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Clinical Practice Guidelines

Familial aspects of cancer: A guide to clinical practice

NHMRC
National Health and Medical Research Council
Clinical practice guidelines

Familial aspects of cancer: a guide to clinical practice

Endorsed November 1999

NHMRC
National Health and Medical Research Council
The strategic intent of the National Health and Medical Research Council (NHMRC) is to work with others for the health of all Australians, by promoting informed debate on ethics and policy, providing knowledge-based advice, fostering a high quality and internationally recognised research base, and applying research rigour to health issues.

NHMRC documents are prepared by panels of experts drawn from appropriate Australian academic, professional, community and government organisations. The NHMRC is grateful to these people for the excellent work they do on its behalf. The work is usually performed on an honorary basis and in addition to their usual work commitments.

Consultant authors:
Australian Cancer Network.

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ACKNOWLEDGMENTS

The Australian Cancer Network would like to thank all those who contributed to this document.

In addition to members of the Working Party, the Australian Cancer Network would like to thank:

- the Anti-Cancer Council of Victoria’s Cancer Genetics Ethics Committee, chaired by Professor Emeritus Richard Lovell, for its work in preparing a comprehensive legal/ethics document with final guidelines for clinical practice, which is reproduced here as Chapter 2; and

- the Royal Australian College of Obstetricians and Gynaecologists’ Working Party on Familial Ovarian Cancer, under the chairmanship of Dr Robert Rome, whose consensus statement underpins Chapter 8.

Others who contributed to the formation of these guidelines, whether by drafting sections or by reviewing and providing comments, include: Dr Glen Begley, Ms Julie French, Dr Jane Halliday, Dr Amanda McBride, Professor Graeme Morgan, Ms Dorothy Reading, Professor Alan Rodger, Professor Martin Tattersall, Ms Helen Varney.

IMPORTANT NOTICE

This document is a guide to appropriate practice, to be followed only subject to the clinician’s judgement in each individual case.

The guidelines are designed to provide information to assist decision making and are based on the best evidence available at time of publication. They are not meant to be prescriptive.
INTRODUCTION

In 1994, the Commonwealth Government published the report Better Health Outcomes for All Australians (DHSH 1994), which recognised cancer as a major health problem in Australia and identified it as one of the four priority areas for setting national and State/Territory goals and targets. The goals for cancer cover the areas of primary prevention, screening, early detection, optimal cancer management, quality of life, health inequalities, information, research and workforce issues.

Family history is widely recognised as an important risk factor for common cancers, and 5–10% of cancers are considered to be attributable to an inherited cancer predisposition.

During the past decade there have been major developments in cancer genetics, with the identification and characterisation of genes involved in the inherited forms of several common human cancers.

The improved ability to detect individuals at high risk through analysis of their family history and/or genetic testing has been accompanied by major advances in screening, surveillance and prevention. Thus, the identification of individuals at high genetic risk of cancer, and the application of developments in management to these individuals, offer a real prospect of making an important impact on the national goals of cancer control identified in Better Health Outcomes for All Australians (DHSH 1994).

The need for a coordinated national policy on cancer genetics is apparent at many levels for the following reasons:

- heightened public awareness and demand from those at perceived risk of familial cancer for access to familial cancer services, which has led to a shift of genetic technologies from research to diagnostic application;

- a professional recognition of a serious deficiency in human and physical resources to meet these new demands;

- concerns expressed by health authorities about the potential proliferation of unregulated, unevaluated genetic testing for cancer, as has occurred in the United States and the United Kingdom, and the need for public education and guidance;

- challenges faced by scientists in assuring quality for complex, new and constantly evolving diagnostic tests, overcoming difficulties in resource management, and ensuring the translation of relevant technologies from a research to a diagnostic environment; and
recognition by researchers of the need for collaborative consortia to answer the complex but critical genetic epidemiological and molecular biological questions relevant to the Australian population.

With the objective of addressing these needs, the Australian Cancer Network, in joint sponsorship with the National Health and Medical Research Council (NHMRC) National Breast Cancer Centre convened a working party — the Australian Cancer Network Cancer Genetics Working Party — in March 1995 to draft national guidelines on cancer genetics. Membership of the working party is shown in Appendix A.

This consensus document is the culmination of extensive consultation with relevant professional bodies across Australia, including the Human Genetics Society of Australasia, the NHMRC National Breast Cancer Centre, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian College of Obstetricians and Gynaecologists, the Royal Australasian College of Radiologists, the Royal College of Pathologists of Australasia, the Royal Australian College of General Practitioners, State/Territory health departments, State/Territory cancer councils, cancer registries and consumers. Major contributions were also received from genetic services in New Zealand. For further details on the development of these guidelines see Appendix B.

Consensus on key issues was reached at two national workshops, each held over two days, in August 1995 and April 1996, sponsored by the Australian Cancer Network, the NHMRC National Breast Cancer Centre and the Human Genetics Society of Australasia. This document is the result of this extensive consultative process.

These guidelines address the needs of the major groups with proved or suspected familial predisposition to cancer. The target audience includes all health professionals who may be involved with families seeking advice concerning familial aspects of cancer. More specifically, the document is aimed at health professionals directly involved in the care and management of individuals and families who may have a genetic susceptibility to malignancy.

Part 1 covers general issues relating to familial cancer services, whilst Part 2 looks at the requirements for particular cancers. This document attempts to provide up-to-date guidelines, many of which are based on recent reports in the scientific literature. The speed with which new information is becoming available makes it essential that the detailed guidelines be kept under regular review.

The working party used the NHMRC four-point rating system shown below to identify the evidence for key decision points, as recommended by the NHMRC in its booklet A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines (NHMRC 1999a).
Levels of evidence ratings

I  Evidence obtained from a systematic review of all relevant randomised controlled trials.

II  Evidence obtained from at least one properly designed randomised controlled trial.

III-1 Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time-series with a control group.

III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time-series without a parallel control group.

IV  Evidence obtained from case series, either post-test or pre- and post-test.

Expert opinion was included in the scale in a previous edition of the NHMRC guidelines (NHMRC 1995), but has been dropped since the publication of the revised guidelines (NHMRC 1999a). However, as in many other areas of modern medicine, clinicians in cancer genetics continue to face decision making in the absence of highest quality evidence. In this situation, broad agreement by peers can safeguard against random decisions and ensure a uniform and consistent approach, which can be used as the basis for future evaluation. Consequently, where higher levels of evidence were not available, the working party elected to include guidelines based on expert opinion (ie recommended practice for which there is no published evidence). Such opinion-based guidelines are identified by ‘—’ throughout the document and occur frequently, testifying to the need for high-quality research in this field.

Conducting randomised controlled trials (RCT) to confirm many of these recommendations would be impractical and, in some cases, unethical because of the small sample sizes and the high risk for cancer development in those carrying genetic alterations associated with cancer predisposition. However, RCTs have an important role in assessing the value of proposed interventions in areas such as primary prevention or chemoprevention. Such studies currently in progress deserve the strongest support.

The working party has received consistent cooperation and support throughout Australia, and now looks forward to the prospect of endorsement of a set of guiding principles, which will serve as a basis for the management of familial cancer in Australia. Recommendations resulting from these guidelines will serve as a powerful statement to government and research funding agencies about national priorities for resource allocation.
The field of cancer genetics is evolving so rapidly that any attempt to frame guidelines will be, in part, obsolete on the day of printing. The Australian Cancer Network Cancer Genetics Working Party is committed to a regular review of the field and aims to publish updated guidelines regularly. In the interim, major changes will be notified by the issuing of special alerts.

The process towards this consensus has forged strong and important new professional links across Australia. The strength of this unity provides a powerful foundation for the continuing process of refining, evaluating and improving familial cancer services nationally.

My special thanks go to members of the working party who have never failed in the diligence and thoroughness of their input; to Monica Johns at the Health Advisory Unit of the NHMRC and to Emeritus Professor Tom Reeve, Executive Officer and Christine Vuletich of the Australian Cancer Network. Professor Reeve’s constant energy and organisational skills were the driving force for completion of this complex project.

Richard Kefford
Chairman
Australian Cancer Network Cancer Genetics Working Party
November 1999
SUMMARY AND GUIDELINES

• Between five and ten per cent of the common cancers in Australians are attributable to an inherited cancer predisposition. Such cancers are due to heritable (germline) mutations in cancer susceptibility genes. Recently many of the responsible genes have been identified and characterised. The improved ability to detect individuals at high risk through analysis of their family history and/or gene testing has been accompanied by major advances in screening, surveillance and prevention. Thus, the identification of individuals at high genetic risk of cancer, and the application of these advances in the management of such individuals, offers a real prospect of making an impact on national goals of cancer control.

