapy. If LGD is confirmed, proceed as outlined for LGD above. | 3 |
| **CROHN'S DISEASE**<br>All individuals with extensive colorectal Crohn's disease should undergo surveillance procedures as detailed for individuals with extensive UC. | 4 |

# GROUPS AT INCREASED RISK OF COLORECTAL CANCER: IDENTIFICATION AND SURVEILLANCE



## OVERVIEW

- An increased risk of developing CRC is identified in individuals with:
  - a family history of CRC
  - a personal history of colorectal adenoma, CRC or longstanding extensive inflammatory bowel disease.
- Colonoscopy is the surveillance tool of choice for individuals identified as having a moderate-to-high lifetime risk of developing CRC.
- Colonoscopy is generally a safe procedure. Significant complications are rare.
- Surveillance colonoscopy should be performed in well individuals by experienced operators with acceptable completion rates to the caecum (>95%). It is important to establish ongoing monitoring of performance using identified, colonoscopy-specific quality indicators.
- The potential risks and benefits of surveillance colonoscopy need to be appraised for individuals of all ages. Surveillance colonoscopy is not usually advised after 75 years of age because remaining life expectancy is likely to be less than the average time required for new adenomas or dysplasia to progress to malignancy and the potential risks associated with surveillance are likely to outweigh the benefits. Surveillance colonoscopy may not be appropriate in some individuals under 75 years who have serious comorbid conditions.
- The decision to undertake each surveillance colonoscopy is dependent on the previously detected pathology and on the individual's decision after they have been fully informed regarding the risks and benefits of colonoscopy.

## IDENTIFICATION

The recommendations made by the National Health Committee's Working Party on Screening for Colorectal Cancer[1] apply to asymptomatic, average-risk individuals – that is, the general population within the age group at which CRC is most likely to develop.

However, an increased risk of developing CRC is identified in individuals with:

- a family history of CRC
- a personal history of colorectal adenoma, CRC or longstanding extensive inflammatory bowel disease.

It is important to identify such individuals to ensure that they are offered appropriate surveillance advice.

# 2 SURVEILLANCE

## Population Screening Versus Surveillance in Groups at Increased Risk

Screening is the examination of asymptomatic or well individuals in order to classify them as unlikely or likely to have a disease. A national screening programme is an example of a population preventive strategy, where everyone in a particular age-group is invited to participate. A population preventive strategy has the potential to identify a high proportion of individuals with early disease in a population.[2] In a screening programme, this proportion is dependent on the uptake of screening and the sensitivity of the test, both of which were low in population-based randomised controlled trials of faecal occult blood test (FOBT) screening for CRC.[3,4]

Even in cancer screening programmes where uptake is high and the screening test is very sensitive, the vast majority of individuals who take part will not have cancer, so that the potential benefits of screening are available to a relatively small group. However, any risks associated with screening have the potential to affect a large number of individuals. In the context of population-based screening, such individuals were previously well and would not have experienced the risks had they not been invited to take part in the screening programme. Thus, it is very important that there is good evidence of benefit from screening, and that screening tests and follow-up investigations carry low risks.[5]

Surveillance, as opposed to screening, refers to monitoring individuals known to have a disease or to be at increased risk of a disease. In these guidelines, recommendations are made on the follow-up and management of individuals identified to be at increased risk of developing CRC and therefore the term surveillance rather than screening is appropriate. A greater proportion of this group could potentially benefit from surveillance because the prevalence of the disease is likely to be higher. Thus, the benefit-to-risk ratio of surveillance (as opposed to population screening) is more favourable. Consequently, if asked, individuals who believe themselves to be at increased risk of developing CRC may be more willing to accept the risks associated with surveillance.

Colonoscopy, as opposed to FOBT, is widely recommended for surveillance in individuals with a significant increase in risk of developing CRC.[6] Ideally, evidence from randomised controlled trials is required before instituting a surveillance programme. However, evidence from randomised controlled trials is not currently available for colonoscopic surveillance of groups at increased risk of CRC, and it is unlikely that randomised controlled trials will be carried out in the future due to ethical constraints. There is evidence from observational studies of the benefits of colonoscopic surveillance in these groups and therefore undertaking randomised controlled trials could be regarded as unethical.

Further, there are ethical differences between population-based screening for CRC using FOBT and colonoscopic surveillance of individuals at increased risk of CRC. For individuals at increased risk of CRC who have already approached the health system because of poor health (eg, individuals with inflammatory bowel disease), colonoscopy may already be part of the routine investigation of their illness. Any associated risks may be offset by the potential gain from appropriate investigation

and treatment. By definition, individuals who have a significantly increased risk of developing CRC have a higher risk of CRC than individuals in the general population, and some are at considerably higher risk. These individuals may be more inclined to accept the risks associated with surveillance colonoscopy than would healthy, average-risk individuals.

For those asymptomatic individuals with an inherited predisposition to CRC (eg, those identified after a relative has been diagnosed with CRC) – as opposed to those at increased risk of this condition because of a personal history of disease – the decision to proceed with colonoscopic surveillance may be less straightforward. Although these individuals are at increased risk, they have not necessarily approached the health system and currently may be in good health. The risks and benefits of colonoscopic surveillance would have to be explained so that these individuals could decide whether to participate in a surveillance programme. For individuals at very high risk of CRC (eg, at risk member of an hereditary non-polyposis CRC family), the risks associated with colonoscopy may be regarded as negligible compared with the risk of developing, and dying from CRC.



There are several advantages of a high-risk preventive strategy,[2] and these apply to colonoscopic surveillance.

1. The intervention is appropriate for the individual, and avoids interference with those who are not at significant risk.
2. The strategy is readily accommodated within medical care (especially for individuals with inflammatory bowel disease or previous CRC) because it may already be part of routine follow-up.
3. Individuals at high risk of CRC have the greatest potential to benefit from a surveillance strategy as the benefit-to-risk ratio and the cost-effectiveness of surveillance for this group are greater than for screening of individuals at average risk.

There are also disadvantages associated with a high-risk preventive strategy.[2] As a public health strategy, this approach is limited in that it does not address the underlying causes of CRC. Although it targets those individuals who are at increased risk within the community, this group may comprise only a very small proportion of those who later go on to develop CRC. In a country such as New Zealand, where CRC is relatively common, a large number of individuals exposed to a small risk of CRC may generate many more cases of CRC than a small number exposed to a high risk of CRC. Thus, the contribution of such a strategy to the overall control of CRC in New Zealand may be small. It may also be difficult and expensive to identify individuals at high risk for the disease.

# SURVEILLANCE COLONOSCOPY

Colonoscopy is regarded as the gold standard investigation of the large bowel. It is therefore the surveillance tool of choice for individuals identified to have a moderate to high increase in their lifetime risk of CRC by virtue of their personal history of colorectal pathology or their family history of CRC.

## Sensitivity of Colonoscopy for the Detection of CRC and Colorectal Adenomas

A comparative study found the sensitivity of colonoscopy for CRC to be 95% compared with 82% for double-contrast barium enema, with an odds ratio of 3.83 for a missed CRC by double-contrast barium enema compared with colonoscopy.[7] However, it is not always possible to reach the caecum at colonoscopy and CRC may be missed by failure to recognise this and to arrange a back-up double-contrast barium enema where necessary to complete visualisation of this region.

With respect to adenoma detection by colonoscopy, a tandem study revealed that 6% of lesions greater than 10 mm were missed, compared with a miss rate of 27% for adenomas under 5 mm and of 13% for adenomas 6 to 9 mm in size.[8] As with colonoscopy, the sensitivity of double-contrast barium enema for polyp detection varies in accordance with polyp size:[9] the vast majority of missed polyps are under 10 mm and therefore not associated with an appreciable CRC risk, but 30% or more of polyps over 10 mm may also be missed on double-contrast barium enema examination. The sensitivity of colonoscopy and barium enema for the detection of CRCs and adenomas are discussed in detail in the working party's population screening report.[1]



Subsequent to publication of the working party report and in the context of the implications for colorectal cancer screening and training there has been further documentation of the considerable inter-observer variation, even amongst experts for the diagnosis of neoplasia on DCBE.[10]

Virtual colonoscopy has also emerged as an evolving technique for examination of the large bowel. Data from computed tomography (CT) are used to generate both two-dimensional and three-dimensional displays of the colon and rectum. This minimally invasive method, also called CT colonography, could become an alternative to colonoscopy in screening for colorectal neoplasia. Although the performance characteristics of virtual colonoscopy as a screening test have been encouraging in some trials,[11] a recent multi-centre study suggests that improvement is required in both technique and training before widespread clinical application can be considered.[12,13]

## Complications of Colonoscopy

Colonoscopy is generally a safe procedure, and significant complications are considered rare.

Complications may arise as a result of:

- the procedure and interventions performed
- sedation
- cardiopulmonary events (particularly in those individuals with pre-existing cardiorespiratory disease).

Potential complications of most concern are bleeding and perforation, which can result from the procedure itself or from interventions performed during the procedure, namely polypectomy. Surgery may subsequently be necessary and rarely death may result.

The majority of studies reporting colonoscopy complications are retrospective studies with the limitations inherent in this research design. Bias (eg, sampling/selection, confounding, and measurement) is a common problem in the collection and reporting of data on colonoscopy complications.[14]

Perforation during diagnostic colonoscopy has been reported to occur in 0.045 to 0.17% of procedures, and mortality in 0.006 to 0.02% of procedures.[15,16] The higher figures generally relate to the time when the use of colonoscopy was in its infancy. The subsequent reductions in complication rates are considered to relate to physician training and changes in the performance characteristics of endoscopes. Polypectomy is associated with a higher perforation rate (0.41%) and haemorrhage is reported in approximately 0.03% of procedures.[16] Complication rates also vary with the level of expertise of the operator.[17]

Surveillance procedures are generally performed in well individuals and it has therefore been postulated that the complication rates for colonoscopy in this situation may be lower. Table 4 documents the reported colonoscopy complications for the population-based FOBT screening trials;[3,4,18] however, the scale of these studies should be noted and it is not known whether the mortality observed was lower than could be expected in the clinical setting. According to the formula of Hanley and Lippman-Hand[19] for such infrequent events as perforation and death in order to rule out a risk of death of 0.02%, a mortality rate of zero deaths in 15,000 consecutive colonoscopies would be required.

*Table 4: Reported colonoscopy complications in population-based FOBT screening trials*

| | Nottingham* | Funen* | Minnesota[18] |
|---|---|---|---|
| No. of procedures | 1778 | 1000 | 12,246 |
| Perforation diagnostic | 1 | nr | 4 (0.03%) |
| Perforation therapeutic | 4 | nr | nr |
| Major bleed | 1 | nr | 11 |
| Snare entrapment | 1 | nr | nr |
| Death | 0 | 1 | 0 |

*Personal communication

nr = not reported

In the Veterans colonoscopy screening trial,[20] colonoscopy was performed by experienced operators and completion to the caecum was achieved in 3121 of 3196 individuals (97.6%; mean age 62.9 years). At least one polyp was resected in 1672 individuals. There was no perforation or death directly related to the procedure. Major morbidity considered related to colonoscopy occurred in 9 of 3196 procedures (0.3%). Of these, there were 6 instances of lower gastrointestinal (GI) bleeding requiring intervention, 2 of myocardial infarction and/or cerebrovascular accident, and 1 of thrombophlebitis. In subjects undergoing diagnostic procedures only, the major complication rate was 0.1%.

The risk of complications resulting from colonoscopy has to be weighed against the indications for colonoscopy. Barium enema is a safer procedure than colonoscopy but many of the abnormalities identified by this examination require subsequent follow-up colonoscopic investigation.

## Colonoscopy and Quality Assurance

Colonoscopy complication rates vary with the level of expertise of the operator.[17] Consequently, surveillance colonoscopy in well individuals should be performed by experienced operators with acceptable documented completion rates to the caecum (>95%). Colonoscopy quality improvement questionnaires have been developed and used in New Zealand to assess identified colonoscopy-specific quality indicators. Acceptable colonoscopy performance within an endoscopy unit can be demonstrated and areas for improvement identified.[21] Ongoing monitoring establishes consistency of performance and improvement in areas of concern. In addition, individuals presenting for colonoscopy can be reassured regarding the quality of procedures performed in the unit.

## Surveillance Colonoscopy: Impact of Age and Serious Comorbidity

Surveillance colonoscopy is not usually advised after the age of 75 years as the remaining life expectancy is likely to be less than the average time required for new adenomas or dysplasia to become malignant and the potential risks associated with ongoing surveillance are likely to outweigh the benefits of such procedures. Surveillance may also not be appropriate in some individuals under the age of 75 years who have serious comorbid conditions.

The potential risks and benefits of surveillance need to be considered in individuals of all ages, particularly in individuals who have significant comorbidity. The decision to undertake each surveillance colonoscopy is dependent on the previously detected pathology and on the individual's decision after they have been fully informed regarding the risks and benefits of colonoscopy. The appropriateness of ongoing surveillance colonoscopy should preferably be reviewed before attendance for each examination.[22]

# 2

# FAMILY HISTORY OF COLORECTAL CANCER



## OVERVIEW

- A family history of CRC is associated with an increased risk of the disease for relatives.
- The level of increased familial risk (excluding those relatives of families with the well-defined hereditary CRC syndromes familial adenomatous polyposis (FAP) and heredity non-polyposis CRC (HNPCC) largely depends on the number of first-degree relatives affected and the age at which these relatives were diagnosed with CRC.
- Despite the absence of published mortality data, there is a consensus that it is appropriate to offer colonoscopic surveillance to individuals considered to be at moderately-increased risk of developing CRC on the basis of a family history (ie, those with 1 first-degree relative diagnosed under the age of 55 years or 2 first-degree relatives on the same side of the family with CRC diagnosed at any age).
- Individuals offered colonoscopic surveillance should be fully informed regarding their risk of developing CRC, and that colonoscopy is generally a safe procedure, but as it is also invasive, it has some rare but recognised risks.
- Given the low baseline level of surveillance performed on the basis of a family history of CRC in New Zealand, increased colonoscopic resources and funding are likely to be necessary. The recommendation to offer colonoscopic surveillance to those at moderately-increased risk on the basis of a family history of developing CRC could result in an estimated 15 to 25% increase in the number of colonoscopies performed annually in the public hospital system.
- There is controversy regarding appropriate surveillance advice for those relatives assessed as having a slightly increased risk of developing CRC on the basis of a family history of the disease. Therefore, no specific surveillance recommendations are made for this group at this time.
- A detailed family history of colorectal and other cancers in the family, ideally spanning three generations, is paramount in assessing an individual's risk for developing CRC and providing appropriate surveillance advice.
- Familial bowel cancer registries fulfill an important role in the diagnosis, management and coordination of surveillance for individuals with hereditary CRC syndromes. This is associated with a reduction in cancer incidence.

The majority of CRCs, whether associated with familial syndromes or not associated with familial syndromes ('common' CRC type), arise from benign adenomas as a result of a gradual malignant progression. This progression is due to a stepwise accumulation of genetic abnormalities, which has been relatively well-characterised.[1, 2] The mutations generally occur spontaneously, but the initiation and consequence of such events are influenced by inherited and environmental factors. Since chromosomes are paired, in cases of common CRC, both chromosomes at the site of a cancer gene have to develop a mutation before loss of normal function for the gene occurs. Affected members of families with dominantly inherited forms of CRC – due to the familial syndromes HNPCC and FAP – are at high risk of developing CRC because they already have an inherited mutation in one of the genes which is known to predispose to CRC.

Individuals are classified on the basis of their family history of CRC into one of three categories relating to their estimated potential lifetime risk for developing CRC compared with the average lifetime risk of the general population. In New Zealand the average lifetime risk for developing CRC is 5.9% by the age of 75 years.[3] The three categories are listed below.

**Category 1:** Individuals with a slight increase in risk of CRC.

**Category 2:** Individuals with a moderate increase in risk of CRC.

**Category 3:** Individuals with a potentially high (50%) risk of CRC.

## COMMON CRC AND FAMILIAL RISK

Approximately 20% of all individuals with CRC have a family history of the disease (a minority being related to the well-established familial syndromes). Environmental factors may contribute in part but an inherited susceptibility, not yet well-characterised, is considered to account for some of the mild-to-moderate increase in risk associated with a family history of sporadic CRC.[4]

In New Zealand, the lifetime risk of developing CRC is 5.9% by the age of 75 years.[3] The level of increased risk for CRC in relatives (excluding those relatives of families with the well-defined hereditary CRC syndromes FAP and HNPCC), compared with the lifetime risk of CRC for the average New Zealander with no family history of the disease, largely depends on the number of first-degree relatives affected and the age at which such relatives were diagnosed with CRC.[5-8]

- For those with one first-degree relative diagnosed with CRC at 55 years of age or older there is approximately a 2-fold increase in their lifetime risk for developing CRC (category 1).
- For those with one first-degree relative diagnosed with CRC between the ages of 45 and 55 years there is approximately a 3-fold increase in their lifetime risk for developing CRC (category 2).
- For those with one first-degree relative diagnosed with CRC when younger than 45 years of age there is approximately a 4-fold increase in their lifetime risk for developing CRC (category 2).
- For those with two or more first-degree relatives affected with CRC on the same side of the family there is a 3 to 6-fold increase in their lifetime risk for developing CRC (category 2).

Figure 2 shows the cumulative incidence of CRC in first-degree relatives of cases and controls in a case-control family study, in relation to the age at diagnosis of CRC for cases.[5]

*Figure 2: Cumulative incidence of CRC in FDRs in a case-control family study*[5]

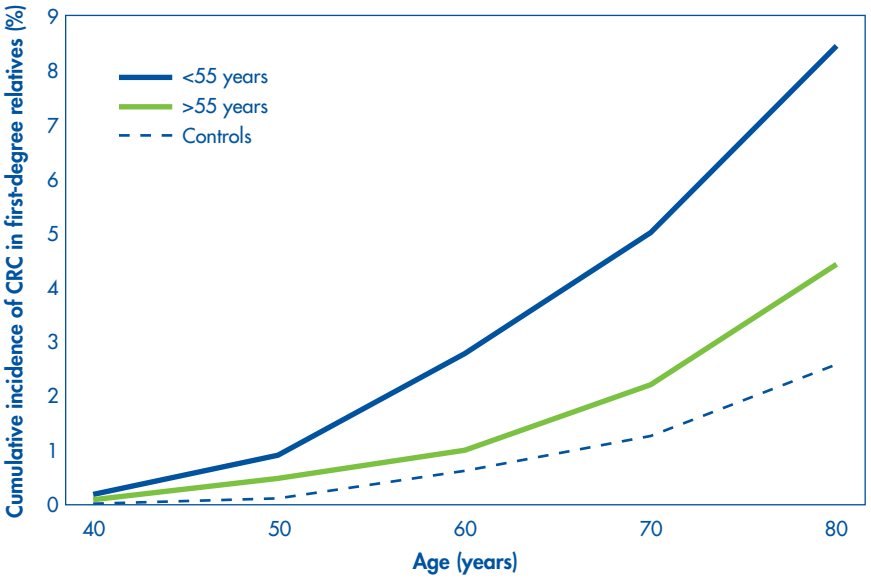




Figure 2 documents the continuation of increased risk at older ages. However, in the prospective study by Fuchs *et al*,[6] the risk to relatives was shown to decrease with age. This is probably because two different measures of incidence were used in the two studies. Cumulative incidence (ie, the proportion of relatives who developed CRC up to a given age) was calculated in the former study by St John *et al*.[5] In the Fuchs *et al* study, incidence rates were calculated by age. Note that even if age-specific risks decline with increasing age, the *cumulative risk* will continue to increase with increasing age. Also, if there is a genetic component, it might be expected that CRC incidence in relatives decreases with increasing age (since hereditary cancers tend to occur at younger ages than do sporadic cancers). There is also the problem of 'competing risks' at older ages. Older people are at increased risk from many health problems, including other cancers and cardiovascular disease. Because of this, the incidence of CRC may be seen to decline in older age-groups.