• A need for national guidelines on familial cancer was recognised because of heightened public awareness, demand from those who perceive themselves to be at increased risk because of family history, and concerns about a potential proliferation of unregulated and unevaluated genetic testing for cancer susceptibility.

• The organisation of familial cancer services presents particular challenges for health services because of the rapid evolution of knowledge within the field, and the potential for significant morbidity from inappropriate genetic testing or advice. Chapter 1 outlines the aims of a familial cancer service, the requirements in expertise and staffing, and the protocols, standards and evaluation requirements of such a service. Certain options for accreditation are also presented.

• Cancers due to inherited gene mutations differ from many other genetically determined conditions: not all those with a mutation will develop the disease; and inherited cancers generally develop in adult life. There is a wide spectrum in the efficacy and utility of screening, surveillance and prevention strategies. Because of these features, complex ethical issues surround the subject. These are considered in Chapter 2.

• There is a potential for a new service of this type to be overwhelmed with inappropriate demand. Public and professional education is therefore a high priority. Research is required urgently at all levels to provide evidence on which to base rational counselling and clinical management of those at high risk due to inherited cancer predisposition. These issues are considered in Chapters 3 and 4.

• The detection of a mutation in a gene predisposing to cancer has far-reaching implications for an individual and his or her family. The maintenance of the highest standards in laboratories carrying out cancer testing is crucial.
genetic testing and processes for implementation, review and regulation of the standards are considered in Chapter 5.

- Three common cancers: breast cancer, colorectal cancer, and ovarian cancer, are considered in detail in Chapters 6, 7 and 8 respectively. These are all cancers for which the genetic basis has already been partially defined and for which there are already evidence-based clinical applications of current genetic knowledge.

- In the case of breast cancer, considered in Chapter 6, mutations in the genes BRCA1 and BRCA2 may be responsible for the majority of those Australians with truly inherited breast cancer. The presence of such mutations confers a lifetime risk of up to 80%. There remain significant technical difficulties with genetic testing. Negative tests, in particular, require careful and informed interpretation. Women can be divided into three groups on the basis of their family history: those at, or slightly above, average risk; those at a moderately increased risk; and those at a potentially high risk. Detailed advice on specific programs of prevention and surveillance is outlined for each group, together with guidelines concerning genetic counselling and testing. Genetic testing should only be performed in the context of genetic counselling, usually in familial cancer clinics.

- Those with a family history of colorectal cancer may also be divided into different risk categories by the density of disease within kindred, and the ages of onset of affected relatives. Chapter 7 considers strategies for prevention and screening within the different risk categories. The genes associated with two particular forms of colorectal cancer, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), have been defined, and issues relating to genetic testing, prevention, and screening for these are also considered in detail. In the case of FAP, prophylactic surgery improves survival for gene carriers.

- Specific hereditary predisposition to ovarian cancer occurs in certain kindreds. In others, ovarian cancer may occur in association with hereditary predisposition to breast cancer. Cancer of the ovary and uterus may also occur in association with HNPCC. Chapter 8 deals with the prediction of risk based on a family history, and on suggested strategies for screening and prevention.

- Family history is a recognised risk factor for many other cancers and is examined in Chapter 9. However, in diseases like melanoma and prostate cancer the field is still limited by the lack of specific knowledge of the genes concerned, or by the limited utility of existing techniques of screening and surveillance. There are a number of rarer hereditary cancer syndromes for which genetic testing may be appropriate.
Guidelines

The following tables list the evidence-based guidelines given in the text of the document. Readers should refer to the appropriate chapters when considering the application of these guidelines.

The guidelines are based on evidence, which is rated using the NHMRC four-part scale (levels I-IV). Advice based on expert opinion (ie recommended practice for which there is no published evidence) is indicated by ‘— ’.

Part 1 General issues concerning familial cancer services

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<td><strong>Location of cancer genetic services</strong></td>
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<td></td>
<td>Clinical cancer genetic services should be situated in institutions with a cancer service, but their ideal location is dependent upon local factors.</td>
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<td><strong>Training programs</strong></td>
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<td>Specialist colleges should be encouraged to devise joint training programs for advanced trainees in clinical cancer genetics.</td>
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<td></td>
<td>The Human Genetics Society of Australasia and the Clinical Oncology Society of Australia should be encouraged to jointly devise an accredited training program for counsellors in cancer genetics.</td>
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<td><strong>Staffing and facilities</strong></td>
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<td>A familial cancer service should have appropriate medical, counselling and administrative staff, and be linked to appropriate laboratory and disease register facilities.</td>
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<td><strong>Code of practice</strong></td>
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<td>An Australian consortium of familial cancer clinics should be formed. The primary function of such a body would be to establish a uniform code of practice for familial cancer services to serve as the basis for self-regulation.</td>
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<td>ETHICAL ISSUES</td>
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<td></td>
<td>There are no individual guidelines for this chapter, but the whole chapter provides guidelines on the ethical issues relating to familial cancer. The chapter has been reproduced from <em>Ethics and Familial Cancers</em>, a report prepared by the Cancer Genetics Ethics Committee of the Anti-Cancer Council of Victoria in 1996; available from the Anti-Cancer Council of Victoria or on the Internet at: <a href="http://www.dhs.vic.gov.au/phd/hdev/genetics/append6.htm">www.dhs.vic.gov.au/phd/hdev/genetics/append6.htm</a>.</td>
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<td>Guidelines should be developed for health care professionals on risk estimation, prevention strategies, surveillance and genetic testing for specific types of cancer.</td>
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<td>An individual’s family history of cancer should be regularly updated to ensure that information given to that person is appropriate.</td>
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<td>Professional awareness of familial cancer registers should be a focus of educational initiatives.</td>
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<td><strong>Coordination of education</strong></td>
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<td>Education about familial cancer should be coordinated nationally.</td>
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<td>Education of the public and professionals should be coordinated.</td>
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<td>Educational resources, research data and information on knowledge and attitudes to familial cancer should be collated.</td>
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<td><strong>Determining what is needed</strong></td>
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<td>Research should be undertaken into public and professional knowledge, misconceptions and attitudes regarding familial cancer and genetic testing.</td>
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<td>Resource requirements for teachers should be determined.</td>
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### Chapter Guidelines

#### Strategies for education
- Information should be produced regarding current knowledge of familial cancers and services available. — 26
- Consumer versions should accompany all material developed for professionals. — 26
- Information should address gaps in knowledge and misconceptions, and should not increase public anxiety. — 26
- Strategies should be developed for effective use of the media. — 26
- Educational programs should be evaluated. — 26

#### Researching family history
- The public, particularly those concerned about their family history of cancer, or who have cancer, should be encouraged and assisted to research their family health history. — 27
- People concerned about their risk of inherited cancer after researching their family health history should be encouraged to consult their medical adviser. — 27

### RESEARCH

#### Research principles
- The Australian Cancer Network should notify funding bodies of the special concerns and requirements relating to proposals in the field of cancer genetics, particularly the need for a coordinated national approach by investigators. — 31
- The Australian Cancer Network should initiate formation of national consortia for research into heritable cancers, such as the Kathleen Cuningham Foundation National Consortium for Research on Familial Breast Cancer (kConFab), recognising the particularly urgent need for evidence on which to base the rational surveillance and screening of carriers of mutations in cancer susceptibility genes. — 31
- National symposia should be initiated to ensure the rapid dissemination of advances in the technology of cancer gene mutation analysis. — 31
- Collaboration with international research groups may be important for the rarer familial cancers or for studies requiring large numbers of participants. — 31
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<td>5</td>
<td>LABORATORY STANDARDS</td>
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<td><strong>Laboratory accreditation</strong></td>
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<td></td>
<td>A submission should be made to NATA that compliance with these guidelines be a prerequisite for accreditation of a diagnostic molecular genetics laboratory offering tests related to familial cancer.</td>
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<td></td>
<td><strong>Current laboratory services</strong></td>
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<td>A survey of laboratories should be undertaken to determine what genes are being studied, the methods being used, and the personnel and expertise in cancer genetic testing available throughout Australia.</td>
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<td><strong>Sample throughput</strong></td>
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<td>Once a method has been established in a laboratory, the laboratory should handle at least 20 DNA samples per year for each gene being analysed for mutations. This would include initial mutation identification in probands and presymptomatic screening in family members. Mutation detection in rare disorders (eg von Hippel–Lindau syndrome) should not be subject to this requirement.</td>
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<td><strong>Experience and training</strong></td>
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<td>The person supervising genetic testing should have appropriate training and expertise in clinical molecular genetics. In the current absence of an accreditation program, the laboratory supervisor should have a medical degree or PhD with the equivalent of at least three years’ full-time postgraduate experience in the application of human molecular genetics in clinical medicine.</td>
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<td></td>
<td>The Human Genetics Society of Australasia and the Royal College of Pathologists of Australasia should ensure compatibility and (as appropriate) reciprocity between their training and accreditation programs.</td>
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<tr>
<td>5 (contd)</td>
<td><strong>Quality assurance</strong></td>
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<td>All laboratories should be involved in a relevant quality assurance program, which should be administered by a body representing the expertise of both the Royal College of Pathologists of Australasia and the Human Genetics Society of Australasia. An Australian quality assurance program should be developed which addresses the following issues:</td>
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<td>• diseases and techniques;</td>
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<td></td>
<td>• source and form of test samples (human genomic DNA, genomic DNA from cell lines, or PCR-amplified alleles);</td>
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<td>• provision of samples;</td>
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<td>• sample preparation;</td>
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<td>• distribution of samples;</td>
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<td>• collation and scoring of responses;</td>
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<td>• frequency of quality assurance program;</td>
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<td>• cost of the quality assurance program; and</td>
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<td>• infrastructure for quality assurance program.</td>
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<td>Where there is insufficient demand in Australia to warrant creating a quality assurance program for a specific gene, a laboratory should seek to join a quality assurance program established overseas. A register of quality assurance programs that may be suitable should be established by the Royal College of Pathologists of Australasia/Human Genetics Society of Australasia.</td>
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<td><strong>Laboratory techniques</strong></td>
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<td>Laboratories should be encouraged to use the most accurate method for identifying mutations in a specific gene. A mechanism for determining which methods are recommended for specific analyses should be established.</td>
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<td>If no specific mutation has been identified in a given family, the laboratory should be committed to retesting the DNA sample of an affected family member at a later date as relevant new techniques or information become available.</td>
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<td><strong>Registry of control DNA samples</strong></td>
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<td>A bank or registry of control DNA samples should be established as part of the quality assurance program.</td>
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Storage of samples

In the current developmental phase of genetic testing in cancer, all laboratories should retain DNA samples under the guidelines recommended by the Human Genetics Society of Australasia.

Subject to appropriate legal and ethical guidelines, molecular data should be made available to other laboratories if requested for studies of other members of the pedigree.

Reporting of test results

Each report should contain:

- collection date and identifying information;
- indication for testing;
- method used (including unpublished modifications);
- molecular data;
- interpretation of the raw data in clear and concise text which is appropriate for an accredited counsellor who is not a geneticist;
- details of further tests or information that may be required; and
- a statement regarding the possibility of inaccuracy due to nonpaternity, incorrect diagnosis etc.

Liaison with counselling services

Molecular genetic tests in familial cancer should be performed only within the context of a comprehensive counselling and follow-up program. This precludes a private or public sector laboratory providing a stand-alone testing service, and should also preclude ‘mail order tests’ not associated with a counselling service. It does not preclude a private laboratory from developing a close affiliation with a comprehensive counselling program and performing these investigations.

Any proposal to include genetic testing in cancer on the Medicare schedule should explicitly include this requirement for affiliation with a counselling service.
## Part 2  Issues relating to specific cancers

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<td></td>
<td><strong>Family history of breast cancer</strong></td>
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<td></td>
<td>General practitioners and other primary health care providers should take</td>
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<td>a family history, and update it regularly. Taking a family history involves</td>
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<td>asking about any cancer in all first- and second-degree relatives, male</td>
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<td>or female, on both the maternal and paternal sides of the family. Attempts</td>
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<td>should be made to verify all reports of all cancers. The Family Health Tree</td>
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<td>Guide may assist in completing a family history chart.</td>
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<td>General practitioners and other health professionals who are unsure about</td>
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<td>the appropriate management associated with an individual's family history</td>
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<td>should seek advice from a familial cancer service.</td>
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<td>General practitioners and other health care professionals should consider</td>
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<td>referral individuals and families they consider to be at high risk of familial cancer.</td>
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<td><strong>Breast cancer risk based on family history</strong></td>
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<td>When advising Australian women about absolute risk based on family history,</td>
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<td>using tables based on United States data from past case-control studies it</td>
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<td>is appropriate to quote risk as lying within a range of from 50 to 75% of</td>
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<td>the published United States risk. In this way, the approximate nature of all</td>
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<td>these risk estimates is conveyed.</td>
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<td><strong>Genetic testing for breast cancer</strong></td>
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<td>Genetic testing should only be offered with pre- and post-test counselling</td>
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<td>conducted in conjunction with a specialist genetics service for breast</td>
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<td>cancer. Individuals undergoing testing should be made aware of the</td>
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<td>limitations of genetic tests for breast cancer.</td>
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<td><strong>Management (average/slightly increased breast cancer risk)</strong></td>
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<td>The initial step in the management of women at average or slightly above</td>
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<td>average risk of breast cancer must be to exclude malignancy by physical</td>
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<td>examination. Thereafter, early detection should be emphasised.</td>
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<td>A woman who is considered on the basis of family history to be at average</td>
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<td>or slightly above average risk of breast cancer should be advised to:</td>
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</table>
• maintain breast awareness (Miller 1997);
• visit her general practitioner promptly if she notices any breast changes; and
• attend for mammographic screening every second year from the age of 50 years (Kerlikowske et al 1995).

Management (moderate risk of breast cancer)

The initial step in the management of a woman at moderately increased risk must be to exclude malignancy by physical examination. Thereafter, early detection should be emphasised. Women in this group should be advised to:

• maintain breast awareness (Miller 1997);
• at the very least, attend for second yearly mammographic screening from the age of 50 years — additional surveillance, such as mammogram from a younger age or more frequently, should be considered on an individual basis, as evidence about optimal strategies in this group does not currently exist (Kerlikowske et al 1995); and
• visit her general practitioner promptly with any breast changes.

These women may also be advised to attend annually for clinical breast examination from the age of 40 years.

Women in this category may need more precise risk assessment. If this is the case, it is recommended that the treating doctor consult specialist cancer or genetic services for advice and formulate an appropriate counselling and management plan (see Appendix D).

Possible participation in a relevant approved clinical trial for the prevention of breast cancer should be discussed. The tamoxifen chemoprevention trial for women who have an increased risk of developing breast cancer is ongoing in Australia through the Australian and New Zealand Breast Cancer Trials Group (see Appendix D) (Fisher et al 1998).
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<td><strong>Management (high risk of breast cancer)</strong></td>
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For women at a potentially high risk whose DNA status is unknown, the initial step must be to exclude malignancy by physical examination. Thereafter, early detection should be emphasised. Women in this group should be advised to:

- maintain breast awareness (Miller 1997);
- attend for 6 to 12 monthly clinical breast examination (Clarke et al 1998);
- report to her general practitioner promptly with any breast changes;
- attend for annual mammographic screening (and possibly ultrasound) commencing at age 40, and consider starting five years earlier than the age at diagnosis of the youngest breast cancer case in the family, whichever is earlier (Kerlikowske et al 1995; Burke et al 1997a);
- attend a cancer specialist for further advice about surveillance, screening and management of breast and ovarian cancers;
- attend a familial cancer service for specialist genetic services, advice and counselling; if they wish to clarify the genetic risk for themselves or family members; and
- discuss possible participation in relevant approved clinical trials for the prevention of breast cancer such as the International Breast Cancer Intervention Study tamoxifen prevention trial (Fisher et al 1998).