In both the St John *et al*[5] and the Fuchs *et al*[6] studies, no detectable difference in risk to relatives according to the specific site of the index tumour within the colon was identified. St John *et al* reported no significant difference in overall occurrence of non-colorectal malignancy in the relatives of individuals with CRC (members of FAP and HNPCC families were excluded from the study).[5]

For those with second- and third-degree relatives with CRC, there is a slight increase in risk for developing CRC, in the range of a 1.3- to 1.5-fold increase,[7] but this is less well-characterised.

## Surveillance and Adenoma Detection in First-degree Relatives

A number of studies on surveillance of relatives of individuals with CRC have been published. However, few have been controlled studies and in most, relatives have not been stratified according to risk at the outset of the study. Mortality from CRC has not been an endpoint in any study. Brewer *et al*[9] reviewed the studies published to 1994, and concluded that:

- first-degree relatives of individuals with CRC have a higher incidence of neoplasm (ie, adenomas and carcinomas) compared with individuals with no family history of CRC
- incidence is higher in those individuals with more than one affected first-degree relative
- the risk was seen to increase with advancing age (this review predated the prospective studies reported in the previous section)
- colonoscopy appears to have a detection advantage as a screening tool.

The distribution of neoplasms in screened relatives does not appear to differ from that in the general population. Up to 48% of lesions were considered beyond the reach of the flexible sigmoidoscope and 5 to 22% had no sentinel neoplasms distal to the splenic flexure.

Two prospective studies have evaluated first-degree relatives of individuals with CRC using colonoscopy,[10,11] one being subsequent to the Brewer *et al* review. Guillem *et al*[10] completed colonoscopic evaluation in 181 asymptomatic first-degree relatives of individuals with CRC and 83 asymptomatic controls (spouses of first-degree relative subjects and others actively recruited through a medical centre) without a family history of CRC. The majority of relatives studied had only one first-degree relative with CRC. There was no statistically significant difference found in the overall detection rate of adenomatous polyps between the first-degree relative and control groups. However, first-degree relatives tended to develop adenomas at an earlier age than controls. A greater proportion of adenomas were found to be beyond the reach of the flexible sigmoidoscope in the first-degree relative group than in the controls (48 vs 25%). Logistic regression analyses revealed that age, male sex and first-degree relative status were independent risk factors for the presence of colonic adenomatous polyps.

Pariente *et al*[11] offered colonoscopy to 476 first-degree relatives of 195 individuals with CRC in a case-control study. Of the 476 first-degree relatives, only 185 (38.9%) agreed to participate in the study. The controls were 370 individuals who had recently undergone colonoscopy but had no family or personal history of CRC. Logistic regression analysis showed that one first-degree relative was a significant risk factor for large adenomas (≥10 mm) and high-risk adenomas (>10 mm and/or with a villous component). The prevalence of high-risk adenomas in relatives was higher when the index case was under 65 years, male, and the location of the CRC was distal rather than proximal. Families where HNPCC was suspected had been excluded from the study.

In 1995, Bazzoli *et al*[12] retrospectively evaluated the frequency of a history of one first-degree relative with CRC in 397 asymptomatic individuals (considered inappropriate referrals) who underwent colonoscopy. Of these individuals, 155 had at least one adenomatous colorectal polyp and the remaining 242 did not have adenomas. Individuals reporting a family history of CRC were required to provide documented evidence of this. Multiple logistic regression analysis of risk factors associated with adenomatous polyps revealed an adjusted odds ratio for a positive family history of 1.9 (95% CI, 1.3 – 2.8). There was a significant difference in the frequency with which proximally located adenomas (proximal to the splenic flexure) were detected in those with and without a family history of CRC (Chi squared test; P=0.006; odds ratio 3.2). A higher frequency of severely dysplastic adenomatous lesions was also seen in those with adenomas and a family history of CRC (Chi squared test; P=0.04; odds ratio 2.9).

A randomised controlled trial of flexible sigmoidoscopy or colonoscopy in New Zealand involving 232 subjects, 137 with a family history of colorectal adenoma or cancer and 95 without such a history, found that polyps (adenomas + hyperplastic polyps) were more common in those with a family history The prevalence was 41% in those with a family history compared with 24% for those with no family history (p=0.04), but for adenomas and carcinomas the difference between these groups was not significant.[13]

These later studies, although not documenting a statistically significant increase in the number of adenomas detected in first-degree relatives compared with controls, did report a trend in that direction. The finding of differences in the number of larger or high-risk adenomas detected in first-degree relatives compared with controls[11,12] raises the possibility that the inherited predisposition may operate to influence adenoma growth rather than adenoma origin. The reported trend to proximal location of adenomas in first-degree relatives supports the use of colonoscopy as the surveillance tool in this situation.

However, selection bias is a potential problem in all these studies because none have utilised an ideal comparison group. Ideally, the comparison group should be 'average-risk' individuals, and

both the first-degree relative group and the comparison group should be asymptomatic. In addition, there is the problem of confounding in these studies because there may be differences between first-degree relatives and 'average-risk' asymptomatic individuals (other than family history) that could be associated with polyps and CRC. Some of the studies have addressed confounding by age and sex, but there may be other unidentified confounding factors (eg, diet).

The results of the studies discussed in this section are summarised in Table 5.

*Table 5: Results of studies on screening of first-degree relatives of individuals with CRC*

| Study | Numbers | | Adenomas (%) | | Significant risk factors | Participation level |
|---|---|---|---|---|---|---|
| | FDR* | Controls | FDR | Controls | | |
| Guillem *et al*[10] prospective; controlled | 181 | 83 | 14.4 | 8.4 | Increasing age; male sex; FDR status (92% one FDR) | 42% |
| Pariente *et al*[11] | 185 | 370 paired controls | 23.2 | 17.3 | Large adenomas + villous component; greater if family history of CRC; greater if index person >65 years | 39% |
| Bazzoli *et al*[12] retrospective; asymptomatic individuals | 155 adenomas<br>242 no adenomas | – | 17.4% with a family history of CRC<br>5.0% with a family history of CRC | na | Age >50 years; male sex; positive family history; increased risk of severely dysplastic adenomas if a family history of CRC | na |
| Elwood *et al*[13] prospective; offered flexible sigmoidoscopy or colonoscopy | 137 | 95 | 21.4 | 14.8 | Not significant for adenoma + ca | 65% |

*First-degree relatives

na = not applicable

Despite the absence of published mortality data, there is a consensus that it is appropriate to offer colonoscopic surveillance to individuals considered to be at moderately-increased risk of developing CRC on the basis of a family history.

## Colonoscopic Findings in Relatives Stratified for Risk

In 1995 the Family Cancer Clinic at St Marks Hospital reported the results of screening procedures performed for individuals referred to the clinic.[14] Colonoscopy was performed in 644 asymptomatic

individuals with a family history of CRC from 436 families (including 69 families with HNPCC according to the Amsterdam Criteria). Seven cases of CRC were diagnosed at an average age of 49 years, six at Dukes' type A stage and four in families with Amsterdam Criteria HNPCC. Adenomas were detected in 26.8% of those from the Amsterdam Criteria HNPCC group compared with 21.3% in those with a family history of CRC but not considered to have HNPCC. Multivariate analysis revealed that independent variables significantly related to risk of adenomas were increasing age, male sex and the number of generations (>1) affected with CRC.



In 1998, Hunt *et al*[15] reported the findings following prospective CRC screening for 331 relatives according to protocol. Flexible sigmoidoscopy was offered to individuals with a single first-degree relative with CRC diagnosed at over 50 years of age or to individuals with a first- and second-degree relative diagnosed with CRC over the age of 50 years. Colonoscopy was offered to those with two or more affected relatives or those with one first-degree relative diagnosed with CRC under the age of 50 years. In the group screened primarily by colonoscopy (which included relatives from families with HNPCC), adenomas were found in 12% and adenomas larger than 10 mm in 8%. Of those with neoplasia (adenoma or cancer), 26% had lesions at or proximal to the splenic flexure. Neoplasia was found in 9.5% (neoplasia >10 mm in 4%) of those screened by flexible sigmoidoscopy. It was concluded that flexible sigmoidoscopy may be useful in those at lower levels of risk for CRC.

In the New Zealand study the cost advantage of flexible sigmoidoscopy was largely offset by the cost of follow-up colonoscopy for all subjects with polyps.[13] Adherence was similar for the two procedures. Currently in New Zealand flexible sigmoidoscopy is not widely utilised.

## Is Surveillance Justified?

Prospective studies and a case-control study have documented an increased risk for CRC in first-degree relatives of individuals diagnosed with CRC compared with individuals who do not have a family history of CRC. The level of increased risk (excluding relatives of families with the well-defined hereditary CRC syndromes FAP and HNPCC) depends on the number of first-degree relatives affected and the age at which such relatives were diagnosed to have CRC.[5-8]

Screening the average-risk population with FOBT has been shown in randomised controlled trials to result in a modest reduction in mortality from CRC. Colonoscopic surveillance in at-risk family members of HNPCC kindreds reduces the incidence of CRC in those participating in surveillance programmes compared with those at-risk members not undergoing surveillance and decreases overall mortality by 65%.[16] The US National Polyp Study reported a decrease in the incidence of CRC following colonoscopy and polypectomy, but the comparison was with historical controls.[17] There is an absence of published data documenting a reduction in incidence of, or mortality from, CRC as a result of colonoscopic surveillance in relatives of individuals with CRC (excluding those relatives of families with FAP and HNPCC). Randomised controlled trials addressing this question are unlikely to be performed in the future given the documented increased risk of CRC in first-degree relatives. Studies of colonoscopic surveillance in relatives of individuals with CRC show a trend towards an increase in the number of adenomas and in the number of high-risk adenomas, but selection bias and confounding have been a problem. The evidence that colonoscopic surveillance in relatives of individuals with CRC will reduce mortality from this disease is indirect.

Current surveillance recommendations for relatives are essentially empiric, being based on the known effectiveness of screening tools and the increased risk observed in family studies.

In assessing CRC risk, Lang and Ransohoff[18] make the point that it is important to consider absolute as well as relative risk. Although a family history of CRC is associated with a substantially increased relative risk of CRC at younger ages, the absolute risk at younger ages remains low. However, although loss of life from potentially preventable CRC at younger ages is significant, the effort and risk involved

in intensive colonoscopic surveillance are relatively large. Dunlop and Campbell[19] comment that when offering advice to an individual it is essential to balance the cumulative absolute risk of cancer in the coming years with the cumulative risk of complications from colonoscopy, reserving invasive screening for individuals with a substantial absolute risk of CRC. This is particularly important for those with only a slight increase in risk for developing CRC.

*Table 6: Age-specific CRC incidence in New Zealand, 1998*[3]

| Age group (years) | Colorectal cancer registrations | Rate per 100,000 | Risk during 5-year period (%) | Cumulative risk to end of 5-year period (%) |
|---|---|---|---|---|
| **0 – 24** | 1 | 0.1 | <0.1 | <0.1 |
| **25 – 29** | 8 | 2.8 | <0.1 | <0.1 |
| **30 – 34** | 7 | 2.4 | <0.1 | <0.1 |
| **35 – 39** | 26 | 8.4 | <0.1 | 0.1 |
| **40 – 44** | 38 | 13.7 | 0.1 | 0.1 |
| **45 – 49** | 73 | 29.1 | 0.1 | 0.3 |
| **50 – 54** | 140 | 64.4 | 0.3 | 0.6 |
| **55 – 59** | 233 | 133.2 | 0.7 | 1.3 |
| **60 – 64** | 288 | 205.4 | 1.0 | 2.3 |
| **65 – 69** | 380 | 287.1 | 1.4 | 3.7 |
| **70 – 74** | 438 | 372.4 | 1.9 | 5.6 |
| **75 – 79** | 319 | 356.6 | 1.8 | 7.4 |
| **80 – 84** | 272 | 471.1 | 2.4 | 9.7 |
| **>85** | 210 | 488.0 | 2.4 | 12.2 |

Table 6 outlines the risk of developing CRC for New Zealanders at average risk over 5-year intervals from the age of 30 to 80 years.[3] Multiplying these figures by the appropriate risk factor, as determined by age and the number of first-degree relatives, allows assessment of the absolute risk of CRC at any age for first-degree relatives of individuals with CRC.

The recommendation to offer colonoscopic surveillance to those at moderately-increased risk of developing CRC on the basis of a family history could result in an estimated 15 to 25% increase in the number of colonoscopies performed annually in the public hospital system. Given the low baseline level of surveillance currently performed in New Zealand on the basis of a family history of CRC, increased colonoscopic resources and funding are likely to be necessary.

There is controversy regarding appropriate surveillance advice for those relatives assessed as having a slightly increased risk of developing CRC on the basis of a family history of the disease. Therefore, no specific surveillance recommendations are made for this group at this time.

## Cost-effectiveness of Surveillance Strategies

Few cost analyses have been performed of surveillance strategies in individuals with a family history of CRC (excluding those with FAP and HNPCC).

An Israeli study by Rozen and Ron,[20] using a range of costs from the US and based on the results of a screening programme for families of individuals with CRC, indicated that screening asymptomatic adults by colonoscopy is markedly (ie, 4-fold) more cost-effective if they have two or more first-degree relatives with CRC. There were limitations to this study, with only a small number of participants having more than one first-degree relative with CRC.

# ASSESSMENT OF RISK

Obtaining a detailed family history of colorectal and other cancers is essential in assessing an individual's risk for developing CRC and providing appropriate surveillance advice. The family history would optimally span three generations and include all family members – that is, those affected with cancer (colorectal and/or other cancers) and those members unaffected with cancer. The number of family members affected and the age at diagnosis need to be recorded, as does whether the affected family members are on the same or both (ie, maternal and/or paternal) sides of the family. It is helpful to construct a family tree. Detailed instructions on taking a family history and constructing a family tree are provided in Appendix A. Given that there is a false-positive rate of approximately 30% for reported CRC in first-degree relatives,[5] confirmation of the CRC diagnosis from death certificates or hospital records is prudent. This is usually performed on referral to a clinical genetic service or the familial bowel cancer registry.

# CATEGORY 1: INDIVIDUALS WITH A SLIGHT INCREASE IN RISK FOR CRC

| RECOMMENDATIONS: INDIVIDUALS WITH A SLIGHT INCREASE IN RISK OF CRC DUE TO FAMILY HISTORY (UP TO 2-FOLD COMPARED WITH THE GENERAL POPULATION)<br>• One first-degree relative with CRC diagnosed over the age of 55 years | |
|---|---|
| No specific surveillance recommendations are made for this group at this time given the slight increase in risk, the uncertainty regarding the age at which this additional risk is expressed and the concern regarding the appropriateness of colonoscopy as a surveillance procedure in this group. | 5 |
| Prompt investigation of lower bowel symptoms is advised. | 5 |
| Individuals requesting information should be fully informed regarding their absolute risk of developing CRC and advised of the reasons for this recommendation. | 5 |

This category constitutes individuals with a single affected first-degree relative (eg, parent, siblings, children) diagnosed with CRC after the age of 55 years. They are assessed to have up to a 2-fold increase in their lifetime risk of developing CRC compared with the average-risk general population. The age at which this risk is expressed is uncertain. Within this group there will be subsets of individuals with higher (eg, unrecognised members of families with HNPCC) and lower risks for CRC. It is also likely that the impact of dietary and other environmental factors on CRC risk will be different for individuals with different genotypes.[21] At this stage, however, individuals within such subsets remain unidentifiable.

The majority of individuals with a family history of CRC will be in this category, and most of them (approximately 90% by age 75 years) will not have developed CRC. In the absence of controlled study data, there is no consensus on surveillance recommendations for this category. American clinical guidelines for CRC screening offer a range of screening options for those at average risk, with the same range of options being offered to individuals with a family history of CRC diagnosed after the age of 40 years. No stratification of risk is made for first-degree relatives in these protocols.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*
**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

The National Health and Medical Research Council of Australia (NHMRC) guidelines acknowledge the variation in practice in this area.[22] Some doctors advise colonoscopy on the basis of the studies reviewed previously in this chapter. Others are concerned that the degree of risk does not warrant invasive surveillance procedures and conclude that this group should be managed in the same way as the general population.[19] At this time, population-based screening for CRC with FOBT or other modalities is not recommended in New Zealand.[23]

# CATEGORY 2: INDIVIDUALS WITH A MODERATE INCREASE IN RISK FOR CRC



| RECOMMENDATIONS: INDIVIDUALS WITH A MODERATE INCREASE IN RISK OF CRC (3- TO 6-FOLD COMPARED WITH THE GENERAL POPULATION)<br>• One first-degree relative with CRC diagnosed under the age of 55 years<br>• Two first-degree relatives on the same side of the family with CRC diagnosed at any age | |
|---|---|
| Offer colonoscopy every 5 years from the age of 50 years (or from an age 10 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). | 3 |
| Fully inform individuals in category 2 about their risk of developing CRC and the reason for this recommendation. | 5 |
| Individuals in category 2 should be informed that colonoscopy is generally a safe procedure, but it is an invasive procedure with some rare but recognised risks. | 5 |

This group constitutes individuals with a 3- to 6-fold increase in their lifetime risk of developing CRC compared with the general population and includes those with one first-degree relative diagnosed with CRC at age 55 years or less OR with two first-degree relatives (eg, parent, siblings, children) on the same side of the family diagnosed with CRC at any age (without features of category 3).

In its published guidelines on *Familial Aspects of Cancer*,[24] the NHMRC stated that the use of colonoscopic surveillance in first-degree relatives of individuals with CRC appeared to be prudent in those at a 3- to 6-fold increased risk despite the absence of published mortality data, but that the optimal frequency and age of commencement was not known. The NHMRC, in its clinical practice guidelines on *The Prevention, Early Detection and Management of Colorectal Cancer*,[22] also stated that it is important to point out that colonoscopy is not totally without risk as it is an invasive procedure. The risks of colonoscopy are fully reviewed in the working party's report on *Population Screening for Colorectal Cancer in New Zealand*,[23] and discussed elsewhere in this guideline.

Colonoscopic surveillance is advised for individuals in category 2. This surveillance (5-yearly) should begin at 50 years of age or from an age 10 years younger than the earliest age at which CRC developed in the family member, whichever comes first. Surveillance procedures should be performed by skilled endoscopists, preferably with audited documentation of acceptable completion rates to the caecum and safety of practice. Flexible sigmoidoscopy with a double-contrast barium enema is considered an acceptable alternative to colonoscopy;[25] however, at this time flexible sigmoidoscopy is not routinely available in New Zealand.

## Resource Implications

In 1998, 293 CRCs were registered as occurring in individuals under the age of 55 years.[3] Each individual registered is likely to have two siblings who would qualify for colonoscopic screening. The majority of these cancers were in the 45 to 55 year age group, and therefore it is unlikely that

colonoscopic surveillance would be appropriate for the parents of those affected at this age. Allowing for a participation level of 40 to 65%, it is reasonable to assume that approximately 234 to 391 first-degree relatives would begin colonoscopic surveillance each year. After 5 years, the initial group would re-present for a subsequent examination (a percentage of these would have required an earlier procedure because of detected pathology).

Approximately 0.4% of the population have two first-degree relatives with CRC:[19] for New Zealand this would be approximately 14,000 individuals, 27% of whom, according to the 1996 census,[26] are aged between 45 and 75 years (ie, 3780). Assuming a participation level of 40 to 65%, 1512 to 2457 first-degree relatives would begin a colonoscopic surveillance programme. Two factors would affect this estimate. The likelihood of double-counting of relatives between the two groups (ie, the group with hereditary CRC syndromes, and the group with a moderately strong family history of CRC) needs to be considered, as does the fact that it would be a number of years before all eligible relatives in this category were identified and offered colonoscopic surveillance.