Consideration should also be given to screening for ovarian cancer (see Chapter 8).
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| 6 (contd) | For women shown by genetic testing to carry a high-risk mutation, in addition to the above, consideration should be given to advising women:  
  - to attend for annual transvaginal pelvic ultrasonography, preferably with colour Doppler measurements, commencing at age 25 to 30, or at least five years earlier than the age at diagnosis of the youngest ovarian cancer case in the family, whichever is earlier. Annual CA125 may be appropriate as an additional screening test after the menopause;  
  - that prudence suggests it would be wise to avoid high alcohol intake, to avoid long-term use (more than 10 years) of oral contraceptives, and to avoid long-term use of hormone replacement therapy unless there are severe menopausal symptoms, or a personal or family history of cardiovascular disease or osteoporosis; and  
  - that prophylactic surgery (such as total bilateral mastectomy or oophorectomy) may be an option in some highly selected individuals, but only after extensive counselling (Burke et al 1997a). | — | 58 |

Management (history of breast cancer)

Where DNA status is unknown, women at high risk who have already had breast cancer should be advised:  
  - to continue regular clinical surveillance as determined by the cancer specialist;  
  - to maintain breast awareness;  
  - to report to her general practitioner or cancer specialist promptly with any breast changes;  
  - to attend for annual mammographic screening (and possibly ultrasonography);  
  - that if they wish to clarify the genetic risk for themselves or their family, they should attend a familial cancer service for specialist genetic services, advice and counselling;  
  - to attend for annual transvaginal pelvic ultrasonography, preferably with colour Doppler, commencing at age 25 to 30, or at least five years earlier than the age at diagnosis of the youngest affected case of cancer in the family, whichever is earlier. Annual CA125 measurement may be appropriate as an additional screening test after the menopause; and | — | 59 |
that the degree of surveillance for ovarian cancer may be reduced by laparoscopic oophorectomy, which may also offer a survival benefit as adjuvant therapy for stage II breast cancer. Following oophorectomy, indefinite follow-up using annual CA125 measurement is appropriate.

Women shown by genetic testing to carry a high-risk mutation should be advised according to the guideline for management of women at high risk of breast cancer.

**Updating breast cancer information**

Appropriate educational information should continue to be prepared and distributed to women, professional carers and medical practitioners, taking into account the availability and capacity of the groups and the limitations of current knowledge.

**Breast cancer data collection**

Means should be sought to ensure that relevant Australian data on breast cancer are collected, maintained and updated, in order to prepare for the demand for genetic testing.

**National network of breast cancer clinics**

A network of breast cancer family clinics linked with genetic testing laboratories and nationally coordinated research groups should be established and supported.

**National database of breast cancer families**

A national database of families at high risk of breast cancer may be established to facilitate clinical treatment, counselling and research. The database could be based on a common protocol for collecting genetic and epidemiological information, and maintained in accordance with the NHMRC Guidelines for Genetic Registers and Associated Genetic Material (NHMRC 1999b) and Section 14 (Epidemiological Research) in the *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC 1999c).

**Appropriate facilities**

Health professionals and cancer organisations should not promote family cancer clinics or genetic testing until appropriate facilities are established.
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<td>COLORECTAL CANCER</td>
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<td><strong>Genetic testing (FAP families)</strong></td>
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<td></td>
<td>In familial adenomatous polyposis (FAP) families where the family-specific genetic mutation has been identified, genetic testing should be offered to all at-risk relatives.</td>
<td>— 66</td>
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<td></td>
<td>Such testing should be offered when sigmoidoscopic surveillance is due to commence. This is usually between the ages of 10 and 15, depending on family details and dynamics. Testing in children younger than 10 should be performed only under exceptional circumstances.</td>
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<td></td>
<td>Genetic testing should proceed only in the context of genetic counselling.</td>
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<td><strong>Surveillance (FAP families)</strong></td>
<td>III 66</td>
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<td></td>
<td>In familial adenomatous polyposis (FAP) families, yearly or second-yearly flexible sigmoidoscopy should commence from the age of 10–15 years in known mutation carriers and in at-risk family members of unknown genetic status. In known mutation carriers, yearly or second-yearly sigmoidoscopy should be continued until polyposis develops.</td>
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<td>In family members of unknown genetic status, this should change to third-yearly sigmoidoscopy at age 35, then to colorectal cancer screening as recommended for the general population at age 55.</td>
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<td>In families known to have a proximal 5' mutation, surveillance should be based on colonoscopy rather than sigmoidoscopy.</td>
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<td><strong>Prophylactic colectomy in FAP</strong></td>
<td>III 67</td>
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<td></td>
<td>Prophylactic surgery should be considered for all patients with FAP on the basis of the sigmoidoscopic finding of multiple adenomas in those with an identified adenomatous polyposis coli mutation, positive family history of FAP, or typical FAP phenotype.</td>
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<td>Surgery may consist of total colectomy and ileorectal anastomosis, or restorative proctocolectomy.</td>
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<td>After ileorectal anastomosis, sigmoidoscopy should be performed each 6–12 months with removal or destruction of polyps. It should be performed six-monthly from the age of 45.</td>
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<td>Proctectomy (with or without pouch construction) should be performed if polyps are not controllable or when cancer intervenes. Proctectomy with pouch construction should be considered at age 40–50 in all patients with ileorectal anastomosis.</td>
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**Sulindac prophylaxis in FAP**

Sulindac chemoprevention should be considered in FAP patients with rectal adenomas after ileorectal anastomosis and/or with duodenal adenomas.

**Surveillance of stomach and duodenum**

Surveillance of the upper gastrointestinal tract should be considered once colonic polyposis has been diagnosed.

Upper gastrointestinal endoscopy should be considered before proceeding with prophylactic colectomy to allow any large gastric or duodenal adenomas to be removed during surgery. Then annual or biennial upper gastrointestinal endoscopy should be continued if adenomas are present.

The management of patients with identified adenomas is controversial, ranging from simple observation, particularly for those with just small polyps, to surgical removal of large or malignant polyps, or to endoscopic destruction of all identified polyps.

**Identification of HNPCC families**

The modified Amsterdam criteria can be applied to identify families with suspected hereditary nonpolyposis colorectal cancer (HNPCC), but the limitations of these criteria should be recognised, as there are some families with HNPCC where the family history does not meet the criteria.

The identification of colorectal cancers and other syndrome cancers with microsatellite instability will help identify families with mismatch repair gene mutations.

In HNPCC families where a specific mutation has been identified, genetic testing should be offered to all at-risk relatives.
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<td>Genetic testing should be offered when endoscopic surveillance is due to commence — either at age 25, or five years earlier than the age of the youngest affected relative, whichever comes first. The precise age will depend on family details and dynamics. Genetic testing should proceed only in the context of genetic counselling.</td>
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**Surveillance (HNPCC families)**

For individuals at risk of hereditary nonpolyposis colorectal cancer (HNPCC), second-yearly colonoscopy is recommended from the age of 25, or five years earlier than the age of the youngest affected relative, whichever comes first. Annual colonoscopy should be considered in known mutation carriers.

Faecal occult blood testing may be offered in intervening years, and to those with poor compliance for colonoscopy.

For individuals at risk of HNPCC there are options for surveillance at other sites, usually from age 25–35, which may include:

- annual transvaginal ultrasonography, preferably with colour flow Doppler imaging, together with endometrial sampling;
- annual check of CA125 level (after the menopause);
- second-yearly upper gastrointestinal endoscopy; and
- annual urinalysis and cytology.

**Surgery (HNPCC)**

Total colectomy with ileorectal anastomosis or restorative proctocolectomy should be considered as the primary surgical option for colorectal cancer in hereditary nonpolyposis colorectal cancer (HNPCC).

Annual surveillance endoscopy should be performed on any residual large bowel.

**Prophylactic surgery (HNPCC)**

The option of prophylactic surgery rather than surveillance for hereditary nonpolyposis colorectal cancer (HNPCC) should be discussed with known mutation carriers.
### Identification of colorectal cancer risk

Where there is a family history of colorectal cancer, a full and detailed family medical history, including the ages of onset of all cancers in the family, can be used to help determine the most appropriate management of this group.

### Surveillance (moderately increased risk of colorectal cancer)

For those at three- to six-fold increased risk of colorectal cancer, the following should be considered:

- annual faecal occult blood testing starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Colonoscopic follow-up (or flexible sigmoidoscopy plus double contrast barium enema if colonoscopy is unavailable) is necessary for those with a positive faecal occult blood test; and
- colonoscopy every five years starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Flexible sigmoidoscopy plus double contrast barium enema is an acceptable alternative to colonoscopy if the latter is unavailable.

### Surveillance (at slightly above average risk of colorectal cancer)

For those at two-fold increased risk of colorectal cancer, the following are advised:

- faecal occult blood testing should be offered annually from the age of 50.
- sigmoidoscopy (preferably flexible) should be considered every five years from the age of 50 (Selby et al 1992).

### Surveillance (non-FAP polyposis syndromes)

People with Peutz–Jeghers syndrome or juvenile polyposis should be encouraged to seek medical advice promptly if they develop rectal bleeding or other symptoms suggestive of colorectal cancer.

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<td><strong>Identification of colorectal cancer risk</strong></td>
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<td>Where there is a family history of colorectal cancer, a full and detailed family medical history, including the ages of onset of all cancers in the family, can be used to help determine the most appropriate management of this group.</td>
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<td><strong>Surveillance (moderately increased risk of colorectal cancer)</strong></td>
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<td>- colonoscopy every five years starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Flexible sigmoidoscopy plus double contrast barium enema is an acceptable alternative to colonoscopy if the latter is unavailable.</td>
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<td>7 (contd)</td>
<td><strong>Primary prevention of colorectal cancer</strong></td>
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<td>The World Health Organization guidelines for primary prevention of colorectal cancer should be made known to all individuals with elevated risk on the basis of family history. They are:</td>
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<td>• fat consumption to be less than 20% of total calories;</td>
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<td>• a balanced diet should be consumed, containing five to eight servings of fruit, vegetables, wholegrain cereals (especially wheat bran) and breads in order to provide adequate fibre, vitamins and other components with anticarcinogenic effects;</td>
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<td>• fibre intake should exceed 25 grams/day;</td>
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<td>• obesity should be avoided;</td>
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<td>• tobacco should be avoided; and</td>
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<td>• physical activity should be incorporated into daily routine.</td>
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<td><strong>Aspirin prophylaxis for colorectal cancer</strong></td>
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<td>Medical attendants should discuss the risks and benefits associated with aspirin prophylaxis with those at high risk of colorectal cancer.</td>
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<td></td>
<td><strong>Genetic registers (colorectal cancer)</strong></td>
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<td>Clinicians should notify consenting patients with an hereditary colorectal cancer syndrome (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz–Jeghers syndrome, juvenile polyposis etc) to the appropriate State or Territory register. Such registers should conform to the NHMRC Guidelines for Genetic Registers and Associated Genetic Material (NHMRC 1999b).</td>
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Chapter Guidelines

### Identification (at or slightly above average ovarian cancer risk)

The following women should be advised that they are either at or only slightly above the average risk of ovarian cancer. This group covers over 99% of the population, and consists of women with:

- no confirmed family history of ovarian cancer; or
- one first-degree relative diagnosed with ovarian cancer at age 50 or older; or
- one second-degree relative diagnosed with ovarian cancer at any age; or
- two first- or second-degree relatives diagnosed with ovarian cancer, at age 50 or older, but on different sides of the family.

### Management (at or slightly above average ovarian cancer risk)

Women at low risk of ovarian cancer should be:

- reassured that their chances of not developing ovarian cancer are greater than 95%;
- made aware of the current best practice for the prevention of cancers in the general population.

### Identification (moderately increased ovarian cancer risk)

A small number of women (less than 1%) are at a moderately increased risk of ovarian cancer. This group comprises women with:

- one first-degree relative diagnosed with ovarian cancer before the age of 50 (but without the additional features of the potentially high-risk group — see below); or
- two first- or second-degree relatives, on the same side of the family, diagnosed with ovarian cancer (but without the additional features of the potentially high-risk group — see below).
**Management (moderately increased ovarian cancer risk)**

Women with moderately increased risk of ovarian cancer should be informed that:

- there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality from ovarian cancer in women at risk;
- unnecessary intervention can sometimes result after a false positive test; and
- interval cancers can develop between tests.

Methods that may be considered as screening tools include tumour markers, specifically CA125, and transvaginal ultrasonography as well as colour Doppler imaging.

**Identification (potentially high ovarian cancer risk)**

The following women should be advised that they have a potentially high risk of developing ovarian cancer and perhaps other cancers. This group includes much less than 1% of the population, and comprises women who have:

- breast or ovarian cancer diagnosed in three or more first- or second-degree relatives on the same side of the family; or
- two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, plus one or more of the following features (on the same side of the family):
  - onset of ovarian cancer before the age of 50,
  - onset of breast cancer before the age of 40,
  - breast and ovarian cancer in one individual,
  - Jewish ancestry,
  - breast cancer in a male relative; or
- three or more first- or second-degree relatives on the same side of the family with cancers including early onset colorectal cancer (age less than 50 at diagnosis) in particular, but also with endometrial cancer, ovarian cancer, gastric cancer, colorectal cancer or cancers involving the renal tract—features consistent with hereditary nonpolyposis colorectal cancer; or
- a member of a family with a demonstrated germline mutation in a high-risk ovarian cancer-associated gene such as BRCA1, BRCA2 or one of the DNA mismatch repair genes.
For women at potentially high risk of ovarian cancer, whose ovarian cancer-associated gene status is unknown, the initial step must be to exclude malignancy. Thereafter, early detection should be emphasised.

Women in this category should be advised:

- that there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality of ovarian cancer in women at risk;
- that unnecessary intervention can sometimes result after a false positive test and that interval cancers can develop between tests;
- to attend for annual transvaginal pelvic ultrasonography, preferably with colour flow Doppler, commencing at age 25 to 30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier;
- that annual CA125 measurement may be appropriate as an additional screening test after menopause; and
- that prophylactic surgery (bilateral oophorectomy) may be offered as an option in some highly selected individuals, after extensive counselling.

In women at potentially high risk of ovarian cancer who have been shown by genetic testing to carry a high-risk mutation in a gene that predisposes to ovarian cancer, the first step is to exclude cancer. Following that, consideration should be given to advising women:

- to attend for annual transvaginal pelvic ultrasonography, preferably with colour flow Doppler, commencing at age 25 to 30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier;
- that annual CA125 measurement may be appropriate as an additional screening test after menopause; and
- that prophylactic surgery (bilateral oophorectomy) could be considered as an option, usually from the age of 30 to 35 years or when their child-bearing has been completed. This may also reduce the risk of breast cancer. Women with HNPCC may also consider prophylactic hysterectomy.
Management (high melanoma risk)

Given current gaps in knowledge about the expression of melanoma susceptibility genes in the population, genetic testing cannot be used as a guide to clinical practice of prevention and surveillance. All individuals deemed to be at high risk of melanoma should be managed with the same attention to the measures given below.

For families with a high genetic risk of melanoma, parents should be educated about sun protection and examination for young infants and children, including:

- use of sun-protective clothing and hats;
- use of 15+ or stronger sunscreens;
- avoidance of peak ultraviolet (UV) conditions; and
- ABCD rules—note any change of area, border irregularity, colour change, or diameter of skin lesion > 0.5 cm.

Commencing at age 10 years, management should include:

- education of the individual and parent/partner/family member in skin examination, the hallmarks of suspicion in pigmented skin lesions (ABCD rules), and the importance of reporting new naevi or change in existing naevi;
- three-monthly self-examination and examination by parent/partner/family member;
- six-monthly dermatological examination until competent in self-surveillance, then annually;
- annual examination should include adequate examination of the scalp;
- skin-surface microscopy (epiluminescence microscopy) may be helpful;
- a careful initial extended family history is imperative, including the ages and verified histological diagnoses of all family members with cancer. The pedigree should be revised annually;
- baseline full-skin surface photography and close-up photography of selected lesions may be helpful for the detection of new lesions and change in existing lesions; and
- excision biopsy of suspicious skin lesions.
### Guidelines

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<tr>
<td>9</td>
<td>For families with a genetic predisposition to melanoma, screening and surveillance guidelines for the general population should be adhered to, with the following possible special considerations:</td>
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<td>• melanoma in the context of the Li–Fraumeni syndrome, the hallmark for which is the presence of sarcoma in the pedigree. Screening should be conducted in accordance with guidelines for this condition;</td>
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<td>• presence of a strong family history of pancreatic cancer. Certain families carrying CDKN2A/p164A mutations have a high incidence of pancreatic adenocarcinoma. At present there is no reliable screening method for early, operable, pancreatic carcinoma. However, on an experimental basis, at-risk individuals in such kindreds, where there is a demonstrable family history of pancreatic tumours, may be advised to undergo endoscopic ultrasound, perhaps on an annual basis from an age five years earlier than the earliest case of pancreatic carcinoma in the family. Positron emission tomographic (PET) scanning is a highly sensitive, noninvasive, technique, the cost-effectiveness of which may warrant further investigation in very high-risk cohorts; and</td>
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<td>• where ocular melanoma has occurred in the family annual fundoscopy after adequate mydriasis is recommended, although is of unproved efficacy.</td>
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**Individuals (high prostate cancer risk)**

Family history is a risk factor for prostate cancer. Recording of the family history may be used to identify men at high risk. It is anticipated that genetic testing may eventually be used to accurately identify high-risk men who may benefit from targeted screening.