As a result of the recommendations for colonoscopic surveillance in those with a moderate increase in risk for developing CRC, approximately 1700 to 2800 first-degree relatives of individuals with diagnosed CRC could present for colonoscopy each year. Approximately 11,000 colonoscopies are performed in the public hospital system each year (10,937 outpatient colonoscopies).[27] The additional 1700 to 2800 procedures would represent a 15 to 25% increase in the number of colonoscopies performed each year in the public hospital system. For comparison, it has been estimated that if population screening for CRC using FOBT had been adopted in New Zealand, it would have resulted in a 33 to 40% increase in the number of colonoscopies performed each year in the public hospital system.[24]

Given the routinely collected data available, the possible double-counting between relative groups, and the assumptions regarding participation, it must be acknowledged that these estimates are, of necessity, imprecise. In addition, no allowance has been made for the predicted decline in incidence of CRC in New Zealand [28]

Furthermore, it is unknown what percentage of colonoscopies currently performed in the public hospital system are attributable to surveillance for a family history of CRC. An audit of colonoscopy indications over two years (1999 – 2001) at Middlemore Hospital, Auckland, suggests this to be approximately 8.5%.[29] Generalised for procedures in the public system throughout New Zealand, this would account for approximately 850 procedures per year.

There is wide variation in indications for and clinical practice of surveillance for familial CRC.[30,31] Evidence-based guidelines could rationalise resources with a reduction in the use of colonoscopy for surveillance in those considered to have a slight increase in risk for developing CRC. However, since the baseline level of such surveillance in the public hospital sector appears to be low, increased colonoscopic resources and funding are likely to be necessary. These costs would probably be offset by an anticipated reduction in the incidence and mortality from CRC in those individuals in this category who undergo regular colonoscopic surveillance.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

# CATEGORY 3: INDIVIDUALS WITH A POTENTIALLY HIGH (50%) RISK OF CRC

RECOMMENDATIONS: INDIVIDUALS WITH A POTENTIALLY HIGH (50%) RISK OF CRC

- A family history of familial adenomatous polyposis, hereditary non-polyposis colorectal cancer or other familial CRC syndromes
- One first-degree relative plus two or more first- or second-degree relatives, all on the same side of the family, with a diagnosis of CRC, at any age
- Two first-degree relatives, or one first-degree relative plus one or more second-degree relatives, all on the same side of the family, with a diagnosis of CRC and one such relative
  - was diagnosed with CRC under the age of 55 years, or
  - developed multiple bowel cancers, or
  - developed an extracolonic tumour suggestive of hereditary non-polyposis colorectal cancer (ie, endometrial, ovarian, stomach, small bowel, upper renal tract, pancreas or brain)
- At least one first- or second-degree family member diagnosed with CRC in association with multiple bowel polyps
- A personal history or one first-degree relative with CRC diagnosed under the age of 50, particularly where colorectal tumour immunohistochemistry has revealed loss of protein expression for one of the mismatch repair genes (hMLH1 or hMSH2).

Refer to:

- a genetic specialist/family cancer clinic or familial bowel cancer registry for further risk assessment and possible genetic testing (for contact details see Appendix B)
- a bowel cancer specialist to plan appropriate surveillance and management.

5

Individuals at potentially high risk for CRC because of a personal or family history suggestive of one of the dominantly inherited CRC syndromes (as defined above) should be referred to a genetic specialist/family cancer clinic/familial bowel cancer registry and a bowel cancer specialist. A number of well-defined hereditary syndromes are associated with an increased risk of developing CRC. Recommendations relating to these conditions are outlined in the subsequent sections of this chapter.

# Familial Adenomatous Polyposis

| RECOMMENDATIONS: FAMILIAL ADENOMATOUS POLYPOSIS<br>Familial adenomatous polyposis is an autosomal-dominant inherited disease characterised by the presence of multiple small adenomas (>100) throughout the colon and rectum. These polyps develop in the early-to-midteens. The median age at diagnosis for CRC in untreated affected individuals is 40 years. | |
|---|---|
| **Genetic testing**<br>Offer referral to a genetic service for consideration of genetic testing within the context of appropriate counselling to:<br>• individuals with a clinical diagnosis of FAP<br>• all at-risk family members if a family-specific genetic mutation has been identified<br>at the age when sigmoidoscopic surveillance would normally begin. | 5 |
| **Bowel surveillance**<br>Sigmoidoscopy 1- to 2-yearly from the age of 12 to15 years is recommended for asymptomatic individuals with an identified disease-causing FAP mutation and for all at-risk members of families with FAP if genetic testing is not available or is non-informative.<br>Individuals found to have colorectal adenomas should be referred to a bowel cancer specialist.<br>Increase the interval for sigmoidoscopic surveillance to 3-yearly at 35 years if previous examinations have been normal. Consider cessation at 55 years.<br>If attenuated FAP is suspected colonoscopy is advised. Depending on the family history this may begin as late as 18 years and continue beyond 55 years. | 3 |
| **Prophylactic colectomy**<br>Prophylactic colectomy comprises total colectomy and ileo-rectal anastomosis or restorative proctocolectomy procedures. The choice of procedure is influenced by the rectal polyp burden and the individual's preference.<br>Offer to individuals with an established diagnosis of FAP.<br>The timing of surgery is individualised but is usually performed by the late teenage years.<br>Following colectomy and ileo-rectal anastomosis, annual surveillance of the rectum by sigmoidoscopy with removal and destruction of polyps is advised until restorative proctectomy with ileo-anal pouch construction is performed. This surgery should be considered in all such individuals at age 45 to 50 years because of the increasing risk of rectal cancer.<br>Proctectomy should be performed at an earlier age if polyps are not adequately controlled or CRC develops. | 3 |

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

| RECOMMENDATIONS: FAMILIAL ADENOMATOUS POLYPOSIS (CONTINUED) | |
|---|---|
| **Surveillance of upper gastrointestinal tract**<br>There are no published data demonstrating a reduction in mortality from duodenal cancer as a consequence of upper gastrointestinal surveillance.<br>Gastroduodenoscopy to detect duodenal adenomas at 1- to 3-yearly intervals from 30 to 35 years of age is commonly advised, as most advanced duodenal adenomas develop after the age of 40 years.<br>The Spigelman Criteria may be used to guide surveillance interval.<br>Pancreaticoduodenectomy should be considered in those with advanced but benign disease (Spigelman Stage IV). | 3 |



Familial adenomatous polyposis is an autosomal-dominant inherited disease with almost complete penetrance. The reported incidence is approximately one in 10,000 births, with new mutations being considered to be responsible for 25% of cases where there is no discernible genetic predisposition.[32] FAP has been estimated to account for 1% or less of cases of CRC, but more recent figures indicate that this is now around 0.2%.[33] This decrease is considered to reflect the improved management of FAP families, with sigmoidoscopy surveillance and colectomy for affected individuals becoming standard practice. The disease is characterised by the presence of multiple small polyps (>100) throughout the colon and rectum. These polyps develop in the early- to mid-teens, and in over 95% of gene carriers multiple adenomas are present by the age of 20 years.[34] The median age at diagnosis for CRC in untreated affected individuals is 40 years. An attenuated form of FAP has been described, with fewer colonic adenomas and the development of CRC at a later age.[35]

In individuals affected with FAP, polyps can be found in other parts of the gastrointestinal tract, particularly the duodenum where adenomas are identified in approximately 90%[36] and duodenal or periampullary cancer develops in approximately 5 to 8%.[37-39] Extracolonic malignancies associated with FAP include cancer of the thyroid, pancreas,[40] biliary tree and brain,[41] in addition to hepatoblastomas.[42] Other benign extra-intestinal manifestations of the disease include osteomas, congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, dental anomalies, and desmoid tumours (slow growing, locally invasive proliferations of fibroblasts). Gardner's syndrome was the name previously ascribed to individuals or families with FAP in whom extra-intestinal manifestations of the disease were prominent.

The majority of cases of FAP are associated with mutations in the APC gene on the long arm of chromosome 5q21.[43,44] The APC gene is subdivided into 15 coding exons, with the last exon accounting for most of the coding sequence of the gene. Most known mutations in FAP occur in exon 15. There is some phenotype-genotype correlation and certain clinical features may be linked with specific mutations.[45]

## Management of FAP

### *Genetic Testing*

A number of genetic tests for the diagnosis of FAP are available. The protein truncation test (PTT) takes advantage of the fact that the majority of disease-causing mutations in the APC gene result in truncation of the APC protein, and thus individuals can be identified as having the disease in the absence of other family information. PTT can identify up to 90% of affected individuals,[46] but if the disease-causing mutation in the family does not result in a truncated protein other approaches are required. Although PTT does not show the location of the mutation, the size of the protein detected

provides information that directs subsequent DNA sequencing. Linkage testing requires a firm clinical diagnosis in at least two affected family members before the DNA markers can be used to imply genetic diagnoses in other family members. Direct DNA sequencing in families with FAP to identify the specific disease-causing mutation for each family is a laborious process, but the use of a mutation screening test, with direct sequencing performed on the samples showing an alteration, can allow a more rapid process.[47]

Genetic testing may be offered, within the context of genetic counselling, to individuals with a clinical diagnosis of FAP and all at-risk members of FAP families if a family-specific genetic mutation has been identified. Genetic testing is offered to children at a time when sigmoidoscopic surveillance is clinically appropriate; it is not recommended for children under the age of 10 years. Genetic testing for FAP is available in New Zealand. This is performed at the Auckland City Hospital laboratory and can be accessed by genetic services.



## *Bowel Surveillance*

As the rectum is usually involved in FAP, sigmoidoscopic surveillance is the mainstay of disease detection. Rigid sigmoidoscopy is routinely used in New Zealand because of ease of access, but flexible sigmoidoscopy is often necessary to permit more extensive mucosal visualisation. Sigmoidoscopic surveillance should be offered at 1- to 2-yearly intervals from the age of 12 to 15 years to those asymptomatic individuals identified as carrying disease-causing mutations and to all at-risk family members if genetic testing is not available or is non-informative.

The decision about the age at which to begin sigmoidoscopic surveillance should be made carefully. Approximately 1% of individuals with polyposis will develop CRC before the age of 15 years. For this reason most clinicians advise beginning surveillance at around 12 years of age. A survey in the Netherlands of individuals with FAP revealed that 70% agreed that surveillance should start between the ages of 10 and 15 years because of the cancer risk; the same percentage felt endoscopy would be better accepted before puberty. However, only 51% agreed that surveillance should begin between the ages of 10 and 12 years.[48]

Individuals identified as having colorectal adenomas at surveillance sigmoidoscopy should be referred to a bowel cancer specialist. Individuals at risk of developing FAP who develop gastrointestinal symptoms that could relate to manifestations of the disease should also be referred to a bowel cancer specialist.

The majority of FAP-affected individuals (95%) will develop multiple rectal adenomas by the age of 20 years.[34] Therefore, at 35 years of age, if all previous procedures have been negative for adenomas, the frequency of sigmoidoscopic surveillance should be reduced to every 3 years. Surveillance advice from the age of 55 years generally reverts to that recommended for the general population of the country in question.

If attenuated FAP is suspected in a family – because of the presence of fewer colonic adenomas and the development of CRC at a later age – colonoscopic surveillance rather than sigmoidoscopic surveillance is advised and, depending on the family history, may begin as late as 18 years and continue beyond 55 years.

## *Prophylactic Colectomy*

Prophylactic colectomy comprises total colectomy and ileo-rectal anastomosis or restorative proctocolectomy. A prophylactic colectomy reduces the incidence and mortality of CRC in individuals with FAP,[33] but the relative risk of dying despite prophylactic colectomy is still 3.35 times higher than a matched group of the general population.[37] The majority (55%) of deaths post-colectomy relate to malignancy (upper gastrointestinal cancer or rectal cancer, if ileo-rectal anastomosis was performed

initially), with an additional 10% of deaths attributable to desmoid disease. Perioperative mortality is now low.

Total colectomy with ileo-rectal anastomosis, or restorative proctocolectomy and ileo-anal pouch anastomosis, is advised for those identified as affected. The choice of procedure is influenced by the rectal polyp burden and the individual's preference. The timing of surgery is individualised but cancer is rarely documented under the age of 20 years and therefore surgery is usually performed before the late teenage years.

If colectomy with ileo-rectal anastomosis is the initial operation, sigmoidoscopic surveillance of the remaining rectum needs to be continued on a yearly basis until restorative proctectomy with ileo-anal pouch construction is performed. This surgery should be considered in all such individuals at age 45 to 50 years because of the increasing risk of rectal cancer.[49,50] A proctectomy should be performed at an earlier age if polyps are not adequately controlled or cancer develops.



## *Surveillance of the Upper Gastrointestinal Tract*

Gastroscopy to detect duodenal adenomas is widely advised at 1- to 3-yearly intervals from the age of 30 to 35 years; however, there is little data to guide decisions regarding the age at which to commence this surveillance and the frequency with which it should be performed. Most advanced duodenal adenomas develop after the age of 40 years.[51] Gastroscopy may be considered prior to colectomy to allow the removal of large gastric or duodenal adenomas at the time of surgery. To date, however, there are no published data demonstrating a reduction in mortality from duodenal cancer as a consequence of upper gastrointestinal surveillance.

The Spigelman Classification, based on risk factors for cancer, can be used to clinically stage individuals with duodenal adenomas and to determine surveillance intervals, with procedures every 2 to 3 years for stages 0 to II and 6- to 12-monthly for stages III and IV disease.[51] In one study of 106 individuals with FAP and duodenal adenomas with a mean period of 46 months between endoscopies, the clinical staging of duodenal adenomas advanced in 9% of individuals.[52]

*Table 7: Spigelman Classification*

| | **Duodenal disease grading: points** | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| **Polyp number** | 1 – 4 | 5 – 20 | >20 |
| **Polyp size (mm)** | 1 – 4 | 5 – 10 | >10 |
| **Histology** | Tubular* | Tubulo-villous | Villous |
| **Dysplasia** | Mild | Moderate | Severe |

Stage 0 = 0 points; I = 1–4 points; II = 5–6 points; III = 7–8 points, IV = 9–12 points

* or hyperplasia inflammation

The optimal management of duodenal adenomas is also unresolved. Attempts to remove all small polyps by snare, electrocautery or laser should be avoided because of the risk of perforation. Local excision of duodenal adenomas is also an unsatisfactory treatment option.[52] If possible, surveillance and management of duodenal adenomas in FAP should be performed in a research setting. Difficult cases require joint management by skilled endoscopists and surgeons specialising in the upper gastrointestinal tract. The St Marks Polyposis Registry recently reported the 10-year follow-up data for 114 individuals with FAP prospectively screened for the presence and severity of duodenal adenomas. Six (median age 64 years) developed duodenal adenocarcinoma, with four of these being in individuals who originally had Spigelman stage IV disease. [53] Pancreaticoduodenectomy should therefore be considered in selected individuals with advanced but benign disease (Spigelman

stage IV). Comprehensive endoscopic surveillance is important to avoid underestimating the severity of high-risk stage III and IV disease.

Surveillance for other extracolonic malignancies may include annual examination of the thyroid gland.[40]

### *Chemoprevention*

Sulindac and celecoxib (a cyclooxygenase-2 inhibitor) have been shown to reduce adenomas in FAP.[54,55] These agents may be appropriate as an adjunct to polypectomy in controlling adenomas in the residual rectum after colectomy or in individuals who are awaiting colectomy. Protection against the development of cancer has not been established,[56,57] and therefore endoscopic surveillance should continue alongside chemoprevention. Routine use of these agents is not recommended and individuals should be informed of the risks and benefits of using these drug therapies. The role of these agents in reducing duodenal adenomas has not been established.



## Hereditary Non-polyposis Colorectal Cancer

| RECOMMENDATIONS: HEREDITARY NON-POLYPOSIS COLORECTAL CANCER<br>HPNCC cancer is an autosomal-dominant inherited condition characterised by the development of CRC at a mean age of 45 years, and was previously known as Lynch Syndrome. | |
|---|---|
| **Genetic testing**<br>Offer referral to a genetic service for consideration of genetic testing, within the context of appropriate counselling, to all at-risk members of families with HNPCC, at the age when colonoscopic surveillance would normally begin. | 5 |
| **Bowel surveillance**<br>Colonoscopy is recommended 2-yearly from the age of 25 years (or from an age 5 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). Consider annual colonoscopy in known mutation carriers. | 3 |
| **Surgery**<br>Colectomy with ileo-rectal anastomosis is advised once cancer develops in known mutation carriers or at-risk members of families with HNPCC.<br>Annual surveillance sigmoidoscopy of any residual large bowel should be performed. | 5 |
| **Prophylactic surgery**<br>Prophylactic subtotal colectomy should be discussed with individuals who are known mutation carriers and have recurrent adenomas with a high degree of dysplasia or a villous growth pattern.<br>Prophylactic colorectal surgery in known mutation carriers without any colorectal pathology (ie, negative colonoscopies) is not indicated because 10 to 20% of such individuals will not develop CRC in their lifetime.<br>Consider prophylactic surgery in known mutation carriers who are not willing or are unable to undergo periodic surveillance colonoscopy. | 5 |

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

## RECOMMENDATIONS: HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (CONTINUED)

**Extracolonic surveillance** 5

Surveillance for at-risk members of families with HNPCC or known mutation carriers takes into account the pattern of cancers occurring in particular families and the gene location of the disease-causing mutation, if known.

**Surveillance for endometrial cancer**

This is the most common extracolonic malignancy. Surveillance with annual transvaginal ultrasound (+/- endometrial aspiration biopsy) is usually advised for:

- known mutation carriers
- at-risk members of families with HNPCC as determined by the Amsterdam Criteria if there is a family history of uterine cancer and/or genetic testing is non-informative.

The efficacy of these surveillance tools remains uncertain in premenopausal younger women.



HNPCC is an autosomal-dominant inherited condition estimated to account for 1 to 4% of all cases of CRC. It is characterised by the development of CRC at a mean age of 45 years,[58] and was previously known as Lynch syndrome. The colonic tumours tend to be right-sided and may be multiple. Histological features include poor differentiation, abundant mucin production and lymphocytic infiltration.[59] Extracolonic cancers also occur, particularly endometrial cancers, but the stomach, ovary, small bowel, pancreas, urinary tract and biliary system can also be involved.[60] The lifetime risk of developing bowel cancer is 70 to 82% by the age of 70 years, but for women is variably reported to be 30 to 80%.[61-63] The lifetime risk of endometrial cancer is 42 to 60%.[61,63]

The term 'non-polyposis' is used to distinguish this form of inherited predisposition to CRC from FAP. However, the development of most CRC in HNPCC is considered to be through the adenoma-carcinoma sequence, albeit with an accelerated time sequence.[64] The number and distribution of adenomas throughout the colon is the same as that of the general population, but they develop at an earlier age and tend to display more severe histological features.

The Amsterdam Criteria were developed to identify families with HNPCC and provide uniformity in genetic diagnosis.[65] Three or more relatives on the same side of the family with verified CRC are required by the criteria, one of whom is a first-degree relative of the other two. CRC should involve two generations, and one or more cancer cases must be diagnosed before the age of 50 years. The limitations of these criteria, particularly the lack of reference to extracolonic tumours or family size, need to be recognised. To address this, modified Amsterdam Criteria were proposed in 1999.[66] The change to the criteria made was that there should be three relatives with an HNPCC-related cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis); other criteria remain unchanged.

*Figure 3: Revised International Collaborative Group HNPCC Criteria (Amsterdam II) for HNPCC*

There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis):

- one should be a first-degree relative of the other two
- at least two successive generations should be affected
- at least one should be diagnosed before age 50 years
- FAP should be excluded in the CRC case(s), if any
- tumours should be verified by pathological examination.

HNPCC has been demonstrated to be caused by mutations in one of four mismatch repair genes,[67-70] although the majority of mutations occur in two of the four genes (hMLH1 and hMSH2). These genes normally repair errors that occur in DNA as a result of normal cell replication. Mutations in these genes, which are most likely to be identified in families meeting the Amsterdam Criteria (45 – 64%),[71] result in the accumulation of mutations in other genes. Tumours resulting from defective mismatch repair can be detected by particular genetic techniques and are said to show replication error phenotype RER+, or microsatellite instability (MSI). This phenotype is seen in 70 to 90% of colon cancers from HNPCC patients,[72] but in only about 15% of sporadic cases of CRC.[72,73] Loss of protein expression for hMLH1 and hMSH2, as determined by immunohistochemical testing of colorectal tumours, correlates with the presence of MSI in tumours.[74,75] The heavy mutation burden affecting mismatch repair-deficient tumour cells may contribute to the better prognosis of CRC in HNPCC compared with sporadic CRC.[76]

With the advent of genetic testing it became apparent that even the modified Amsterdam Criteria excluded a significant number of families with mutations in the mismatch repair genes.[77] To address this concern and help identify individuals at highest risk of HNPCC, the Bethesda Criteria for testing colorectal tumours for MSI were developed in 1997.[78]

*Figure 4: The Revised Bethesda Guidelines for testing colorectal tumours for microsatellite instability (MSI)*

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.