**Management (RET mutation)**

For individuals with a RET germline mutation, screening for phaeochromocytoma should be performed annually, or whenever symptoms suggest, with urine catecholamine and metanephrine measurements. Screening for hyperparathyroidism should be performed annually by measuring serum ionised calcium (or total calcium corrected for albumin), phosphate and parathyroid hormone levels.
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<td>9 (contd)</td>
<td><strong>Management of families with a history of a rare cancer syndrome</strong>&lt;br&gt;Families with a history consistent with one of the rare familial cancer syndromes require counselling. In some cases, they will be candidates for genetic testing. Such testing may be available only with the cooperation of research laboratories.</td>
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PART 1

GENERAL ISSUES CONCERNING FAMILIAR CANCER SERVICES
CHAPTER 1

CLINICAL SERVICES: STANDARDS AND TRAINING

A number of specialised cancer genetic counselling and testing centres are being established around Australia. At present, there is neither data regarding the composition of these services nor any consensus as to the desirable constituents of such a familial cancer service (Ponder 1994).

This is a new field, and evidence-based guidelines for genetic testing, screening and surveillance of high-risk groups attending familial cancer services are in an early stage of evolution. Significant morbidity could arise from inappropriate genetic testing or advice. A mechanism is therefore required to achieve high and uniform national standards for clinics providing familial cancer services.

This chapter outlines the aims of a familial cancer service and the expertise, staff, guidelines, protocols, standards and evaluation such a service would require. It also proposes several options for accreditation.

1.1 Aims of a familial cancer service

The goals of a familial cancer service are to:

• reduce the morbidity and mortality associated with cancer by identifying individuals with an inherited predisposition; and

• address the concerns of people with a family history of cancer.

The aims are to:

• achieve these goals in a cost-effective way;

• collect, confirm, extend and interpret pedigrees of people with a family history of cancer;

• estimate cancer risk based on family history and other risk factors, including measured genetic information;

• communicate the risk to the individual;

• advise about inheritance and testing of cancer predisposition genes, where appropriate;
identify other high-risk relatives and, through their relatives, offer appropriate local services;

advise individuals and doctors about strategies for cancer screening, early detection and prevention in those at high genetic risk;

counsel individuals seeking genetic testing about the uncertainties, risks and benefits associated with positive and negative test results;

arrange and supervise the giving of results of any genetic testing performed;

provide follow-up and review where necessary, particularly the provision of a registry-based reminder service for surveillance and screening programs;

provide a resource for research including an evaluation of the clinic itself; and

provide a resource for education.

1.2 Clinic type

Clinics fall into two categories.

- **Site-specific clinics** have a multidisciplinary approach to one disease, such as breast or colorectal cancer, and the patient has access to a team with genetic, diagnostic and management expertise.

- **General familial cancer clinics** have an emphasis on cancer risk assessment, surveillance strategies and clarification of the possibilities for genetic testing where appropriate.

Although it is mandatory that these services are set up in an institution with a cancer service, beyond this the ideal location is the subject of debate and will depend upon local factors. The critical element is that it be a joint operation by those with cancer, genetic and counselling expertise, and that it be linked to a genetics laboratory.

The optimum number of familial cancer services required per million of population will represent a balance between maintaining a concentration of expertise, the requirements of different teaching hospitals and geographic accessibility. Currently, the United Kingdom has one familial cancer service per 3.5 million population (Ponder 1994). Whether this is relevant to the Australian situation or not is not yet clear.
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<th>Guideline — location of cancer genetic services</th>
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<td>Clinical cancer genetic services should be situated in institutions with a cancer service, but their ideal location is dependent upon local factors.</td>
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### 1.3 Resource allocation

The issues surrounding the funding of genetic counselling and testing services are complex. Specific practice differences which impact on the use of resources, and measurement of outcomes in this field, include the following:

- it is necessary to provide clinical services to the extended families of clients with a genetic predisposition to cancer;

- families may be living interstate or overseas;

- patients are not usually admitted to hospital, and funding systems tend to favour inpatients;

- the service is provided to well people, rather than the sick;

- the service has a higher proportion of client contact via telephone and letter than many other clinical services; and

- outreach facilities need to be further developed.

### 1.4 Skills

The knowledge and skills required of personnel in a familial cancer service include:

- biology, genetic epidemiology and molecular genetics of cancer;

- pedigree analysis;

- the principles and practice of genetic testing by linkage analysis, haplotype sharing and direct mutation analysis;

- risk assessment and age-specific risks of cancer;

- surveillance measures in cancer;

- risk reduction in cancer prevention;
- the treatment of cancer;
- presymptomatic genetic testing;
- the complexities of genetic counselling with the attendant psychodynamic, emotional and ethical issues;
- ethical issues specific to the field of cancer genetics; and
- computerised data management and secretarial skills.

## 1.5 Staff

### 1.5.1 Specialist medical practitioner

The clinic should include at least one specialist medical practitioner with skills and experience relevant to familial cancer work, as described above. The person embodying these skills may be a clinical oncologist, a medical geneticist with accreditation from the Human Genetics Society of Australasia (or equivalent), a system-related specialist with an interest and expertise (hands-on experience with genetic testing desirable, but not essential), or a combination of all three. This person should ideally be accredited as a cancer genetic specialist. A joint training program is under consideration by the specialist advisory committees in genetics and medical oncology of the Royal Australasian College of Physicians. It may be possible for other colleges to use that training program, allowing specialists in other disciplines to train and gain accreditation in cancer genetics.

### 1.5.2 Counsellor in cancer genetics

A counsellor in cancer genetics could be either a genetic counsellor with experience in cancer genetics, an oncology nurse with experience in genetics, or a social worker or psychologist with experience in either oncology or genetics. Training issues and accreditation need to be addressed, preferably with a national accreditation process. Appropriate accrediting bodies, such as the Human Genetics Society of Australasia and the College of Counselling, should have some input into the proposed training program. The Human Genetics Society of Australasia Board of Censors for Genetic Counselling has established a curriculum that includes training in the theoretical and practical skills necessary for a general genetic counsellor. Core components of this could be incorporated into a more specific program for cancer genetic counsellors.

Legislation has been used to guarantee pretest counselling in relation to Huntington’s disease in Canada and in vitro fertilisation technology in Victoria. This should be considered in relation to familial cancer.
1.5.3 Scientific staff
Access to, and close liaison with, a National Association of Testing Authorities (NATA) accredited cancer genetics laboratory is vital (see Chapter 5).

1.5.4 Secretarial/ data manager
Secretarial/clerical staff are essential for the effective operation and evaluation of the clinic. A minimum data set should be obtained on all patients\(^1\) in relation to each specific cancer. The data should be kept in a format agreed to by a consortium of familial cancer services. The compilation and maintenance of accurate pedigrees, verification of diagnoses and reinforcement of compliance with follow-up protocols requires the allocation of considerable clerical resources.

1.5.5 Psychosocial liaison staff
An appropriate mix of staff and facilities for a familial cancer service may include the following:

- specialist medical practitioner in cancer genetics;
- counsellor in cancer genetics;
- access to and close liaison with an accredited DNA laboratory;
- secretarial/data manager;
- consulting staff in psychiatry, psychology and social work; and
- access to and close liaison with specific disease register.

1 Such a minimum data set for breast/ovarian kindreds has been published by the NHMRC National Breast Cancer Centre (see Appendix D).
1.6 Protocols

Standard protocols based on available scientific evidence should be developed by familial cancer services. Such protocols would allow for more rapid collation of data on the outcomes of cancer genetic counselling and testing, and allow the interchange of information about families (with informed consent). This would ensure uniformity in the advice given to different members of the same family, and prevent the conflict that may arise when different family members are approached by separate familial cancer services, sometimes from different States or Territories.

The NHMRC National Breast Cancer Centre document National Best Practice Guidelines for Familial Cancer Clinics (Kirk and Tucker 1997) provides a model, and outlines specific protocols in the following areas:

- exclusion of undiagnosed cancer in the consulting individual, usually by referral to an appropriate specialist;
- pedigree construction and extension;
- verification of diagnoses;
- consent for release of information or tumour material from patients or from next of kin of deceased patients;
- data collection and recording, preferably in the same form as other centres so that data can be pooled;
- surveillance, screening and prevention;
- mechanisms for ensuring adherence with follow-up schedules;
- evaluation and peer review; and
- clinical trials.

1.7 Achieving high and uniform standards

An appropriate code of practice will encourage:

- adequate counselling prior to presymptomatic genetic testing;
- appropriate quality control so that test results are accurate; and
• the collection of data prospectively and retrospectively to assess the efficacy of the recommendations of such clinics.

The potential for harm to the Australian community from indiscriminate use of genetic testing for cancer susceptibility is such that some form of regulation of familial cancer services is necessary. Initially, self-regulation by the medical and related professions should be piloted in this small but specialised field. Self-regulation would take the form of agreed adherence to a code of practice for familial cancer services, outlined above, with a system of regular external review by an Australian consortium of familial cancer clinics. Only if such a voluntary system fails would there be a need to move to more formal procedures of accreditation, the most extreme of which would include legislation to restrict services to those familial cancer services satisfying strict criteria.