* Hereditary non-polyposis colorectal cancer (HNPCC)-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumours, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.[78]

† MSI-H = microsatellite instability - high in tumours refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.

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

§ There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

# Management of HNPCC

## *Genetic testing*

In HNPCC, disease-causing mutations can occur in one of four genes, making genetic testing for HNPCC more complex than it is for FAP. Such testing is generally confined to members of well-defined families with HNPCC and is usually requested by clinical genetic services after the family has been appropriately assessed. Currently, these tests are usually performed at credentialled laboratories in

Australia. Genetic testing, if available, should be offered at the age at which colonoscopic surveillance is scheduled to begin but, in general, not to those younger than 16 to 18 years and only in the context of appropriate genetic counselling.

Determining the microsatellite status of colorectal tumours can help define families where HNPCC is considered likely and the modified Bethesda Criteria (but NOT the Amsterdam Criteria) are met. This test is not routinely available in New Zealand. However, colorectal tumour immunohistochemistry for hMLH1 and hMSH2 expression may also be helpful in this situation and is now beginning to be used in clinical practice in New Zealand. Loss of expression of hMLH1 and hMSH2 in tumours correlates with the presence of MSI.[74,75]



## Bowel Surveillance

Colonoscopic surveillance of at-risk relatives or carriers of mismatch repair gene mutations is shown to decrease the incidence of CRCs in those screened.[16,79] This is usually advised from the age of 25 years (or at an age 5 years younger than the age of the earliest affected member, whichever comes first) at 2-yearly intervals. A consensus statement from the Cancer Genetics Consortium in the United States recommended an interval of 1 to 3 years,[80] with the shorter interval generally being reserved for confirmed mutation carriers.[81] In the studies reported by Jarvinen *et al*,[16,79] no interval cancers were reported within 24 months of a previous colonoscopy. Two-yearly FOBT does not seem to be necessary for individuals undergoing regular colonoscopic surveillance.[82]

## Surgery in HNPCC

The risk of a metachronous CRC (ie, another new cancer) after limited bowel resection for CRC in HNPCC is 30% at 10 years and 50% at 15 years.[83,84] Colectomy with ileo-rectal anastomosis is therefore usually advised once CRC develops in at-risk individuals or known mutation carriers. Annual surveillance sigmoidoscopy should be performed on any residual large bowel.

## Prophylactic Surgery

The option of prophylactic subtotal colectomy should be discussed with individuals who are known mutation carriers and have recurrent adenomas with a high degree of dysplasia or a villous growth pattern.[80,85] Prophylactic colorectal surgery in known mutation carriers without any colorectal pathology (ie, with negative colonoscopies) should probably be avoided,[80,85] because of the morbidity associated with the operation and the fact that 10 to 20% of such individuals will not develop CRC in their lifetime.[61-63] However, if such individuals are not willing or are unable to undergo periodic surveillance colonoscopy, prophylactic surgery could be considered.

## Extracolonic Surveillance

Endometrial cancer is the most common extracolonic malignancy reported in HNPCC (42 – 60%), followed by gastric (13% by age 70 years), ovarian (12% by age 70 years), urinary tract (4% by age 70 years) and biliary tract (2% by age 70 years) malignancies.[63] The lifetime risk for other HNPCC-related cancer types, such as small bowel carcinoma and brain tumours, is much less, at around 1%.[63] Screening for tumours at other sites is determined to some extent by the pattern of cancers occurring in particular families and by the gene location of the disease-causing mutation in the family, if this is known.

The risk for endometrial cancer has been reported as higher in those with hMSH2 mutations (61%) compared with those with hMLH1 mutations (42%),[61] but the difference shown was not statistically significant. Recently, endometrial cancer has also been reported to be a frequent manifestation in some families with hMSH6 mutations.[86] The risk of endometrial cancer is considered sufficient to justify

annual surveillance from the age of 25 to 35 years in known mutation carriers and in those at-risk members of families with HNPCC, as determined by the revised Amsterdam Criteria, where there is a history of endometrial cancer and/or genetic testing is non-informative.[87]

There is no consensus on the optimal surveillance method for endometrial cancer, but transvaginal ultrasonography is usually recommended and endometrial aspiration may be considered. However, the efficacy of each as a screening tool remains uncertain in premenopausal younger women. There are insufficient data to make other surveillance recommendations in individuals with HNPCC.[80] Surveillance for ovarian or genitourinary tract tumours is recommended by some when there is a family history of these cancers.[60]



There is insufficient evidence to recommend for or against prophylactic hysterectomy and oophorectomy as a means to reduce cancer risk. Women who are known carriers of HNPCC-associated mutations should be aware that this option is available to them,[60] and if presenting with CRC after completion of their families, total hysterectomy and/or bilateral salpingo-oophorectomy should be considered at the time of colectomy.

## Hamartomatous Polyposis Syndromes

| RECOMMENDATION: HAMARTOMATOUS POLYPOSIS SYNDROMES | |
|---|---|
| Individuals with hamartomatous polyps of the large or small bowel, or those with a first-degree relative known to have multiple polyps alone or associated with CRC should be referred to the appropriate bowel and genetic specialists. | 5 |

Hamartomatous polyposis syndromes are rare syndromes with autosomal-dominant inheritance associated with hamartomas in the small and large bowel. The risk of CRC is increased but the magnitude of this risk is not clearly established. The Peutz-Jeghers syndrome is characterised by predominantly small bowel hamartomas and cutaneous pigmentation, particularly involving the lips and peri-oral area. In juvenile polyposis the hamartomatous polyps are predominantly colonic. The risk for colonic cancer in this condition has been estimated to be at least 9%.[88] Gastric and duodenal carcinomas have also been reported.

Individuals identified as having hamartomatous polyps of the large or small bowel, or who have a first-degree relative known to have multiple polyps alone or associated with CRC should be referred to the appropriate bowel and genetic specialists.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*
**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

# Hyperplastic Polyposis Syndrome

| RECOMMENDATION: HYPERPLASTIC POLYPOSIS SYNDROME | |
|---|---|
| Individuals identified to have hyperplastic polyps beyond the rectosigmoid junction with risk features should be referred to the appropriate bowel and genetic specialists.<br>Risk features include:<br>• unusual numbers (>20)<br>• unusual size (≥10 mm)<br>• location in the proximal colon<br>• presence of high-grade dysplasia<br>• coincidental adenomas<br>• a first-degree relative with high-risk hyperplastic polyps<br>• a first-degree relative with CRC. | 5 |



This syndrome is characterised by the presence within the colon of multiple large hyperplastic polyps that have been associated with CRC. It is uncommon and was first described in the early 1980s. The condition is quite separate from the common sporadic small hyperplastic polyps seen within the rectosigmoid region. On the basis of current and evolving knowledge for this syndrome risk features include:

- unusual numbers (>20)
- unusual size (≥10 mm)
- location in the proximal colon
- presence of high-grade dysplasia
- coincidental adenomas
- a first-degree relative with high-risk hyperplastic polyps
- a first-degree relative with CRC.

The multiplicity and the size of the polyps, with 12 to greater than 100 polyps being reported, often 10 mm or larger, are important features.[89] Another important characteristic of the syndrome is the distribution of the hyperplastic lesions evenly throughout the colon. Additionally, the polypoid lesions tend to show atypical cytological features, while maintaining the serrated architecture of the hyperplastic polyp.[90] This combination is variously referred to as a mixed hyperplastic polyp or serrated adenoma.

A specific genetic mutation associated with this condition has not been identified to date, but ongoing colonoscopic surveillance with removal of the polyps is advised. If this abnormality is detected in association with a personal history of CRC and the polyps are multiple and difficult to control, colectomy with ileo-rectal anastomosis may be considered. Individuals identified to have multiple hyperplastic polyps with risk features should be referred to the appropriate bowel and genetic specialists.

## Familial Bowel Cancer Registries

| RECOMMENDATIONS: FAMILIAL BOWEL CANCER REGISTRIES | |
|---|---|
| There is a need for a national registry in New Zealand.<br>Familial bowel cancer registries facilitate:<br>• the diagnosis of hereditary CRC<br>• the maintenance of a confidential family database<br>• coordination of cancer surveillance<br>• multidisciplinary clinical management<br>• education for both families and medical practitioners. | 5 |
| Individuals or families with hereditary CRC syndromes should be offered referral to a familiar bowel cancer registry as coordination of cancer surveillance by registries in familial colorectal syndromes is associated with a reduction in cancer incidence (see Appendix B). | 3 |
| A working party is advised to review guidelines for the functioning of a national registry, particularly with regard to informed consent and confidentiality of registry information. | 5 |

Familial bowel cancer registries have been established in a number of medical centres to facilitate the diagnosis and treatment of individuals suspected to have hereditary CRC. The registries are usually staffed by a multidisciplinary team comprising specialists in genetics, gastroenterology, surgery, counselling, oncology and pathology. An important role of a registry is to obtain an accurate family history with confirmatory data from hospital records, pathology departments and death certificates. This clinical, demographical and genealogical information provides the basis for a diagnosis of hereditary CRC and subsequent assessment of cancer risk for family members. Genetic testing, within the context of appropriate counselling, can be facilitated through the registry. Coordination of cancer surveillance – a demanding administrative task – is another major function of the registry. The information provided by registry-initiated referrals for surveillance colonoscopies can also ensure appropriate priority grading for these procedures. Studies reporting a reduction of cancer incidence in members of families with FAP or HNPCC have used such registries.[80,91-93] Individuals or families identified to have an hereditary CRC syndrome should therefore be offered the opportunity of referral to family registries.

The concentration of expertise provided by the multidisciplinary registry team also facilitates education for both families and medical practitioners. This is particularly important with the advent of sophisticated molecular approaches to diagnosis and their implications for management. Clinicians and investigators from registries worldwide have now formed collaborative groups with the aim of furthering knowledge regarding these familial CRC syndromes.[50,65]

In New Zealand, as elsewhere internationally, the establishment of a registry has been crucial in facilitating research into the genetic basis and management of these conditions.[94,95] The Familial Bowel Cancer Registry, incorporating the FAP and HNPCC registries, and linked with the worldwide collaborative groups outlined above, was established in 1995 by the Northern Regional Genetic Services of the Auckland District Health Board's predecessor to provide services to a defined region. However, family members are spread throughout New Zealand. To ensure consistency in family

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assessment and advice, a national registry to facilitate diagnosis and genetic testing, in addition to coordinating cancer surveillance, is necessary.[96] A Southern registry with functional links to the Northern service has recently been established at Christchurch Hospital. Individuals or families with hereditary CRC syndromes should be offered referral to the closest familial bowel cancer registry.

A working party is advised to review guidelines for the functioning of a national registry, particularly with regard to informed consent and confidentiality of registry information. A major concern for registries is the preservation of confidentiality and privacy to protect registered individuals from genetic discrimination and to ensure that information is not disclosed to third parties unless consent has been obtained.[97] For this reason, guidelines for genetic registers have been established.[98]

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
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# PERSONAL HISTORY OF COLORECTAL CANCER



## OVERVIEW

- There are insufficient robust data to make strong recommendations on a precise programme of follow-up for individuals who have undergone resection of CRC with curative intent. Opinion is divided on the optimum length, frequency and intensity of follow-up.
- Potential advantages of follow-up include removal of subsequent adenomatous polyps at a curable stage, detection of potentially curable metachronous CRC, detection of potentially curable recurrent CRC, provision of clinical audit, and meeting individuals' expressed preference.
- Potential disadvantages of follow-up include high cost and infrequent complications.
- Individual studies to date have shown an inconsistent survival effect as a result of follow-up. More research is needed to define the role of follow-up in this group.

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL CANCER | |
|---|---|
| Follow-up after resection of CRC with curative intent is recommended as it allows practitioners to monitor treatment outcome and is consistent with the preference of individuals with CRC. | 5 |
| All such individuals should have specialist follow-up over the time period in which the majority of recurrences (local or metastatic) are most likely to occur (3 – 5 years).<br>Follow-up should be appropriate to the clinical context. In deciding on intensity and duration of follow-up, age and comorbid conditions should be considered.<br>Follow-up should occur in conjunction with, and subsequently be continued by, the individual's general practitioner. | 5 |
| Individuals free of recurrent CRC for 3 to 5 years should be entered into a colonoscopy surveillance programme.<br>Colonoscopy should be performed at 3- to 5-yearly intervals. | 5 |
| All individuals with CRC should be informed of the uncertain efficacy of follow-up with regard to survival benefit. | 5 |

A number of papers have been published on follow-up after surgical treatment of CRC. These include the findings of meta-analyses,[1,2] randomised controlled trials,[3-7] cohort studies,[8-10] and reviews,[11-16] and express some conflicting conclusions. The role of follow-up is therefore controversial.

New Zealand has one of the highest rates of CRC in the world.[17] Each year many individuals with this disease undergo resection performed with curative intent. The extent of follow-up of these cases is variable, with intensive follow-up schedules for some and little or no follow-up for others.[18] The need for broad guidelines is therefore evident. It is emphasised that follow-up for symptomatic individuals and for those after resection with palliative intent is not covered in these guidelines. Appropriate follow-up for such individuals should be determined on a case-by-case basis.



# POTENTIAL ADVANTAGES OF FOLLOW-UP

## Detection of Second Primary (Metachronous) Tumours

After surgery for CRC with curative intent, there is an increased risk of subsequent adenomatous polyps and metachronous primary CRC.[19] The incidence of subsequent adenomas is 25 to 30%, and the cumulative incidence of metachronous primary CRC is 3 to 8%,[20-22] with a median time to diagnosis of 10.7 years.[21]

Colonoscopic follow-up may detect metachronous CRCs at an early, treatable stage. Removal of detected adenomas may reduce the subsequent incidence of metachronous primary CRC.

## Detection of Cancer Recurrence

One-third of individuals having surgery for CRC with curative intent will die from recurrent disease,[22] the majority of which will occur at sites distant from the colon (ie, metastatic tumours). The expectation is that regular follow-up may detect recurrences at an early stage when treatment might improve the outcome. Treatable recurrences may be local (ie, related to previous anastomoses), or metastatic (eg, liver or lung tumours).

Four randomised controlled trials of follow-up failed to show a significant survival advantage when compared with less intensive or no follow-up.[3-5,7] This was mainly due to low resectability and cure rates for recurrences, even when detected early by intensive follow-up. For example, in one study comparing frequent with infrequent follow-up in cases of local and distant recurrence, only 1.7 and 0.6% of individuals, respectively, were candidates for curative treatment.[5] Conversely, one randomised controlled trial has shown an improvement in survival with intensive follow-up, particularly for individuals with rectal cancer.[6]

Some of the randomised controlled trials have been criticised for having insufficient numbers and therefore insufficient statistical power to detect small but important effects on survival. The trials were also carried out at a time when few individuals with colorectal cancer were offered potentially curative liver resection and when the choice of systemic chemotherapy agents (for adjuvant or palliative use) was much more limited than currently.

Two meta-analyses (not confined to randomised controlled trials) have been performed in an effort to overcome issues related to the statistical power of individual studies. The first concluded that the best intensive follow-up programmes can improve survival, and should be 'individualised' according to a person's characteristics.[1] The most recent also concluded that intensive follow-up can improve survival.[2]

## Lead-time Bias

The difficulty with comparing the *survival* of groups allocated to different follow-up programmes is that the comparison is likely to be affected by lead-time bias. Lead-time bias is defined as 'overestimation of survival time, due to the backward shift in the starting point for measuring survival that arises when diseases such as cancer are detected early, as by screening procedures'.[23] Intensive follow-up is likely to advance the date at which recurrence is diagnosed, and thereby extend the interval between diagnosis and death (even if the time of death is unchanged). Because survival is measured as the time from diagnosis to death, individuals whose recurrent disease was detected by intensive follow-up will appear to have longer survival than individuals undergoing less intensive follow-up (or no follow-up). This could cause intensive follow-up to seem beneficial, even if it really had no impact on the time of death. Only randomised controlled trials with mortality as the outcome measure avoid lead-time bias.



## Clinical Audit

Follow-up is essential for audit purposes.[24] This may be part of the evaluation of the practice of individual surgeons, of the impact of new treatment guidelines or modalities, or as part of clinical studies.

## Preference of Individuals with CRC

One study of individuals with CRC in a follow-up programme after surgery for CRC indicated that quality of life was not improved by follow-up visits,[25] whereas a further study concluded that a small increase in quality of life could be demonstrated.[26] However, overall, individuals found follow-up reassuring, expressed a strong preference for follow-up, and a preference for follow-up even if it did not lead to earlier detection of recurrence.

# POTENTIAL DISADVANTAGES OF FOLLOW-UP

## Costs

Three studies in the USA, Italy and Germany have examined the costs of follow-up after surgery for CRC.[27-29] These concluded that the costs are generally high. In addition, the costs of different follow-up programmes varied considerably, a particularly important point in the light of data indicating that the survival advantage gained by a more intensive follow-up approach, compared with a less intensive approach, may not be large. Recommendations were that programmes should be tailored according to stage and site of primary cancer in order to reduce costs,[28] and that controlled economic studies are required.[29]

## Risks

The small risks associated with follow-up relate mainly to the investigations employed. The most serious of these are the risks of bleeding and perforation associated with colonoscopy.[30] However, follow-up clinic appointments may also generate anxiety, the person may receive false reassurance and excessive investigation could result in the early diagnosis of untreatable metastatic disease.

# WHICH INDIVIDUALS SHOULD BE SEEN FOR FOLLOW-UP?

It is not currently possible to accurately predict which of those individuals who have undergone resection of CRC with curative intent are likely to have second primary CRCs or treatable recurrent disease. Follow-up should therefore be offered to all individuals who are medically fit for any necessary treatment.[31] There should be specialist follow-up for the time period in which the majority of cancer recurrences (local or metastatic) are most likely to occur (ie, 3 – 5 years).



# WHO SHOULD PERFORM THE FOLLOW-UP?

In New Zealand, the operating surgeon usually undertakes the follow-up. This is in line with most individuals' expectations, and facilitates clinical audit and access to hospital-based investigations (eg, sigmoidoscopy, barium enema, CT scans). Follow-up can be undertaken in collaboration with gastroenterologists, oncologists and general practitioners. Further research is needed to define the optimum roles for these clinicians in the follow-up process.

# FOLLOW-UP PROCEDURES

Follow-up should be appropriate. In initiating and determining the method and length of follow-up, the preference of the individual with CRC, age, and the presence of serious comorbidities that are contraindications for consequent therapeutic intervention should be taken into account.

## Clinical Review

Routine clinical follow-up is common in New Zealand but the frequency and intensity of assessments vary, depending on surgeons.[18] After anterior resection of the rectum, physical examination should be supplemented by sigmoidoscopy in order to detect early suture-line recurrences. An Australian study has confirmed that regular clinical review, with routine blood and faecal tests, can detect both early and late recurrences and metastases, but also reported that overall survival was unchanged.[7]

## Serial Blood Tests

In isolation, routine blood tests (erythrocyte sedimentation rate, white blood cell count and liver function tests) have little value in detecting asymptomatic colorectal primary tumours or recurrences.[1]

Although serum carcinoembryonic antigen (CEA) is not a suitable diagnostic test for primary CRC (as it has low sensitivity and specificity) and its role in the detection of recurrent or metastatic disease is debated, it can detect asymptomatic recurrence.[32] A rise in CEA has been shown to precede the onset of symptomatic recurrence by a median of 4 to 6 months.[33] Follow-up programmes including CEA are shown to be associated with increased 5-year survival rates,[1] although these results may be affected by lead-time bias. However, the increases are small when weighed against the overall costs and other disadvantages.[3,15,32] Other tumour markers used in this context include CA50, CA195, CA242 and CA19-9. None of these has been shown to significantly improve survival during follow-up.

## Faecal Occult Blood Tests

Some follow-up recommendations include annual FOBTs as screening for adenomas and second primary tumours in this high-risk group.[31] However, FOBTs are ineffective at detecting local recurrences, as these are usually extra-luminal.[11]

## Chest X-ray

Although chest x-ray is a sensitive test for pulmonary metastases, there is no evidence that annual chest x-rays increase either the rate of detection of asymptomatic deposits or the survival rate.[7]



## CT Scan/Ultrasound of the Liver

Routine CT or ultrasound scanning of the liver during follow-up will detect some metastases at an asymptomatic stage. The two modalities have not been compared in randomised controlled trials. Choices in the clinical setting are therefore based on other factors (eg, opinion, availability).

Scanning may define a small subgroup of cases in which hepatic resection is indicated. Published studies show no evidence that such early detection improves the overall group survival rate;[7] however, these studies were not powered to look for benefit from screening for liver metastases specifically. In addition, the treatment of liver metastases has also evolved significantly. Treatment with potential survival benefit may now be offered to more individuals with liver metastases than was the case when these studies were completed.[34] Whether or not such outcomes justify the routine use of screening for liver metastases as part of follow-up has not been determined.

After surgery for rectal cancer, routine pelvic scans are frequently completed to detect local recurrences. This is primarily for audit purposes.

## Colonoscopy/Barium Enema

Colonoscopy is the most useful follow-up investigation. It is generally superior to double-contrast barium enema for diagnosis of synchronous, recurrent or metachronous CRCs and adenomas. However, the use of double-contrast barium enema may be indicated when complete visualisation of the colorectum is not possible with colonoscopy, or access to the latter investigation is restricted.

Colonoscopy should be performed before surgery for the index CRC, in order to exclude synchronous adenomas or cancers.[35,36] If this is not possible, then colonoscopy of the residual colorectum should be performed within 6 months of the surgery.[37]

Most CRC recurrences occur within 3 to 5 years after surgery,[38] and after clearance of the colorectum, the development of new adenomas and metachronous cancers is slow.[31,39] It is therefore recommended that a follow-up colonoscopy should be performed after 3 to 5 years.[7]

If there is no evidence of recurrent CRC after 3 to 5 years, it is common practice to enter these individuals into a surveillance programme with colonoscopies at 3- to 5-yearly intervals. The rationale for this approach is that these individuals are at increased risk of developing adenomas or metachronous CRCs. As most randomised controlled trials have only reported follow-up data for 5 years, there is no good evidence that this practice has a significant favourable impact on survival, however. Individuals should be informed of the uncertain efficacy regarding survival benefit.

## SCHEDULE FOR FOLLOW-UP

An example of current practice is as follows:

- after surgery, an early outpatient review
- follow-up 6 monthly for 2 years, then annually afterwards
- each time a history and examination, including digital rectal examination and sigmoidoscopy after anterior resection of the rectum
- a follow-up colonoscopy 3 to 5 years after surgery – this presumes a complete colonoscopy was performed in the peri-operative period
- in those free of recurrence, surveillance colonoscopies at 3- to 5-yearly intervals thereafter.

## FUTURE DEVELOPMENTS

Future investigations may detect the presence of recurrence at an earlier stage and subgroups of individuals who are more likely to benefit from follow-up. Further advances in treatment may make early diagnosis more important.

Further randomised studies are in progress to determine whether follow-up is worthwhile, how intensive it should be and who should perform it. Future randomised controlled trials should use mortality rather than survival as the outcome measure.

Two recently published systematic reviews of 5 randomised controlled trials[40,41] have demonstrated a small overall survival benefit for intensifying follow-up of patients after curative surgery for colorectal cancer. Because of the wide variation in the follow-up programmes used in the included studies it is not possible to infer from the data the best combination and frequency of clinic (or family practice) visits, blood tests, endoscopic procedures and radiological investigations to maximise the outcomes for these patients. Nor is it possible to estimate the potential harms or costs of intensifying follow-up for these patients in order to adopt a cost-effective approach in this clinical area. Large clinical trials underway or about to commence are likely to contribute valuable further information to clarify these areas of clinical uncertainty.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
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# PERSONAL HISTORY OF COLORECTAL ADENOMA



## OVERVIEW

- Adenoma recurrence is documented after colonoscopy and polypectomy. High-risk lesions are most likely to be detected subsequently in those individuals initially identified to have 3 or more adenomas, large adenomas, and adenomas with adverse pathology (severely dysplastic and/or villous lesions).
- Stratification for colonoscopic follow-up into high- and low-risk groups appears appropriate to minimise unnecessary procedures and risk for individuals, and to reduce costs to the health system.
- The first surveillance colonoscopy for individuals identified initially to have high-risk adenomas is advised at 3 years.
- In individuals with low-risk adenomas the first surveillance examination can probably be deferred for 5 to 6 years.
- The duration of follow-up will, to a great extent, be dependent on the findings at each subsequent surveillance colonoscopy and on an individual's comorbid factors.

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL ADENOMA* | | | |
|---|---|---|---|
| **Factor** | **Assessed risk** | **First surveillance colonoscopy** | |
| Adenoma size ≥10 mm | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| ≥3 adenomas | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| Villous lesions and/or severe dysplasia | High: continued surveillance | At 3 years – if negative subsequent colonoscopy at 3 – 5 years† | 3 |
| Adenomas with no high-risk features and: | | | 3 |
| • significant family history of CRC | High: continued surveillance | At 3 years | |
| • no family history of CRC | Low: consider discontinuing surveillance if subsequent surveillance colonoscopy normal. | At 5 – 6 years | |

* Presumes complete excision of previous adenomas.

† Shorter interval may be appropriate if multiple high-risk features at index procedure.

# COLONOSCOPIC FOLLOW-UP

If the adenoma-carcinoma theory is correct, removal of adenomas should reduce the incidence of CRC. However, a randomised controlled trial to prove this would involve a no-intervention control arm, which is not ethically acceptable. A number of observational studies, particularly the National Polyp Study,[1] have demonstrated a reduction in CRC incidence following colonoscopic surveillance with removal of all polyps.

However, autopsy studies have revealed that 30 to 40% of individuals aged 60 years and over have adenomas, yet the lifetime risk for CRC in western countries is around 5%. The potential colonoscopic burden of adenoma surveillance is enormous unless it is targeted at those with high-risk polyps. A Norwegian study estimated that the annual conversion rate to cancer for all adenomas was 0.25%. An increased annual conversion rate was identified in adenomas greater than 10 mm in size (3%), polyps that were villous in nature (17%), and polyps with severe dysplasia (37%).[2] Whereas the risk of malignancy in an adenoma less than 10 mm is small, in adenomas greater than 20 mm the risk of malignancy is approximately 20%. However, the rate of progression from adenoma to carcinoma is usually slow, occurring over many years. One study found a cumulative risk of cancer of 25% at 20 years for adenomas greater than 10 mm.[3]

The aim of colonoscopic follow-up of adenomatous polyps is thus to detect new lesions that would, if left *in situ*, carry a significant risk of eventual carcinomatous change. The frequency of colonoscopic follow-up should be timed to allow detection of high-risk polyps prior to the development of carcinoma. Furthermore, follow-up should be targeted at those most at risk of new polyp formation.

The management of adenomas that are incompletely excised may involve early repeat colonoscopy and/or surgical referral. Likewise, initial incomplete colonoscopy may require early repeat examination. Neither clinical scenario is addressed further in this document.

## Evidence of New Adenoma Formation Following Colonoscopic Polypectomy

New adenomas are found in up to 41% of individuals at 1 year after initial polypectomy,[1] and in up to 60% at 8 years.[4] Although some polyps detected soon after the initial colonoscopy probably represent missed synchronous lesions, there is clear evidence of ongoing adenoma development following initial polypectomy.

## Features of Adenomas Detected at Follow-up

Between 3% and 10% of polyps detected at follow-up are classified as 'high-risk adenomas'. In other words, such adenomas are considered to carry a high-risk of ultimate malignant transformation if the polyp is not completely excised. The definition of such adenomas varies among authors, but broadly includes features of size and histopathology. Polyps greater than 10 mm and/or those with villous architecture are widely regarded as 'high-risk'; conversely, polyps without these features are considered low-risk.[1,5,6] Ideally, surveillance colonoscopy should target individuals most likely to harbour high-risk adenomas. In those individuals with polyps greater than 10 mm, and/or those with villous architecture and/or severe dysplasia, a surveillance colonoscopy is recommended at 3 years (or at a shorter interval if there are multiple high-risk features at the index procedure). If negative, colonoscopic evaluation should be repeated again at 3 to 5 years.

In a prospective study of polyps less than 10 mm in size, growth retardation was shown to exist.[7] Adenomas sized 5 to 9 mm showed a net decrease in size over a 3-year period. Of the 116 individuals enrolled, one individual developed invasive carcinoma at two years. Carcinoma *in situ* was found in

two polyps removed at 3 years. The authors concluded that the interval between colonoscopies could be extended in individuals with small adenomas (<10 mm). Of note, this study also showed that most new polyps developed at sites proximal to the upper limit of rigid sigmoidoscopy.

## Development of Carcinoma Following Colonoscopic Polypectomy

Polypectomy does not completely eliminate the risk of subsequent CRC development. In the St Marks Hospital data, the risk of colon cancer development following polypectomy was greatest in those individuals with large adenomas (≥10 mm) and villous lesions, with the standardised incidence ratio of 3.6 for the subsequent development of colon cancer if the initial polyp was 10 mm or more, tubulovillous or villous.[5] The incidence ratio rose to 6.6 if there were multiple adenomas present. The time to development of cancer detection varied greatly. In prospective surveillance studies, very few cancers were detected as early as 3 or 4 years after polypectomy.[1,2] No increased risk of CRC has been identified in individuals undergoing resection of single small (<10 mm) tubular adenomas.[5,8]



Detection of both adenomas and carcinomas during surveillance may be the detection of either new pathology or pathology missed at a previous examination. An immediate second colonoscopy study showed 13% of adenomas sized 6 to 9 mm were missed on one colonoscopy, along with 6% of adenomas 10 mm or more.[9] These factors may influence the interval between colonoscopies.

## Surveillance Intervals in Adenoma Follow-up

Only 2 randomised controlled trials investigating varying surveillance intervals for individuals with adenoma have been published to date.[1,4] In the United States National Polyp Study,[1] 1418 individuals who had been identified to have at least one adenoma of the colon and rectum, and who had undergone a complete colonoscopy, were randomised into two follow-up groups. Group A was randomised to 1- and 3-year surveillance, while Group B was randomised to 3-year surveillance alone. 'High-risk' polyps were found in 3.3% of individuals in both groups at 3 years. No invasive cancer was found at 1 year and a total of only three cancers was found in the two groups at 3 years. The only feature found to be significantly associated with the detection of high-risk adenomas at follow-up was the presence of 3 or more adenomas at the initial (enrolment) colonoscopy. The authors recommended a 3-year interval (at least) between colonoscopies after the removal of an adenomatous polyp. Thus, the first surveillance colonoscopy for individuals identified initially to have high-risk adenomas (eg, three or more adenomas) is advised at 3 years and if negative, then a subsequent procedure is advised at 3 to 5 years.

In the Funen Adenoma Follow-Up Study,[4] 673 individuals were randomised to 2-yearly (Group A) or 4-yearly (Group B) surveillance colonoscopy. All the individuals in this study had had pedunculated or small, sessile tubular or tubulovillous adenomas removed at the initial colonoscopy. 'High-risk' adenomas were found in 3.4% of individuals at 2 years and in 0.4% of individuals at 4 years in Group A, and in 5.6% of individuals in Group B at 4 years. Factors significantly associated with subsequent detection of 'high-risk' lesions were 3 or more adenomas at the initial colonoscopy, as well as the initial colonoscopy being incomplete. The authors concluded that after removal of pedunculated and small sessile adenomas, the first follow-up colonoscopy might be at 4 years.

A review of 697 individuals seen for follow-up after colonoscopic polypectomy at the Cleveland Clinic concluded that individuals with 3 or more adenomas at the initial colonoscopy (with at least one polyp being ≥10 mm in size) were much more likely to have 'high-risk' adenoma identified at the first surveillance colonoscopy compared with individuals who lacked such features.[6] This study was not randomised and the interval to first surveillance colonoscopy varied considerably. However, the authors concluded that a low-risk group of individuals could be identified, and that first surveillance

colonoscopy could be prolonged for more than 3 years. Thus, in individuals with low-risk adenomas, the first surveillance examination can probably be deferred for 5 to 6 years.

Some individuals will have more than 1 indication for entering a surveillance colonoscopy programme – for example, an individual found to have an adenoma who also has a family history of CRC. In such situations, the colonoscopy regimen is determined by the factor with the highest risk; in other words, if the features of detected adenomas are assessed as 'low-risk' but the family history is one of significant risk, then surveillance should continue as for the highest risk category.

No data exist specifically on the appropriate duration of follow-up. However, based on available data, the ongoing detection of high-risk adenomas mandates follow-up. Data from the US National Polyp Study and from reported experiences with surveillance colonoscopy indicate that after an individual has had one negative follow-up colonoscopy, the subsequent interval may be safely increased to 5 years.[10] However, there is not universal agreement on this; others advise shorter intervals dependent on the number of high-risk adenoma features, particularly in individuals with multiple or large adenomas present at the initial colonoscopy.[11] The first surveillance colonoscopy for individuals identified initially to have high-risk adenomas is advised at 3 years.

In selected older individuals with serious comorbid conditions, no further follow-up may be appropriate. The same is true for younger individuals with serious comorbid conditions.[10,11] There is no evidence to support the '*ad-infinitum*' follow-up of low-risk individuals with single, small, tubular adenomas, particularly for those individuals who are polyp-free at a subsequent surveillance colonoscopy. The duration of follow-up will, to a great extent, be dependent on the findings at each subsequent surveillance colonoscopy as well as on an individual's comorbid factors.

In view of data regarding life expectancy, the time sequence for evolution of adenoma to carcinoma and studies of the natural history of adenomas in advancing age, it is likely that an upper age limit of 75 years is appropriate for surveillance. It may be appropriate to survey some individuals with high-risk polyps beyond this age, depending on factors such as associated comorbidities.

## Prevention of Colorectal Cancer by Colonoscopic Polypectomy

In the United States National Polyp Study (n= 1418),[1] five asymptomatic CRCs were detected at follow-up colonoscopy. Two cancers were detected in the group randomised to 1- and 3-year surveillance and 3 in the group randomised to 3-year surveillance alone. No-one in either group had a symptomatic cancer or died of CRC. The expected number of CRCs in the study cohort compared with 3 reference groups was significantly lower than expected, with reductions in the incidence of CRC of 76 to 90% ($p<0.01$). The reference groups consisted of 2 retrospective cohorts and the USA SEER (Surveillance, Epidemiology, and End Results) age- and sex-specific rates of CRC for the relevant study period.

In the Funen study following up 673 individuals,[4] the incidence of CRC was very low and did not differ from the expected incidence in the general population. In the Telemark follow-up study,[12] 400 men and women aged 50 to 59 years were randomly drawn from the population registry of Telemark, Norway. They were offered a flexible sigmoidoscopy and, if polyps were found, a full colonoscopy with polypectomy and follow-up colonoscopies in 1985 and 1989. A control group of 399 individuals was drawn from the same registry. In 1996 both groups (aged 63 – 72 years) were invited to have a colonoscopic examination. Ten individuals in the control group and two in the screening group were registered as having developed CRC, representing a significant reduction in the incidence of CRC in the screening group (relative risk 0.2; 95% CI, 0.03–0.95, p=0.02). However, it was of concern that a higher overall mortality was observed in the screening group, with 55 (14%) deaths compared with 35 (9%) in the control group (relative risk 1.57; 95% CI, 1.03–2.4, p=0.03). This may be accounted for by underlying differences between the groups before the intervention took place. The possible effect

of screening on overall mortality needs to be addressed in larger studies, conducted with appropriate randomisation.

## COST-EFFECTIVENESS

The cost-effectiveness of surveillance colonoscopy following a polypectomy has been examined.[13] The authors estimated that in a low-risk group, 1131 colonoscopies would be performed to prevent one cancer death and concluded that for individuals at low-risk, such as those in whom a single, small adenoma has been detected, the costs of regular surveillance might be excessive. Stratification for colonoscopic follow-up into high- and low-risk groups therefore appears appropriate, in order to minimise unnecessary procedures and risk for individuals, and to reduce costs to the health system of such follow-up.



No published study appears to have re-classified individuals as low- or high-risk based on findings at surveillance colonoscopy. In other words, once assigned to a particular risk group following the initial colonoscopy, no subsequent adjustments appear to have been made. Such a policy would influence the overall cost of surveillance. Similarly, no significant data exist as to the upper age limit at which surveillance can or should cease; nor are there data addressing total duration of surveillance.

## CURRENT INTERNATIONAL GUIDELINES

There are no globally agreed guidelines on surveillance colonoscopy. In the United States, the first surveillance colonoscopy in individuals with initial 'high-risk' lesions is recommended at 3 years, with possibly a longer interval for low-risk lesions.[14] The polyp guideline for the American College of Gastroenterology advises that after one negative follow-up surveillance colonoscopy, subsequent surveillance intervals may be increased to 5 years.[10] Similar recommendations have been developed in Australia.[15]

In Europe, the European Panel of Appropriateness of Gastrointestinal Endoscopy recommends the first follow-up colonoscopy at 1 year in individuals with initial 'high-risk' polyps and a 5-year interval after excision of a low-risk adenoma.[16] Unfortunately, no data are supplied to support these recommendations.

Overall, individuals with high-risk adenomas require continued follow-up with a further colonoscopy at 3 years. However, there are no data to support continued follow-up *ad infinitum* in individuals with an initial low-risk polyp who are polyp-free at 5 years.

**KEY** - *Grades indicate the strength of the supporting evidence not the importance of the recommendations - see page xii for details*

**1** Randomised controlled trials
**2** Non-randomised controlled trials
**3** Non-randomised historical cohort studies
**4** Case series
**5** Expert (consensus) opinion

# 5

# PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE



## OVERVIEW

- Evidence supporting colonoscopic surveillance procedures to detect CRC in individuals with ulcerative colitis (UC) includes the analysis of a large number of observational studies.
- Carcinomas occurring in UC are accompanied by distant mucosal dysplasia in up to 75% of cases. The rationale for performing surveillance colonoscopy is the detection of dysplasia as a precursor lesion or marker for malignancy.
- Available evidence supports a policy of 2-yearly colonoscopic surveillance for individuals with UC of greater than 10 years' duration, except for those in whom disease is limited to the sigmoid colon and rectum.
- Although based on small figures, the 5-year survival in cancers discovered during surveillance colonoscopy is 80% compared with, at best, 50% in individuals developing CRC outside a surveillance programme (symptomatic cancer). This difference may be partly explained by lead-time bias.
- There is strong evidence that low-grade dysplasia leads to high-grade dysplasia or CRC within 5 years in over 50% of cases, and this and other data on screening supports a screening interval of 2 years.
- An inflammatory bowel disease CRC surveillance programme should include individuals with extensive colonic Crohn's disease.

## RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

### ULCERATIVE COLITIS

**Initial surveillance colonoscopy**

3

After 8 to 10 years, individuals with UC should undergo colonoscopy with serial biopsies (as detailed below) to define disease extent, both macroscopic and microscopic.