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<th>Guideline — code of practice</th>
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<tr>
<td>An Australian consortium of familial cancer clinics should be formed. The primary function of such a body would be to establish a uniform code of practice for familial cancer services to serve as the basis for self-regulation.</td>
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1.7.1 Predictive testing, and pre- and post-test counselling

The results of predictive genetic testing should be given only to those who have received adequate pretest counselling, because of the potential for discrimination, anxiety, loss of self-esteem and family disharmony. Pretest counselling should include a discussion of inheritance, cancer risk, medical management options, confidentiality, the potential advantages and disadvantages of the testing, and should address the impact that such testing may have on the person and on other family members. Guidelines for predictive pre- and post-test counselling have been developed by the Human Genetics Society of Australasia (HGSA), and should be used to establish appropriate protocols (HGSA 1997). Fully informed consent for predictive genetic testing is of paramount importance.

Current technology generally requires the detection of a mutation in a confirmed affected family member who has had cancer, before predictive testing can be offered to other at-risk family members. Counselling for the affected family member with cancer who is offered testing for the detection of a mutation should include all the usual components of counselling that would be offered to the at-risk family members.
1.7.2 Interaction with referring doctors

The purpose of the clinic is not to be a service for acute referrals for diagnosis and management of cancer, but to perform a specialist function. The purpose is to:

- advise and, if appropriate, perform genetic testing; and
- advise the referring doctor of appropriate management.

The general practitioner is an important participant in the management of these families. This predicates a commitment to education and training of referring doctors.

1.7.3 Clinical audit

Regular multidisciplinary meetings within the centre, and less frequently between centres, should be undertaken so as to ensure an appropriate standard of care. Participation in ongoing research into the impact of testing/counselling could form part of an audit.

1.8 Ethical principles

Familial cancer services should adhere to the ethical principles outlined in Chapter 2.

1.9 Nonclinical components of a familial cancer service

1.9.1 Training

In the short-term there is a need for accreditation and training programs designed for those already working in the field to update and consolidate their existing expertise and knowledge.

There is a long-term need to consider the requirements of those trainees who wish to subspecialise in cancer genetics. Some of the training goals might include:

- information needs;
- knowledge of syndromes;
- general knowledge about cancer genes, the carcinogenic process and genetic mutation;
• clinical experience;
• genetic epidemiology;
• laboratory experience, or at least laboratory exposure;
• research experience, training and exposure;
• training and experience in counselling, and understanding of family psychodynamics;
• ethical training;
• involvement in multidisciplinary clinics, and an understanding of the importance of these; and
• training as an educator in patient, public and peer education.

Because the field of cancer genetics is moving so rapidly, a cancer genetic service should demonstrate a commitment to ongoing education for all staff. Education of other health care providers about the potential benefits and pitfalls of this new technology is an essential part of the service.

The training needs of the following groups require consideration:

• clinical genetic trainees;
• oncology trainees in all clinical disciplines;
• surgical trainees;
• gastroenterology trainees;
• general practitioners;
• general physicians;
• obstetric and gynaecological trainees;
• liaison psychiatrists;
• medical students;
• genetic counsellors;
• counsellors in cancer genetics;
• oncology nurses; and
• nonmedical counsellors.

Professional organisations that need to be involved in training include:

• Royal Australasian College of Physicians;
• Royal Australasian College of Surgeons;
• Human Genetics Society of Australasia;
• Royal Australian College of Obstetricians and Gynaecologists;
• Royal Australasian College of Radiologists;
• Royal College of Pathologists of Australasia;
• Royal Australian College of General Practitioners;
• Royal Australian and New Zealand College of Psychiatrists;
• Royal College of Nursing; and
• organisations representing biomedical ethicists, health economists and epidemiologists.

1.9.2 Education
The service should have a commitment to the education of the consultands and their families, their doctors, the wider medical community and the general public. There is a particular need to educate the media so that advances in the field can be reported appropriately and in a timely fashion. These issues are covered in Chapter 3.

1.9.3 Commitment to ongoing research
As there are so many areas where there is no evidence-based data, a commitment to research is important. Priority areas are listed in Chapter 5.
CHAPTER 2

ETHICAL ISSUES

This chapter was originally developed as the final section of Ethical Aspects of Human Genetic Testing, an information paper (NHMRC 2000) and the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999c) especially Section 1, which outlines principles of ethical conduct.

2.1 Introduction

In some families, cases of cancer occur more often than would be expected by chance. This can be due to the inheritance of an altered gene (a gene mutation) or to other causes. It may be possible from the family history alone to give an approximate estimate of the risk which a member of an affected family has of developing the cancer. With some cancers, the precision with which the risk for a family member can be estimated may now be greatly increased by a genetic test, although with other cancers considerable uncertainty will remain despite a test. It is the application of this new technology that has prompted the ethical questions addressed in these guidelines.

Cancers due to inherited gene mutations differ from many other genetically determined conditions in several ways. For example, although in some cases almost everyone with a mutation that predisposes to a cancer will develop the cancer, in other cases the risk is less. Thus, while virtually all who inherit a gene mutation that predisposes to familial adenomatous polyposis (FAP) will develop colorectal cancer, the proportion of women inheriting a gene mutation predisposing to ovarian cancer who actually develop cancer is of the order of 40%. Also, by contrast with many inherited diseases, inherited cancers generally develop in adult life, and in some cases knowledge of an individual’s genetic risk may lead to prevention of the cancer or to surveillance with an expectation that early diagnosis may improve the outlook.
Because of these features, some ethical questions arise during the assessment of the risk of developing inherited cancers that are over and above those that generally arise with hitherto better known inherited conditions.

Issues of unknown parentage may be a problem in this area, particularly unknown paternity and maternity associated with adoption, artificial insemination and donor germ cells.

2.2 Risk assessment and counselling

Assessment of risk starts with a person consulting a health professional about the risk of cancer based on their family history. The process of risk assessment should continue until the questions raised by the inquirer have been resolved, in so far as that is possible, and a management plan for the inquirer has been developed.

Risk assessment should involve a series of steps:

- taking an initial family history and making an initial assessment;
- trying to validate the family history;
- risk assessment and advice on genetic testing;
- genetic testing (if decided upon); and
- further risk assessment and management planning.

Problems associated with the occurrence of an inherited cancer are complex and have an impact both on the inquirer and on the inquirer’s family. During the process of risk assessment, the inquirer needs to be helped to comprehend the medical facts; to appreciate the concepts of inheritance and risk; to understand what is involved in risk assessment, what the consequences may be and what the options are; to choose a course of action; and to make the best possible adjustments as the situation unfolds. To achieve these ends, risk assessment needs to be associated with professional genetic counselling. Individuals from many backgrounds may contribute to counselling but all need special training.

There are potentials for benefit and for harm for individuals who embark on risk assessment. From an early stage in a consultation, inquirers should have these potentials, including the limitations and pitfalls of risk assessment, clearly explained to them.
2.3 Genetic testing

The potential benefits and adverse consequences of having a genetic test are influenced by the precision with which the result of a test predicts the level of risks; also whether, given a high risk, anything can be done to modify it, or anything can be done that is seen to be useful by the individual tested. The following points need to be considered.

For those found to carry a mutation, potential benefits include:

- uncertainty about whether or not they are at risk is removed;
- they can receive a more accurate estimate of their risk than is possible from their family history alone;
- they can be informed of the chances their children have of carrying the mutation; consequently they can contribute to advice given to their children about their being tested;
- they can make informed decisions about initiating a pregnancy, foetal testing and possible termination of pregnancy; and
- they can be advised on surveillance aimed at early diagnosis, and on preventive treatment.

For those found to carry a mutation, potential adverse consequences include:

- anxiety, fear, depression, even with the risk of suicide based on concern for themselves and their own future;
- anxiety and guilt regarding the now high-risk status of their children;
- difficulties to be confronted with regard to choices about future pregnancies;
- the stress of being the bearer of bad news in the family;
- disruption to family relationships;
- concerns about uncertain consequences of the recording of the test result, including possible effects on life insurance, employment and so on; and
- uncertainty about the possible misuse of the information, at present or in the future.

For those found not to carry a mutation, potential benefits include:
• uncertainty they and their progeny may have had is removed; their risk of developing cancer is about the same as the population risk; and

• they and their progeny need not submit to years of surveillance aimed at early diagnosis which, in familial adenomatous polyposis for example, may involve an intrusive procedure like sigmoidoscopy.