All those with significant disease extending proximal to the sigmoid colon should be enrolled in a surveillance programme.

| RECOMMENDATIONS: INDIVIDUALS WITH A PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE (CONTINUED) | |
|---|---|
| **ULCERATIVE COLITIS** | |
| **Surveillance colonoscopy**<br>Colonoscopy is recommended 2-yearly for individuals with UC after 10 years' disease duration. At colonoscopy, 2 to 3 biopsies should be taken from each of 10 sites (caecum, proximal and distal ascending colon, proximal and distal transverse colon, proximal and distal descending colon, proximal and distal sigmoid colon and rectum). Additional biopsies should be taken from any mass lesions, but not from pseudopolyps.<br>Individuals with UC should be informed regarding:<br>• the rationale for surveillance colonoscopy and its limitations in detecting CRC<br>• the failure of studies to establish beyond doubt the value of surveillance in this situation. | 3 |
| **Management of surveillance-detected dysplasia**<br>If high-grade dysplasia (HGD) is present on biopsy (and confirmed on histological review), the individual should be referred for colectomy.<br>If low-grade dysplasia (LGD) is found in the absence of significant inflammation:<br>• shorten the surveillance interval to 1 year<br>• refer for surgical review.<br>If LGD is found in the presence of active inflammation, it is advisable to repeat the colonoscopy after anti-inflammatory therapy. If LGD is confirmed, proceed as outlined for LGD above. | 3 |
| **CROHN'S DISEASE**<br>All individuals with extensive colorectal Crohn's disease should undergo surveillance procedures as detailed for individuals with extensive UC. | 4 |

# COLONOSCOPIC SURVEILLANCE IN ULCERATIVE COLITIS

## Rationale for Surveillance

An increased risk of CRC in individuals with longstanding, extensive UC has been established. Reported incidences vary widely, probably due to selection bias.[1-6] For individuals with pan-colitis, reported cancer incidence may range from 7 to 14% at 25 years,[7] and 30 to 50% after 40 years from disease diagnosis.[8] A recent meta-analysis of 116 studies reported incidence rates of 2 per 1000 patient-years for the first 10 years of disease, 7 per 1000 patient-years in the second decade and 12 per 1000 patient-years in the third decade.[9] These incidence rates correspond to cumulative probabilities of 2% by 10 years, 8% by 20 years and 18% by 30 years. These figures suggest a lower incidence than predicted from an actuarial statistical analysis based on a smaller selection of studies. These suggested a cancer risk of 20% per decade or 2% per year after the first 10 years.[10]

The surgical management policy of hospitals, as evidenced by their elective colectomy rate for inflammatory bowel disease, may have a marked effect on the reported CRC incidence rates for this condition.[11] The incidence at 40 years from diagnosis probably represents a 5- to 8-fold increase

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over the cumulative lifetime risk of CRC in the general population (6%).[12] The median duration of disease at the time of diagnosis of CRC is 18 years. The 5-year survival with symptomatic CRC in people with UC is 31 to 42%.[13,14]

At-risk individuals with UC comprise those who have colitis extending proximal to the recto-sigmoid region and who have disease of greater than 10 years' duration. Only very rarely have cancers been found in individuals who do not meet these criteria. The presence of primary sclerosing cholangitis (PSC) is an additional risk factor.[15] More controversial are early age of onset of disease, and the added risk of sporadic CRC in older people and in those with family histories of CRC.[16] Extent of disease is best determined by histological assessment, and more accurately determined by endoscopic than radiological assessment. Treatment with sulphasalazine (and presumably mesalazine) might have a protective effect, although this information comes from a case-control study with a possibility of selection bias.[17]



Restorative proctocolectomy with ileo-anal pouch anastomosis or pan-proctocolectomy is performed in a proportion of individuals with extreme disability due to longstanding chronic active disease. This group is no longer susceptible to CRC, although theoretically CRC could arise in any residual large intestinal mucosa. For the remainder, the risks of CRC – although substantially greater than for the general population – are probably not great enough to advocate prophylactic colectomy. In the only population-based study, Karlen *et al*,[18] found that in a total population of 3 million providing 4664 individuals with UC, less than 1% (40 individuals) died of CRC; however, the average disease duration was not reported. To advocate prophylactic colectomy for cancer prevention in individuals with chronic extensive UC, an additional measure of risk beyond disease extent and duration is required.

The association of mucosal dysplasia with CRC in UC was reported by Morson and Pang.[19] In up to 75% of cases, dysplasia could be found in colonic mucosal biopsies obtained at a distance from the site of the CRC itself, providing the basis for using dysplasia as a marker for CRC, or the likely imminent development of CRC in UC. Mucosal dysplasia is considered to be a pre-malignant lesion that can lead to the development of CRC within 3 to 5 years. Thus, if dysplasia is found in biopsy specimens at a surveillance colonoscopy, a prophylactic proctocolectomy can be advocated.

## Surveillance Colonoscopy in UC: Efficacy

No randomised controlled trial has been carried out to investigate the efficacy of surveillance colonoscopy in individuals with UC. Using mortality as an endpoint, it has been estimated such a trial would require 1000 individuals and it would be 10 years before an outcome were available. It is unlikely that such a trial will ever be carried out, however, as most clinical investigators would regard it as unethical.

Case-control studies compare CRC rates in screened and non-screened individuals and are open to the criticism of selection bias. The population-based study by Karlen *et al*[18] was a nested case-control study. There were 142 individuals with UC (40 who died from CRC and 102 matched controls) from a study population of 4664 individuals. They were divided into those who had and those who had not undergone at least one surveillance colonoscopy. The relative risk of developing CRC in those who had undergone one screening colonoscopy was 0.29 (95% CI, 0.06–1.31) and in those who had undergone two or more surveillance colonoscopies the relative risk was 0.22 (95% CI, 0.03–1.74). Although not statistically significant, these results suggested a possible decrease in death rates from CRC in individuals with longstanding UC under surveillance. However, this study lacked sufficient statistical power because only 40 individuals died from CRC and only 20% of controls had a history of colonoscopic surveillance.

Decision analysis of surveillance for CRC in UC has been used to assess the feasibility and costs versus benefits of surveillance colonoscopy in preventing death from CRC.[20] These studies use a hypothetical

cohort of individuals, but the results depend entirely on assumptions about the outcomes of various test procedures, which are derived from the literature. Using these approaches it has not been possible to prove whether colonoscopy scheduled at regular intervals is an effective means to manage the increased risk of CRC associated with UC. These studies focus on the benefit of life-years saved weighed against the costs of colonoscopy, proctocolectomy and the terminal care of individuals dying from CRC.

In summary, the evidence that colonoscopic surveillance and the detection of dysplasia can lead to a reduction in CRC mortality in individuals with extensive UC is not strong.



## Surveillance Colonoscopy in UC: Outcomes

There are a number of longitudinal observational studies which essentially compare groups of hospital-based individuals who have undergone surveillance colonoscopy with individuals from the same institution who have not.[21-23] The appropriateness of the non-surveyed control groups has been questioned but in the absence of other data, current recommendations for surveillance colonoscopy must be based on the results of these studies.

CRC detected at surveillance colonoscopy in individuals with UC is more commonly of Dukes' type A and B than those found in symptomatic individuals.[22] Thus, death rates are higher in those not under surveillance; survival rates at 5 years of 77% in those under surveillance and 36% in those not under surveillance have been reported.[21] Even in the report by Lynch entitled 'Failure of Colonoscopic Surveillance in Ulcerative Colitis',[23] there was no extensive cancer found in any individual under regular surveillance colonoscopy. The surveillance programme was considered 'unsuccessful' because the rate of CRC detection was low in the screened group, and seven other cases of UC-associated CRC presented over the same period (presumably, these individuals had not been considered eligible because of erroneous diagnosis of disease extent, duration of disease, or had been lost to follow-up). This might be regarded as primarily a logistical failure of the screening programme.

The St Mark's Hospital surveillance programme began in 1966 and included 332 individuals with UC to the hepatic flexure and disease duration exceeding 10 years.[22] Twenty individuals developed cancer (three of whom had ceased surveillance), and all but two of these occurred at least a decade after the onset of the colitis. Colonoscopic surveillance contributed to diagnosis of CRC in 11 symptomless individuals and dysplasia was found in 12 symptomless individuals; however, 6 symptomatic advanced cancers developed during the inter-surveillance periods. A 5-year survival rate of 87% among individuals who developed CRC during surveillance was reported, which compares with reports from other groups of around 80% 5-year survival.[21] Five-year survival rates of 30 to 50% are reported for individuals developing CRC outside a colonoscopic surveillance programme.[21, 22] The St Mark's results suggest – although do not prove – that surveillance tends to result in earlier diagnosis of cancer and a demonstrable improvement in survival. However, lead-time bias makes it difficult to assess the true impact of colonoscopic surveillance in this study. Surveillance allows earlier detection of CRC and, consequently, the survival time (from diagnosis to death) will be longer for individuals diagnosed with CRC in a surveillance programme than for individuals diagnosed symptomatically, even if surveillance did not alter the time of death.

## Colonoscopic Surveillance in UC: Which Individuals should be Enrolled?

Individuals with total or extensive colitis are at much greater risk of developing CRC than those with left-sided colitis or colitis involving only the rectum and sigmoid colon. Assessment is usually based on macroscopic features of disease. Some studies report results on those screened who have disease extending beyond the splenic flexure,[22, 23] others with disease extending beyond the sigmoid colon.[21] There is little or no risk associated with proctitis and sigmoiditis,[24, 25] but the risk of CRC

increases somewhat in left-sided colitis, the magnitude of risk being 2.18[26] and 2.8[24] times higher than average.

It is generally agreed that an initial surveillance colonoscopy should be performed in all individuals with UC between 8 and 10 years after diagnosis. This enables the extent of disease to be determined. It is well-recognised that a proportion of individuals with distal colitis can progress to more extensive or total colitis over time,[27] and re-definition of extent at 8 to 10 years is the only way to prevent misclassification. After this initial surveillance colonoscopy, all those documented to have significant macroscopic or microscopic disease extending beyond the rectum and sigmoid colon region should be enrolled in a surveillance programme.



Results have been reported for both yearly[23] and 2-yearly[21,22] colonoscopy surveillance procedures but on the basis of these it is not possible to state which is the preferable interval. Therefore, to preserve colonoscopic resources, 2-yearly procedures can be advocated at present.

Individuals with UC should be informed regarding the rationale for surveillance colonoscopy and its limitations in detecting CRC. Individuals should also be informed regarding the failure of studies to establish beyond doubt the value of surveillance in this situation.

## Surveillance Colonoscopy in UC: Performance and Biopsy Techniques

Surveillance colonoscopy in individuals with UC should be performed by experienced colonoscopists who are gastroenterologists or gastrointestinal surgeons. Studies reporting on colonoscopy in this situation document caecal intubation rates of 85 to 95% with no procedure-related mortality.

The extent of dysplasia documented in association with CRC in UC is very variable. Consequently mucosal biopsies are taken at intervals from caecum to rectum, preferably avoiding areas of active inflammation. At least 10 biopsy sites are sampled, including the caecum, proximal and distal ascending colon, proximal and distal transverse colon, proximal and distal descending colon, proximal and distal sigmoid colon, and rectum.[28] Two to three biopsies should be taken from each region. It has been estimated from studies of colectomy specimens, that 30 biopsies are required to identify dysplasia in 90% of cases and around 60 biopsies to detect 95% of cases.[29] These biopsies are taken from flat mucosa; any mass lesions should also be biopsied. There is a high incidence of CRC underlying mass lesions (dysplasia-associated lesion or mass (DALM)).[30] These do not include pseudopolyps, which do not require biopsy.

## Surveillance Colonoscopy in UC: Management of Surveillance-Detected Dysplasia

The finding of high-grade dysplasia (HGD) or CRC that has been confirmed on histological review should lead to a recommendation for colectomy. Colectomy options include restorative proctocolectomy with ileo-anal pouch anastomosis or proctocolectomy with permanent ileostomy. Repeat colonic biopsies in individuals with HGD alone to confirm the diagnosis before surgery is advocated by some but this approach is controversial. Individuals should be advised of the possible advantages and disadvantages of this option at the time of surgical referral. If dysplasia has been detected in association with very active inflammation, repeat biopsy is usually advised after anti-inflammatory therapy.

When the finding is of LGD, there is no consensus approach. Most would seek confirmation and shorten the surveillance interval to 1 year.[31] However, others would recommend colectomy because of the high rate of progression of LGD to HGD and CRC over 5 years (see below); and some would take no action other than to recommend the next surveillance procedure in 2 years' time.[22]

## Surveillance Colonoscopy in UC: Participation Rates

Most studies have shown that individuals enrolled in colonoscopy surveillance programmes have 1 or 2 colonoscopies and then leave the programme. In one study, 41 of 160 individuals entered in a surveillance programme defaulted attendance,[23] although better adherence has been reported by others.[22] Non-attendees are typically given one, or at the most two reminders, and surveillance ceases when the individual reaches the age of 75 years.



## Surveillance Colonoscopy in UC: Frequency with which Dysplasia or CRC Detected

Based on information in the literature, a Dukes' type A or B carcinoma may be found with a frequency as great as 1 in 146 colonoscopies,[22] with an intermediate frequency of 1 in 476 colonoscopies (average from the literature), or as little as 1 in 739 surveillance colonoscopies.[23] HGD can be found with roughly twice the frequency of CRCs. Unfortunately, surveillance colonoscopy as carried out in the reported studies missed at least half the CRCs that developed in the total hospital population at risk. Furthermore, although CRC was found in 25% of individuals with HGD, 25% of those found to have HGD at colonoscopy had no HGD on follow-up colonoscopy or in the colectomy specimen – findings supporting the practice of those who repeat colonoscopy and biopsy before recommending colectomy. Conversely, LGD will progress to HGD or CRC within 5 years in over 50% of cases.[29] This reinforces the validity of the dysplasia-cancer sequence in decision-making.

## Surveillance Colonoscopy in UC: Variation in Practice

Surveys of British gastroenterologists have shown wide variations in current surveillance procedures, including timing of initial and interval colonoscopies, number of biopsies taken and response to histological reports.[31] Only 25% of gastroenterologists undertook surveillance in left-sided disease, biopsy numbers varied from 6 to 20, and surveillance intervals for individuals with a 30-year history of UC varied from 1 to 5 years. LGD prompted most (71%) to repeat the colonoscopy, but only 50% advised colectomy for HGD. HGD was correctly defined by only 50% of United States respondents in another survey and 31% opted for further surveillance rather than colectomy.[32] The lack of strong evidence supporting an effective and cost-effective surveillance algorithm may explain these results.

# CROHN'S DISEASE AND CRC

The incidence of CRC in individuals with colorectal Crohn's disease (CD) was previously thought to be about half that associated with UC,[33] but may be increasing.[34] This may be partly due to histological miscategorisation in earlier years.[33] Recent reports show the median age at diagnosis of CRC in CD is slightly higher than for UC (54 years vs 43 years) and median disease duration is also greater.[35] However, the incidence of CRC and associated dysplasia are similar (CD 73%, UC 79%), as are the histological features of the CRCs and the 5-year survival rates (CD 46%, UC 50%).[35] Cumulative CRC rates after 20 years (CD 7%, UC 8%) are nearly identical. In the most recent report,[36] a 2-yearly screening and surveillance programme in 259 individuals with CD (663 colonoscopies) detected dysplasia or cancer in 16% (10 'indefinite', 23 LGD, 4 HGD, 5 CRCs). The probability of detecting dysplasia or CRC after a negative screening colonoscopy was 22% by the fourth surveillance procedure.

On the basis of these studies, there is considerable logic in including individuals with extensive colonic CD in an inflammatory bowel disease surveillance programme using the same criteria developed for individuals with UC.

# USING THE GUIDELINE IN GENERAL PRACTICE



The development of these guidelines is in part a response to a recognised need to help general practitioners identify and manage individuals at increased risk of CRC and to reduce uncertainty about who should be offered surveillance.[1]

An increased risk of developing CRC is identified in individuals with:

- a family history of CRC
- a personal history of colorectal neoplasia (adenomas or cancer) or longstanding extensive inflammatory bowel.

## FAMILY HISTORY OF CRC

On the basis of their family history of CRC, individuals are classified into one of three categories relating to their estimated potential lifetime risk for developing CRC compared with the average lifetime risk of the general population for developing CRC. In New Zealand the average lifetime risk of developing this condition is 5.9% by the age of 75 years.[2]

**Category 1:** Individuals with a slight increase in risk for CRC.

**Category 2:** Individuals with a moderate increase in risk for CRC.

**Category 3:** Individuals with a potentially high (50%) risk for CRC.

### Category 1: Individuals with a Slight Increase in Risk

Most individuals seen in general practice with a family history of CRC are in this category. Individuals in this group are similar to those addressed in the previous National Health Committee report,[3] which advised against population screening (ie, testing of those without symptoms) using FOBT or other screening tests at this time. This recommendation was based on the inadequate sensitivity of FOBT as a means of detecting CRC, the likely colonoscopy complication rate to which individuals without cancer would subsequently be exposed, and the considerable commitment of resources screening would entail, particularly with regard to colonoscopy. The modest potential benefit was considered to be offset by these factors.

At present there is no proven method of identifying which individuals in category 1 are likely to develop CRC.

Included in category 1 are those with:

- one first-degree (parent, sibling, child) relative with CRC diagnosed at age 55 years or older

No specific surveillance recommendations are made for this group at this time. Individuals in this category requesting information should be fully informed regarding their absolute risk of developing CRC and advised of the reasons for this recommendation. Individuals in this group should be encouraged to report symptoms that may indicate CRC. Individuals with symptoms require investigation in the usual way.

It may be necessary to acknowledge that some individuals may wish to be screened for CRC even though they are at average or slightly above average risk. General practitioners should provide information on the potential benefits and risks of the screening tests being considered. Those requesting screening should also be informed that colonoscopy resources may be restricted and that the investigation of individuals with symptoms suggestive of CRC takes priority over those requiring follow-up to screening.



## Category 2: Individuals with a Moderate Increase in Risk

A much smaller group of individuals is at a moderately increased risk of CRC.[4-7]

Category 2 includes individuals with either of the following:

- one first-degree relative with CRC diagnosed before the age of 55 years, or
- two first-degree relatives on the same side of the family diagnosed at any age (without features of category 3).

Individuals with a family history risk in category 2 should be offered colonoscopic surveillance starting from 50 years of age or at an age 10 years younger than the age of first diagnosis of CRC in the family. If individuals in category 2 wish to accept surveillance – after being informed of their risk of CRC and advised that although colonoscopy is generally safe, it is an invasive procedure with rare but recognisable risks – the subcommittee recommends referral for colonoscopy. Where this service is unavailable, an acceptable alternative is double-contrast barium enema preceded by rigid sigmoidoscopy. Abnormal sigmoidoscopic or radiological findings require referral for specialist assessment.

The subcommittee does not recommend the use of FOBT alone as a surveillance test for individuals in this category because the detection rate in those with CRC is inadequate.

## Category 3: Individuals with a Potentially High (50%) Risk

Category 3 includes the very small group of individuals at potentially high (50%) risk of developing CRC or being affected with one of the dominantly inherited syndromes. This includes those with:

- a family history of FAP, HNPCC or other familial CRC syndromes
- one first-degree relative plus two or more first- or second-degree relatives, all on the same side of the family, with a diagnosis, at any age, of CRC
- two first-degree relatives, or one first-degree relative plus one or more second-degree relatives, all on the same side of the family, with a diagnosis of CRC and one such relative:
  - was diagnosed with CRC under the age of 55 years, or
  - developed multiple bowel cancers, or
  - developed an extracolonic tumour suggestive of HNPCC (ie, endometrial, ovarian, stomach, small bowel, upper renal tract, pancreas or brain)
- at least one first- or second-degree relative diagnosed with CRC in association with multiple bowel polyps

- a personal history or one first-degree relative with CRC diagnosed under the age of 50 years, particularly where colorectal tumour immunohistochemistry has revealed loss of expression for one of the mismatch repair genes (hMLH1 or hMSH2).

In the above situations referral to a family cancer clinic or familial bowel cancer registry to facilitate risk assessment and possible genetic testing is advised, as is referral to a bowel cancer specialist to plan appropriate surveillance and management.

Genetic testing for the dominantly inherited bowel cancer syndromes should only be offered in the context of appropriate genetic counselling.



## PERSONAL HISTORY OF COLORECTAL ADENOMA OR CANCER OR OF LONGSTANDING EXTENSIVE INFLAMMATORY BOWEL DISEASE

Individuals with a past history of CRC may remain under specialist follow-up. Colonoscopic surveillance to identify new colorectal adenomas and cancer lesions may be offered at 3- to 5-yearly intervals after clearance from surgical follow-up.

Similarly, individuals with previously diagnosed colorectal adenomas may be offered ongoing surveillance colonoscopy at 3- to 5-yearly intervals, depending on the number, size and nature of previously identified adenomas. The recommended surveillance interval may be advised at the time of colonoscopic diagnosis and may vary with the specific diagnosis for the affected individual.

Individuals with UC and CD of 8 to 10 years' duration should be referred for colonoscopy. Those with significant disease extending beyond the sigmoid colon should be enrolled in a surveillance programme. Individuals with longstanding inflammatory bowel disease not under surveillance should be referred for specialist review.

## SURVEILLANCE COLONOSCOPY: IMPACT OF AGE AND COMORBIDITY

An upper age limit of 75 years is usually considered appropriate for colonoscopic surveillance because the remaining life expectancy is likely to be less than the average time required for new adenomas or dysplasia to progress to malignancy. After this age the potential risks associated with ongoing surveillance are likely to outweigh the benefits of such procedures. Surveillance may also not be appropriate in some individuals under the age of 75 years who have serious comorbid conditions.

## USING THE GUIDELINES

General practitioners may find the guidelines helpful in a number of clinical situations. Some individuals at increased risk may already be known in the general practice and may not be in a surveillance programme. They may benefit from information to help make a decision about suitable ongoing surveillance. This group may include individuals with previous treatment for CRC and those with a history of inflammatory bowel disease over a period greater than 8 to 10 years.

General practitioners' knowledge of individuals in the practice with CRC may provide opportunities to offer surveillance to relatives. General practitioners and practice nurses may also identify a family history of CRC when enrolling new individuals, updating medical histories or during periodic health checks. Individuals may present with concern about their personal risk of CRC based on family history

or contact with an individual with CRC. The guidelines and consumer information are intended to help plan appropriate surveillance for these situations.

Colonoscopy is generally a safe procedure but it is also invasive and associated with rare and recognised risks. Consequently, it is important to offer this as a surveillance test to those most likely to benefit. Where possible, therefore, the personal or family history of CRC should be confirmed. Some individuals may provide an accurate history from personal knowledge.[8] Other sources of information include an individual's clinical records, hospital records and death certificates. This process can be time consuming and therefore is usually performed on referral to a clinical genetic service or familial bowel cancer registry.



In each area, it may be necessary for general practitioners to ensure that suitable options for referral for colonoscopy or sigmoidoscopy/double-contrast barium enema surveillance are available. It may be necessary for District Health Boards and general practitioner organisations to address the provision of these services. It is recognised that colonoscopy resources may be restricted and that the investigation of individuals with symptoms suggestive of CRC will take priority over surveillance of asymptomatic individuals. Priority should be given to those at greatest risk when resources are limited.

For those accepting referral, the surveillance interval will vary according to the results. It is likely that a colonoscopy report will include the recommended interval for a repeat procedure. This will be determined by the presence or absence of adenomas or cancer. A negative colonoscopy in individuals in category 2 is recommended for repeat in 5 years. In view of the slightly lower sensitivity of sigmoidoscopy/double-contrast barium enema for detecting colorectal neoplasia, a negative test should be repeated after 3 to 5 years. General practitioners are encouraged to recall those who have accepted surveillance, at these intervals.

It is recognised that there are increased costs inherent in the screening process for general practice, including the time involved in reviewing family history, arranging referral for surveillance procedures and recall. There is also an impact on the use of general practice time that may displace other clinical duties. It is suggested that the process of identifying individuals who should be offered surveillance colonoscopy (ie, individuals in categories 2 and 3) may best be undertaken in the context of well-person assessment rather than as a stand-alone activity.

# 7

# IMPLEMENTATION AND EVALUATION



## OVERVIEW

- Specific strategies are outlined to foster successful implementation of the guideline.
- An appropriate response to the guideline will be an increased demand on colonoscopy services. Appropriate access to colonoscopy services will require discussion and organisation at both Ministry of Health and District Health Board levels.
- Clear communication with the public and health care practitioners is required to highlight the factors associated with a moderate increase in risk for developing CRC without encouraging those at average risk to seek out CRC screening tests.
- Evaluation of the success of implementation strategies as well as the impact of the guideline on clinical practice should be carried out and findings requiring attention should be acted upon, where possible.

The aim of these guidelines is to ensure that those individuals with a significantly increased risk of developing CRC who present to relevant services in either the public or private health sectors are:

- identified at general practitioner and speciality level
- provided with appropriate surveillance advice and information relevant to their situation and level of risk
- able to proceed to colonoscopy in the public hospital system within an appropriate time interval if colonoscopy is recommended.

In order to achieve this aim through the successful implementation of the guidelines, the active support and involvement of health care practitioners and policymakers, funders and fund holders will be required.

It is anticipated that an appropriate response to the guidelines will be an increased demand on colonoscopy services. Consequently, it will be important to ensure that existing services are not compromised and that individuals with symptoms requiring investigation by colonoscopy are not adversely affected by increasing delays in the time taken to receive the procedure. A staged approach to the introduction of these guidelines may therefore need to be considered. It is important that members of the public who are not considered to be at high-risk of having CRC are not misled into seeking out a CRC screening test. It is equally important that those who are identified as having a significant risk do not have their expectations of being able to have a timely colonoscopy raised until services are actually able to accommodate this.

# SPECIFIC IMPLEMENTATION STRATEGIES

The following strategies have been identified as being essential to achieve the successful implementation of the guidelines. The strategies identified are practical and realistic for the New Zealand setting and are listed in order to promote a systematic and logical approach to the steps required.

## Endorsement

Endorsement of the guidelines by medical professional organisations is recognised as being an important part of their validation and acceptance by clinicians.



## Quick Reference Clinical Format

Although the full guideline is needed to demonstrate that all aspects of this subject were adequately researched and referenced, information relevant to decision-making needs to be quickly and easily available to the clinician in the clinical setting. The development and availability of a quick reference summary will make the use of the guideline recommendations easier for clinicians.

## Publication of the Full Guideline

The full guideline and quick reference guide will be available in electronic form on the NZGG website at www.nzgg.org.nz There is no charge for downloading these documents. Print copies will also be available.

## Consumer Information

A brochure based on this guideline will be developed for people at increased risk of colorectal cancer and their families.

## Dissemination

Dissemination of the guideline needs to ensure that all interested parties are identified and copies of the guideline are circulated to them.

The summary of the guideline recommendations and details of the website for access to the full guideline will be distributed to the following categories of practitioners and organisations:

### *Health Professionals*

- General practitioners
- General physicians and surgeons
- Gastroenterologists
- Colorectal surgeons
- Clinical geneticists
- Oncologists
- Pathologists
- Genetic counsellors

### *Provider Organisations, Institutions and Professional Bodies*

- Primary Health Organisations
- Independent Practitioner Associations
- District Health Boards
- Academic lecturers/curriculum planners involved in medical training
- Medical colleges/professional bodies

### *Agencies and Community Organisations*

- The Cancer Society of New Zealand Inc. (CSNZ)
- Health insurers (eg, Southern Cross)
- Support groups for individuals with CRC
- Consumer interest groups
- Community health agencies and interest groups



## Events, Presentation and Training

Education and formal presentations regarding the content, recommendations and rationale, as well as the use and applicability of the guideline, are a critical part of the implementation strategy.

They will need to occur at a number of levels and will be ideally facilitated nationally and locally by members of the subcommittee.

The following approaches should be used:

### *National Level*

- Formal endorsement and presentations at appropriate general practitioner/speciality and sub-speciality conferences
- Organising information and education seminars/workshops (based on the guideline) for practitioners, Primary Health Organisations, Independent Practitioner Associations, and District Health Boards
- Specific educational initiatives for particular groups (eg, general practitioners)
- Efforts made to ensure all sessions include the discussion of how information for consumers about screening/surveillance for CRC is appropriately dealt with to avoid overstating the risk and to minimise consumer demand for inappropriate screening
- Training provided for any areas of practice where shortcomings related to the guideline recommendations are identified
- A resource for consumers should be developed to reflect the recommendations in this guideline

### *Local Level*

- Planned regional education sessions for relevant medical specialities
- Providing sessions for the discussion of prioritising colonoscopic services for each region with the aim of updating local referral guidelines to reflect the evidence-based guideline recommendations
- Interactive regional and hospital continuing medical education (CME) sessions
- Educational Independent Practitioner Association outreach activities

## Publicity

This approach will need to be handled with care because currently, after review of the evidence, population-based CRC screening is not advised in New Zealand for individuals at average risk of developing CRC. Informing the public will require considerable clarity to highlight the factors associated with a moderate increase in risk for developing CRC without encouraging those at average risk to seek out CRC screening tests.

### *Journals and Other Publications for Health Professionals*

- Medical journal articles
- Nursing journal articles
- GP Weekly
- Doctor newspaper
- CSNZ Cancer Update in Practice Bulletin

### *Launch of Guideline Combined with an Introductory Seminar*



- Informing the public
- Consumer information leaflet: develop appropriate consumer information leaflet in association with the CSNZ
- Use of lay media to publish articles on CRC that clarify who is at moderate to high risk of developing CRC and who should/should not be referred for surveillance
- Radio interviews: the purpose of this guideline is to clarify who is at high risk of developing CRC so that surveillance activities will be strictly limited to this select group. Radio interviews will need to be carefully considered to ensure they convey the right message and do not serve to generate increased interest and expectations with regard to screening for CRC among those not at high risk

## Access to Colonoscopy Services

It will be necessary to negotiate specific funding for the staff, clinic time and equipment needed to enable the provision of colonoscopy services for asymptomatic individuals identified as having a significant increase in risk of developing CRC, within an appropriate timeframe. It is essential that this be organised in a manner that will not adversely impact on those requiring colonoscopic investigation for symptoms. This matter will need to be discussed at both the national (Ministry of Health) and regional (District Health Board) levels.

# EVALUATION

Evaluating the success of the implementation strategies as well as the impact of the guideline on clinical practice should be carried out using the following question as a focus. It is the intention of the evaluation process that any findings requiring attention are acted upon where possible.

## Do the Right Individuals Know About the Guideline and its Content?

This could be achieved by the commissioning of a post-implementation survey of general practitioners, appropriate speciality groups and medical education programmes to assess the level of awareness of the guideline, as well as the perceived relevance and use of the guideline in practice.

## Impact of the Guideline on Clinical Practice and Access to Colonoscopy Services

The actual impact of the guideline in practice can be evaluated by the collection of the following information:

- **The effect on colonoscopy referral practice**

  Making a comparison of baseline referral information before the distribution of the guideline, and referral numbers and patterns after guideline implementation.
- **Referral indications for colonoscopies performed**

  Making a comparison of before and after referral indications, and identifying the percentage of inappropriate referrals for colonoscopic surveillance of asymptomatic individuals.
- **Waiting times**

  Assessing waiting times for those referred for a surveillance colonoscopy, and assessing and comparing before and after waiting times for those referred for a colonoscopy for investigation of symptoms.



## Quality Assurance and Adverse Events

Colonoscopy is an invasive procedure with rare but significant complications.[1] Colonoscopy surveillance procedures are performed for well individuals. Acceptable colonoscopy performance with regard to completion rates to the caecum (>95%) and complications should be demonstrated for centres where such procedures are performed. Colonoscopy quality improvement questionnaires have been developed and used in New Zealand to assess identified colonoscopy-specific quality indicators.[2] A significant increase in demand on colonoscopy services could put pressure on existing workloads, workforce capacity, and colonoscopy training and supervision. This has the potential to impair performance. Ongoing monitoring establishes consistency of performance, and individuals presenting for colonoscopy can be reassured regarding the quality of procedures performed in a particular unit.

The findings of the evaluation would be reported in the first instance to the NZGG, the Ministry of Health and the National Health Committee, as well as any other party that has contributed to the funding of the evaluation.

# APPENDICES





NEW ZEALAND GUIDELINES GROUP
Promoting Effective Health and Disability Services

# TAKING A FAMILY HISTORY

Collection of family history information[1,2] in a genetics context can best be done by drawing a family tree or pedigree. This provides a clear and permanent record of the relationships between individuals, and information collated can be readily identified at a glance.

For the family history to be credible and useful as a basis for advising on risk and surveillance, it is important to verify as many diagnoses of cancer as possible. This is usually performed on referral to a clinical genetic service or the familial bowel cancer registry.



At the initial consultation, it may not be possible to ascertain much information. Often individuals need to go back and speak to their parents or other relatives about the family's history. This makes the family tree dynamic – that is, new information may become known over time.

Be aware that in some cultures, inter-family adoption is common, but you may be told about those relatives as if they were natural offspring.

Always take at least basic details about both sides of a family as this may impact on risk and therefore on surveillance advice.

Date the pedigree and each subsequent change made.

## METHOD

When taking a pedigree, use the following symbols:

Male Female Gender unknown No offspring

Different cancers are shown by shading different quadrants in the square or circle representing the individual.

Bowel cancer (top left quadrant)

Uterine cancer (bottom right quadrant)

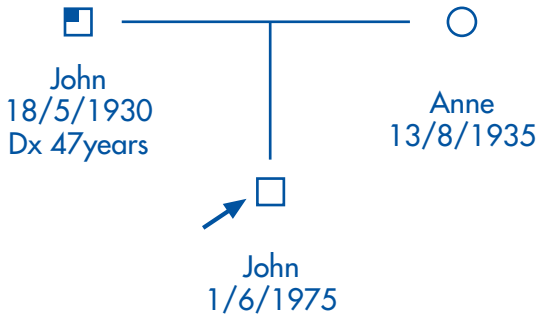
Bowel and Uterine cancer

Begin the family history with the person who is consulting you (ie, the proband). Indicate this person with an arrow.

John

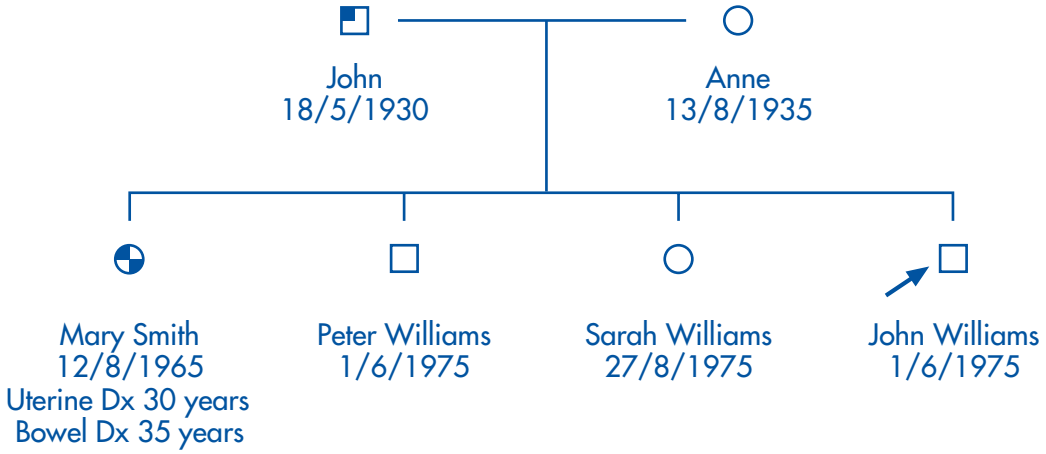
It does not matter whether you extend the pedigree horizontally or vertically first. It is more important to be methodical and establish the family relationships accurately.

Draw in the parents of the proband.



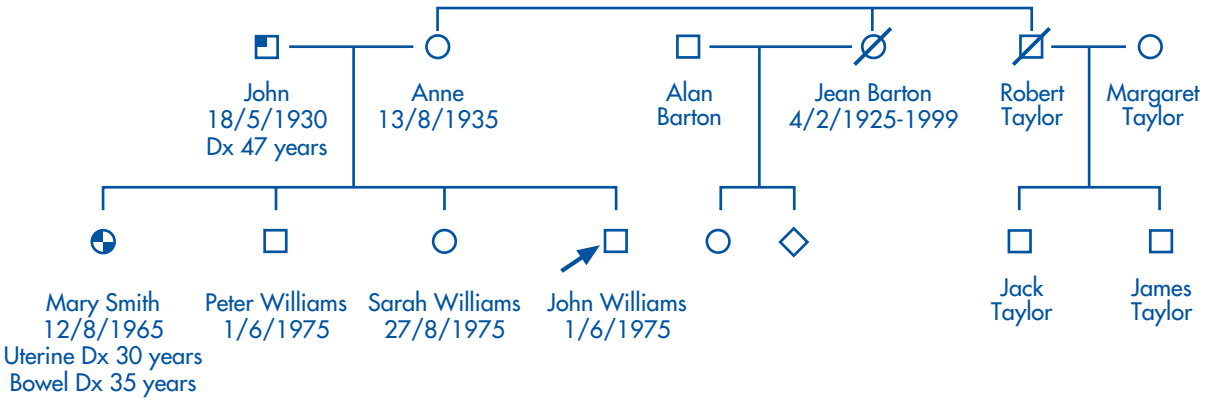

Enquire how many offspring the parents had and, when clarifying sibling relationships, consider asking about half-siblings.

At this point, start collecting information about each person and annotate his or her name and dates of birth (preferably, but record age if not available) and death alongside the appropriate symbol. Ask about a diagnosis of cancer. If the person had cancer, ask at what age the diagnosis was made. Start a key and colour in the symbol. You may need to annotate two cancers for one person (eg, uterine and bowel); in such cases, allocate different quadrants for each cancer. It is important to be consistent throughout the pedigree so that, for example, all bowel cancers are recorded in the upper left quadrant.



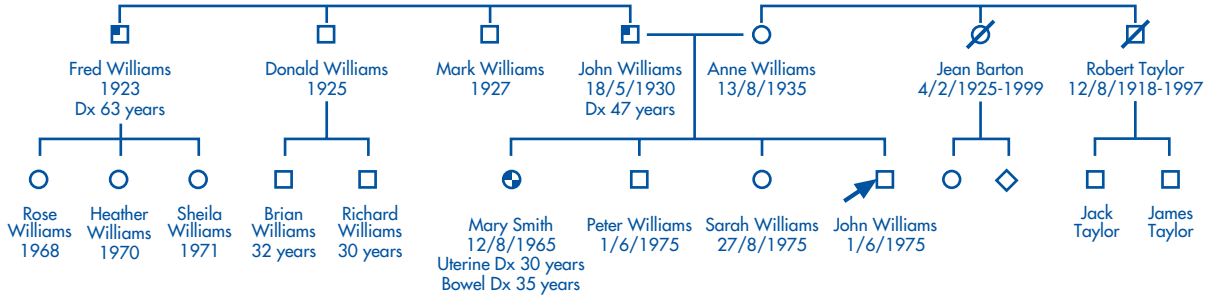

Extend the pedigree into the previous generation.

- How many brothers and sisters did your mother have?
- Did any of them have cancer?
- If so, what type?
- At what age were they diagnosed?






Now explore the other side of the family, asking about the number of paternal brothers and sisters, how many children each one had, and whether any had cancer. Continue as before, annotating names, age at diagnosis, and so on. You may wish to ask about polyps (number, size, type) seen at colonoscopy. Age at diagnosis remains important as an adenoma at 65 years is of less significance than one at 22 years.




This process can then be repeated for each of the proband's grandparents. Again, ask about their siblings, their offspring and causes and ages at death. This completes a three-generation family tree. Asking about children, nieces and nephews of the proband would complete a four-generation family tree.

## SUMMARY

To accurately define the risk and give the best advice, it is important to consider: the number of family members with cancer; the number of generations involved and the relationships between those with cancer (ie, first- or second-degree relationships); age at cancer diagnosis; histology of cancer; multiple primary cancers; number and type of polyps, and age at which they were documented.

## References

1. Church JM, Williams BRG, Casey G. *Family History: The Key to Inherited Colorectal Cancer in Molecular Genetics and Colorectal Neoplasia: a primer for the clinician.* New York: Igaku-Shoin, 1996.
2. Harper PS. *Practical Genetic Counselling.* Oxford: Butterworth Heinemann, 1999.

# CONTACT DETAILS FOR CLINICAL GENETIC SERVICES AND FAMILIAL BOWEL CANCER REGISTRIES



## CLINICAL GENETIC SERVICES

**Northern Regional Genetic Services** – Building 18, Auckland City Hospital, Private Bag 92024, Auckland 1001. Free phone 0800 476 123; Phone 09–307 4949 extn 5530; Fax 09–307 4978; email gensec@adhb.govt.nz

**Central Regional Genetic Services** – Wellington Hospital, Riddiford Street, Private Bag 7902, Wellington South. Free phone 0508 364 436; Phone 04–385 5310; Fax 04–385 5822.

**Southern Regional Genetic Services** – Room 124 Hagley, Christchurch Hospital, PO Box 4710, Christchurch. Freephone 0508 364 436; Phone 03–379 1898; Fax 03–379 1343.

## FAMILIAL BOWEL CANCER REGISTRIES

A national registry has historically been managed through the Northern Regional Genetic Service in Auckland. A southern registry, with functional links to the northern service, is now operational in Christchurch.

**Northern Region** – Lower Ground Floor, Building 18, Auckland City Hospital, Private Bag 92024, Auckland 1001. Free phone 0800 476 123; Phone 09–307 4949; Fax 09–307 4978.

**Southern Region** – Gastroenterology Department, 4th Floor, River Side Block, Christchurch Hospital, PO Box 4710, Christchurch. Phone 03–364 1549; Fax 03–364 0514.

# DYSPLASIA

This term refers to microscopic changes in tissue architecture (usually increased gland complexity) and cellular appearances (usually loss of cell polarity, nuclear enlargement and darker nuclear staining) which are intermediate between normal tissue and cancer. The most severe (high grade) changes of dysplasia include changes resembling cancer but without invasion of surrounding tissues beyond the lamina propria. The least severe changes are the earliest changes from normal that can be recognised microscopically.

Traditionally in the large intestine dysplastic change in adenomas has been graded as mild, moderate or severe representing a continuum of increasingly severe dysplasia but dysplastic change in chronic inflammatory bowel disease has been graded as low grade (mild-moderate) or high grade (moderate-severe).

Increasingly dysplasia is being graded either as low grade or high grade in both adenomas and inflammatory bowel disease.



## References


1. Fenoglio-Preiser CM, Noffsinger AE, Franzin G, Zamboni G, Scarpa A, Geboes K (ed). Other tumours of the large intestine. In: *Gastrointestinal and Pesophageal Pathology*, 2nd Edition. Edinburgh 1995.
2. Hamilton SR, Aaltonen LA (ed): Pathology and Genetics of Tumours of the Digestive System. In: *World Health Organization Classification of Tumours*. Lyon: IARC Press 2000.
3. Weidner N, Cote R, Suster S, Weiss L (ed): *Modern Surgical Pathology*. Philadelphia 2003.
4. Whitehead R (ed). *Gastrointestinal and Oesophageal Pathology*, 2nd Edition. Edinburgh 1995.

# GLOSSARY



**Absolute risk reduction (ARR):** The absolute difference in the rate of events between the experimental group in a study and the control group. If the risk reduction is 0, there is no difference between the groups. For undesirable outcomes such as cancer, a relative risk that is less than 1 means that the intervention has been effective in reducing the risk of that particular outcome.

**Adenoma:** A non-cancerous growth in the lining of the bowel that can progress to cancer. Same as adenomatous polyp.

**Adenomatous polyp:** It is thought that a majority of CRCs develop from pre-existing adenomatous polyps; however, only a minority of adenomatous polyps are thought to progress to cancer. Same as adenoma.

**Adjuvant therapy:** The addition of one or more therapies to aid the original treatment.

**Anastomosis:** The connection of normally separate parts of the body, for example, connecting healthy sections of colon or rectum after cancerous or diseased sections of the bowel have been surgically removed.

**Asymptomatic:** No noticeable symptoms.

**Autosomal dominant:** An autosome is any chromosome that is not a sex chromosome; autosomal dominant is a dominant gene carried on an autosome.

**Barium enema (BE):** X-ray examination using barium sulphate to outline the contour of the large bowel. A double contrast barium enema (DCBE) is an examination in which air is also used to highlight the bowel.

**Biopsy:** The removal of a sample of tissue for examination under a microscope to check for cancer cells.

**Case-control studies:** Sometimes described as retrospective, these studies look back in time at a group of individuals with a particular disease or outcome and compare it with a suitable control group of individuals without the disease or outcome.

**Colectomy:** Surgery during which all or part of the colon (also called the large intestine) is removed. There are a number of different types of colectomies depending on what is removed.

**Colon:** The large bowel (extending from the end of the small intestine to the rectum), excluding the rectum and anus.

**Colonic mucosa:** The lining or surface of the colon.

**Colonoscopy:** Visual examination of the colon via a flexible tube (colonoscope) performed under sedation by a specialist.

**Colorectal neoplasm:** see Neoplasm

**Comorbidity:** The co-existence of two or more diseases.

**Confidence interval (CI):** The range within which the true size of effect of a treatment or intervention (never exactly known) lies with a given degree of assurance. A 95% confidence interval is the interval that includes the true value in 95% of cases.

**Confounding factor:** A factor to consider when looking at the association between exposure to a cause (or risk factor) and the occurrence of disease. Age groups and sex are common confounding factors as they may be associated with some exposures and also the older a person gets the more likely he or she is to develop some diseases.

**Consanguinity:** Blood relationship because of common ancestry, which is relevant when investigating possible genetic factors for diseases.

**Cost-effectiveness analysis:** Cost-effectiveness analysis is a comparative technique. Two or more health programmes, or programme options, are compared in terms of the cost per unit of output (eg, cost per cancer detected) or cost per unit of outcome (eg, cost per life saved, cost per year of life saved, cost per quality-adjusted year of life saved).

**Coverage:** The proportion of all eligible individuals screened by a programme, calculated as the total number screened divided by the number of those who are eligible by age and domicile, according to the census.

**Crohn's disease (CD):** This is a chronic inflammatory disease of the intestines. It primarily causes ulcerations (breaks in the lining) of the small and large intestines, but can affect the digestive system anywhere from the mouth to the anus. It is also called granulomatous enteritis or colitis, regional enteritis, ileitis, or terminal ileitis.

**Cutaneous:** Related to the skin.

**De novo:** New; not pre-existing.

**Desmoid tumour:** Benign soft tissue tumours that occur most often in young adults and involve the limbs or trunk but can also arise in the abdomen or thorax. They never metastasise (spread to other parts of the body) but are very difficult to remove because they intertwine extensively with the surrounding tissues and look like dense scar tissue.

**Detection rate:** The number of individuals with cancers detected within the screening population, calculated by the number with cancer diagnosed by screening divided by the number of individuals screened in a specified time period.

**Distal colon:** A section of the bowel, from the splenic flexure to the rectum.

**Double contrast barium enema (DCBE):** see Barium Enema

**Dukes' classification:** A system of classifying colorectal tumours based on the depth of invasion and degree of metastasis.

**Duodenal:** To do with the duodenum, which is the first part of the small intestine.

**Dysplasia:** Refer to Appendix C.

**Effectiveness:** The extent to which a specific intervention, procedure, regimen or service, when deployed in the field, does what it is intended to do for a defined population.

**Efficacy:** The extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy of CRC screening is based on the results of a randomised controlled trial (with CRC mortality as the outcome measure).

**Endometrial cancer:** Cancer of the lining of the uterus. The endometrium is the inner layer of the uterus.

**Endoscopy:** A visual examination of internal structures of the body with a lighted instrument. Colonoscopy and flexible sigmoidoscopy are endoscopic examinations of the bowel.

**Epithelium:** The layer of cells that covers all the body surface, and lines all the cavities and hollow tracts (eg, the gastrointestinal tract).

**Exudation:** Leakage of fluid and cells from a blood vessel.

**Faecal occult blood tests (FOBT):** Faecal occult blood tests are sensitive chemical tests performed on stool samples to detect the presence of 'occult blood'. These tests are based on the observation that slow bleeding from colon polyps or cancers can cause chronic blood loss from the colon. Such bleeding is often not visible (occult) to the naked eye.



**Familial adenomatous polyposis (FAP):** This hereditary syndrome is characterised by the formation of thousands of polyps in the colon and rectum, with CRC the inevitable consequence. Polyps can also occur in the stomach, duodenum, and ileum. The polyps most often begin to form at puberty with colon cancer occurring 10 to 15 years later. The average age of diagnosis of FAP is 25 years of age, with cancers developing at age 20 to 30 years. However, cancers may arise at any time from late childhood to the 60s. The syndrome is an autosomal dominant disorder. An individual with the disease has a 50% chance of passing the gene on to each of her or his children. Most of those with the gene get the disease.

**Flexible sigmoidoscopy:** see Sigmoidoscopy

**Fluoroscopic examination:** Examination with a fluoroscope, which is an instrument for visual observation of the body using x-ray. Radio opaque agents are often used during this procedure.

**Gastric:** To do with the stomach.

**Gastroscopy:** An examination of the stomach using a gastroscope, which is a flexible, lighted instrument put through the mouth and oesophagus to view the stomach. Tissue from the stomach can be removed through the gastroscope.

**Genetic testing:** Examination of a person's genes to look for particular mutations associated with hereditary conditions.

**Genitourinary (GU):** To do with the genital and urinary systems.

**Germ-line mutation:** A permanent change in a gene that is then able to be inherited. Mutations can occur naturally and spontaneously or they may be due to exposure to mutagens (mutation-causing agents).

**Hamartoma:** A benign (non-cancerous) tumour which is made up of tissues normally found in the area that it is in, but in an unusual mixture.

**Hepatic:** To do with the liver.

**Hereditary non-polyposis colorectal cancer (HNPCC):** Previously known as Lynch syndrome. This is a dominantly inherited colorectal cancer syndrome.

**High-grade dysplasia (HGD):** see Dysplasia

**Histology:** The study and reporting of diseased tissue.

**Hyperplasia:** A condition in which there is an increase in the number of normal cells in a tissue or organ.

**Ileorectal anastomosis:** A connection between the ileum (small bowel) and the rectum; it is not normal for these to be connected.

**In situ:** This is used to refer to a cancer that is confined to the place in which it began and has not spread. Carcinoma in situ is an early-stage tumour.

**Index relative:** The first family member to be identified with an hereditary condition or disease.

**Inflammatory bowel disease (IBD):** Ulcerative colitis and Crohn's diseases are chronic conditions that are frequently referred to as inflammatory bowel disease. IBD can last years to decades, and the constant process of inflammation and repair of the lining of the colon (colonic mucosa) is believed to make the individual more susceptible to developing cancer. The mucosal cells are dividing so rapidly that they are liable to create mistakes (mutations) in their DNA. These mutated cells can then become pre-cancerous (dysplastic) cells, which later can develop into cancer.

**Length bias or lead-time bias:** Tumours grow at different rates and therefore remain for differing periods in the presymptomatic screen-detectable phase. With each screening round, the probability of detecting slow-growing tumours is greater than that of detecting fast-growing tumours, because slower growing tumours remain in the presymptomatic screen-detectable phase for longer. Thus, there will be fewer fast-growing tumours in a screened group compared with an unscreened group. Slow-growing tumours tend to have a better prognosis, which may account for differences in outcome between the groups. If a cancer is detected earlier it may appear that survival has been prolonged, but this may be a lead-time bias because the cancer has been known about for longer than a similar cancer detected at a later stage.

**Low-grade dysplasia (LGD):** see Dysplasia

**Lumen:** The cavity or channel within the intestine.

**Lymphatics:** Capillaries or vessels that collect lymph from the tissues and carry it to the blood stream.

**Mesentery:** A fold of membrane that attaches various organs to the body wall, especially the intestine.

**Meta-analysis:** When statistical techniques are used to combine the results of a number of studies about the same topic. Meta-analysis is often used as part of a systematic review, that uses an explicit approach to identify, select and appraise relevant studies. The studies are then collectively analysed to give pooled results (as opposed to the findings of a single study).

**Metachronous:** Used to refer to cancers arising at a later time than the index lesion. Another new cancer.

**Metastastic disease:** The spread of cancer to other parts of the body.

**Microsatellite instability (MSI):** see Phenotype

**Morphology:** The form and structure of a particular organ, tissue or cell.

**Mucosa:** The mucous membrane that lines certain organs (eg, the colon or rectum).

**Mutation, hereditary:** An inherited change in the DNA of a gene or chromosome in a cell destined to become an egg or a sperm. When transmitted to a child, an hereditary mutation is incorporated in every cell of the body. Hereditary mutations play a key role in genetic diseases and certain types of cancer, such as HNPCC. Hereditary mutations are also called germ-line mutations.

**Negative predictive value:** The probability that a person with a negative test truly does not have the disease.

**Neoplasia:** see Neoplasm

**Neoplasm:** A new, abnormal growth.

**Observational study:** A non-experimental study observing events that take their course without any intervention from researcher/s.

**Odds ratio (OR):** An estimate of the relative risk.

**Opportunity cost:** The opportunity foregone by allocating resources to a particular option.

**Overdiagnosis bias:** Screening detects very early lesions. It is possible that some detected cancers would not affect a person in his or her lifetime (the person remaining asymptomatic and dying from some other cause). Because these cancers are more likely to be found in a screened rather than an unscreened group, comparisons of outcome could favour the screened group irrespective of any real effect of screening.

**Pancolitis:** Ulcerative colitis that involves the entire colon (the large intestine).

**Pathology:** The study of disease. A medical doctor who specialises in pathology is called a pathologist. Pathologists are experts at interpreting microscopic views of body tissues.



**Pedunculated:** On a stalk.

**Perioperative:** Around the time of surgery. More specifically, the period of time extending from when the person goes into the hospital, clinic or doctor's office for surgery until the time he or she is discharged home.

**Perioral:** The area around the mouth.

**Phenotype:** The appearance of an individual, which results from the interaction of the person's genetic make-up and his/her environment. By contrast, the genotype is merely the genetic constitution (genome) of an individual. If a person's genotype includes the gene for HNPCC, the mutations occurring in the genes that normally repair DNA errors can cause a defective repair leading to the development of tumours. The gene is the genotype, and the defective repair mutations are the phenotype. This is sometimes referred to as microsatellite instability (MSI).

**Phenotypic changes:** The expected changes or features expressed in a disease process that aids recognition of the disease.

**Polyp:** A growth in the lining of the bowel (in this report - polyps can occur in other locations). A polyp can be sessile (no stalk) or on a stalk or stem. There are several kinds of polyps: adenomatous polyps can develop into cancer; hyperplastic polyps are not thought to progress to cancer. A minority of colorectal cancers arise from small, flat polyps called flat adenomas.

**Polyp dwell time:** The average period of time an adenomatous polyp takes to evolve from a small adenoma into cancer.

**Polypectomy:** The removal of polyps.

**Polyposis:** The condition of having many polyps in the large bowel.

**Porphyrin:** An iron- or magnesium-free cyclic tetrapyrrole derivative that forms respiratory pigments in animals and plants.

**Positive predictive value:** The probability that a person with a positive test truly has the disease.

**Post-colectomy:** The time after a colectomy has been carried out.

**Primary sclerosing cholangitis (PSC):** A chronic disorder of the liver in which the ducts carrying bile from the liver to the intestine, and often the ducts carrying bile within the liver, become inflamed, thickened, scarred (sclerotic) and obstructed. This relentlessly progressive process can in time destroy the bile ducts and lead to cirrhosis of the liver. PSC can occur by itself or in association with other diseases, including inflammatory bowel disease, especially ulcerative colitis.

**Proband:** The particular family member through whom a family's medical history comes to light. The proband may also be called the index case, propositus (if male) or proposita (if female).

**Proctitis:** Inflammation of the rectum.

**Proctocolectomy:** This is a total colectomy, most commonly considered for individuals with ulcerative colitis either because of failure to respond to treatment or because of the cancer risk associated with the disease.

**Proctoscopy:** Examination of the rectum with a proctoscope (a speculum or tubular instrument with a light).

**Proctosigmoiditis:** Inflammation of the rectum and sigmoid colon.

**Proctosigmoidoscopy:** see Sigmoidoscopy

**Prophylactic colectomy:** Excision of the colon in a person at increased risk of developing a colon cancer.

**Prospective randomised trials (PRTs):** Studies in which the participants are divided into groups with or without the particular intervention being studied before the outcomes have occurred. Randomised controlled trials are always prospective studies.

**Proximal colon:** The caecum, ascending and transverse colons. In this report it often refers to the portion of the bowel not examined by a flexible sigmoidoscope.

**Pseudopolyp:** An enlarged tab of mucous membrane resembling a polyp, caused by ulceration.

**Pulmonary:** To do with the lungs.

**Quality-adjusted life year (QALY):** Each year of life gained by a health programme is weighed by the value of that year. The weight for a QALY year of good health is 1; the weight for a year of poorer health or disability is less than 1. QALYs are used in comparisons of programmes that yield different levels of improvement in health status.

**Randomised controlled trials (RCTs):** Trials in which individuals in a population are randomly allocated into two groups. The two groups are usually called the study or experimental group, and the control group, which does not receive the intervention. For trials assessing screening procedures, the study group is offered screening and the control group is not. The results are assessed by comparing rates of death (or other endpoints) from the disease in the two groups. Randomised controlled trials are generally regarded as the most scientifically rigorous method of assessing the effectiveness of screening.

**Rectosigmoidoscopy:** see Sigmoidoscopy

**Rectum:** The lower section of the bowel ending with the anus.

**Relative risk (RR):** Also called the risk ratio. This is the comparison between a study group and control group of the rate at which individuals develop an undesirable event, and can indicate whether an intervention has been effective.

**Risk factor:** An aspect of a person's condition, lifestyle or environment that increases the probability of occurrence of a disease.

**Sensitivity:** The probability of screening positive if the disease is truly present.

**Sessile:** Describes a polyp that is flat rather than on a stalk.

**Sigmoid colon:** Lower part of the descending colon.

**Sigmoidoscopy:** The examination of the rectum and sigmoid colon using a lighted tube (sigmoidoscope). The sigmoidoscope may be flexible or rigid.

**Snare polypectomy:** A procedure for removing polyps, usually during a colonoscopy, where a thin wire is slipped on the polyp like a snare.

**Somatic mutation:** Any mutation of a cell in the body that is not in a reproductive cell (sex cell).

**Specificity:** The probability of screening negative if the disease is truly absent.

**Splenic flexure:** The bend in the colon between the transverse and descending colons.

**Sporadic cancer:** A cancer that has no genetic or familial link.

**Stage:** Used to describe the size of the tumour, how widely the cancer has spread to adjacent lymph nodes, and distant spread.

**Stoma:** An surgically-created opening that is kept open for drainage. After removal of the colon, a colostomy bag is attached to a stoma in the abdominal wall to collect faecal matter that would normally have passed through the colon and from there to the rectum.

**Surveillance:** Monitoring individuals known to have a disease or to be at increased risk of a disease.



**Synchronous:** Occurring at the same time.

**Tumour marker:** A substance in the body associated with the presence of a cancer.

**Ulcerative colitis (UC):** A chronic inflammation of the large intestine (colon). The colon is the part of the digestive system where waste material is stored. Individuals with ulcerative colitis, ulcers and inflammation of the inner lining of the colon get symptoms of abdominal pain, diarrhoea, and rectal bleeding.

**Villous architecture:** Adenomatous polyps of the colorectum are divided into three main microscopic types: tubular, villous and mixed tubulovillous. Tubular architecture is present when the glands of the tumour form hollow tube-like structures; villous architecture is present when the glands form delicate frond-like (finger-like) structures; tubulovillous architecture is present when tubular or villous architecture forms less than 80% of the total. Villous architecture is associated with the greatest potential to undergo malignant change and tubular architecture with the least potential to undergo malignant change.

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