For those found not to carry a mutation, potential adverse consequences include:

• their relief may be tempered by feelings of guilt that they are to be spared while others in their family are threatened;

• family relationships may be disrupted;

• they may be plagued by disbelief;

• false reassurance; and

• sustained uncertainty.

Diagnostic genetic testing in the symptomatic minor should be considered only if the result is likely to have a direct benefit for the child in planning treatment and surveillance, or if it is thought necessary for the assessment of risk for another family member.

Predictive testing of asymptomatic minors should be carried out only where a specific treatment intervention is available and delay is inappropriate.

2.4 Record holders

During the process of risk assessment, doctors and other health professionals, hospitals and laboratories will come to possess information about the inquirer and his or her relatives. Because of the essentially medical nature of the records made during risk assessment and the clinical activities and advice that come to be derived from them, the responsibility for the use of records should lie with doctors.

At an early stage inquirers should be informed, with regard to confidentiality, of the extent to which it may be necessary for information to be shared among health professionals and family members. They should also be told of the form in which it may be shared, and of the steps that are taken to try to ensure that information is held securely and that privacy is taken into account.

Genetic records include written and electronically recorded material as well as tissue specimens (including blood). Reference to and continuing study of an individual’s genetic records may be of value not only to him or her but also to
relatives in present and future generations. For these reasons, written and electronic records should be retained indefinitely, and it may be appropriate in some circumstances for tissue specimens to be preserved permanently.

The reasons for records, including tissue specimens, to be kept indefinitely should be explained to inquirers. Factors affecting their retention and storage should if possible be discussed in advance of genetic testing.

Inquirers should understand that records, including tissue specimens sent for genetic testing, are the property of the bodies that make the records or hold the tissues.

Individuals providing information and tissues in the course of genetic risk assessment should be led to consider, preferably in advance of genetic testing, the extent to which they have an obligation to have these materials made available to assist their relatives and descendants to make wise decisions regarding their possible individual genetic risks. The presumption should be that relatives and descendants should have access to those materials for purposes of assessment of their own risk.

### 2.5 Confidentiality and the family

People expect that information which doctors and other health professionals come to possess about them will be kept in confidence. In cancer risk assessment, there will sometimes be a tension between a doctor’s commitment to a patient or other inquirer to keep in confidence what passes between them and the doctor’s moral obligation to ensure that the inquirer’s relatives have a chance to learn that they may have inherited a risk of developing cancer, a risk that they could pass on to their children. The obligation could be seen as falling on both doctor and inquirer. The likelihood of relatives needing to share information on their family risk, including details of the relevant gene mutation, should be made clear early in the process of risk assessment.

When, in the course of risk assessment, relatives of an inquirer need to be contacted, the identity of the inquirer and his or her risk status (including the result of any genetic test) should not be passed on to relatives without the inquirer’s consent. The same should apply in the case of relatives who become involved in the inquiry.

In the exceptional situation where a patient or other inquirer objects to information on his or her genetic risk becoming known to relatives, it could still be possible for relatives to be advised that they may be at risk from a family cancer susceptibility, but without identifying the reluctant inquirer. For the purpose of their own genetic testing, the aim should also be to acquaint relatives...
with the specification of the gene mutation carried in their family. Objection by inquirers to knowledge of their risk status being used for the benefit of their relatives and descendants should not in itself be regarded as sufficient reason for the information not to be used in de-identified form. This remains the case even if the inquirer's identity and even risk status may be inferred.

The best person to make initial contact with relatives will generally be the inquirer or a relation suggested by the inquirer. The doctor should take care to ascertain that the inquirer will be able to make contact in an appropriate way. In some cases, the approach may have to come from the doctor or other health professional consulted by the inquirer, directly or through the relation's own doctor. Whoever makes the initial approach, a letter simply advising relatives that there was information to hand, which they might wish to discuss with a doctor could be a discreet and sensitive way of broaching the matter.

When discussing the approach to relatives, doctors should be guided by inquirers about the possibility that some relatives may not wish to know of their potential inherited risk. With a condition like familial adenomatous polyposis, in which virtually all who carry a gene mutation develop cancer, and in which the cancer may be prevented, the strong presumption should be that the relatives will be grateful for being warned. The same presumption should not be made in a cancer such as breast or ovarian cancer, where the risk of developing cancer for a woman with a gene mutation is less than 100% and there is no assurance of a successful medical intervention.

2.6 Spouses and partners

Not all the compelling considerations in favour of patients making available to relatives details of their gene mutation apply to spouses and partners. Spouses and partners do not have the same risk potential as blood relatives, and unlike disclosure of mutation details to blood relatives, any disclosure to spouses or partners necessarily reveals the patient's identity and test status. There may, however, be other compelling considerations in favour of disclosure to actual or intended spouses or partners, most obviously the fact that they have an interest in knowing of the possibility of their offspring being born with a genetic predisposition to cancer. In considering whether disclosure is warranted in particular cases, doctors need to be aware of these differences between what is at issue in disclosure to blood relatives and to spouses or partners.

2.7 Researchers

Individuals undergoing risk assessment for possible inherited cancers should be made aware that it is only as a result of research that the present state of
knowledge, from which they stand to benefit, has been reached, and that advances in knowledge can only come from more research.

Ethical aspects of medical research are regulated in Australia by the NHMRC. Research related to cancer risk assessment and genetic testing should be conducted according to the *Statement on Human Experimentation and Supplementary Notes* (NHMRC 1992).

It should be explained to inquirers, in the course of their risk assessment and before they give blood or tissue for a test for a gene mutation predisposing to cancer, that records of their case may be used in de-identified form for research in accordance with National Health and Medical Research Council guidelines. Where those records may include tissues sent to a laboratory for testing, this should be made clear. It should be emphasised to inquirers that institutional ethics committees will impose significant constraints on the use of their records and tissue in research. If, knowing all this, individuals having genetic tests do not wish their tissue, even in de-identified form, to be used for any research, their wishes should be respected.

A distinction should be made between genetic tests done for clinical purposes and tests done in the course of research projects. Clinical testing is associated with professional counselling that takes account of potential benefits and adverse consequences of knowing the result of a test, but counselling is not always part of a research project. Test results should not therefore be made available as a matter of course to participants in research. Nevertheless, in some research projects there may be good reasons for making results available. Participants should be advised about this situation before entering a research project. In general, individuals in a research project who wish to obtain information about the result of a genetic test should be referred to suitably qualified people for discussion and advice.

### 2.8 Insurance and employment

The finding of a positive test for a cancer predisposition gene could adversely affect an individual seeking life or other forms of insurance. The finding might affect other members of the family. It is also possible that prospects of employment could be affected. Before they decide to have a genetic test, individuals should be acquainted through genetic counselling with the possible implications for themselves and their blood relatives for insurance and employment of having the test.
2.9 Cancer genetic registers

For the management of familial cancers, information on family members needs to be collected and collated. Systematic collections of medical information on family pedigrees are given various names. In the case of familial adenomatous polyposis (FAP), they are called registers. FAP registers are used not only to help detect individuals at risk, but also to provide supporting services for families and their doctors. The following guidelines, while focused on an FAP register, will be relevant in many respects to registers for other cancers.

A register needs to accommodate a wide range of information, but it should not be an undifferentiated collection of data. It should have separate parts that can be handled in different ways and be located in different places, and be linked as necessary through a central mechanism. Some parts, such as those concerning results of genetic tests, will be more sensitive than others. In some instances it will be appropriate for the register simply to indicate the location of certain information and the identity of the individual responsible for it.

A register should be regarded as an extension of ordinary clinical records and, as with other clinical records, responsibility for the use of information in the register should lie with doctors and other health professionals.

Early in the process of assessing risk in members of a cancer family, individuals should have explained to them the importance of information from their medical records being collated in a central register. At the same time they should be clearly informed of the nature of the register and the uses that may be made of information in it. In this connection it is necessary to distinguish between the information base that is used to construct the register and the register proper from which information that identifies individuals is used.

Consent is needed from each individual before his or her name can be entered on the register proper. Failing such consent, only de-identified information can be included on the register proper. When consent is sought, care must be taken to acquaint inquirers with the purpose of the register, how it functions, the nature of the medical and personal details which may be included on it, those to whom the information and names on the register might be released, and the circumstances in which this might occur.

Names on the register, which appear there only with the consent of the individuals named, may be released to appropriate professionals but not to relatives unless specific permission has been given for this in the particular case. If the register is sometimes used as the medium of approach to an inquirer's relatives, only de-identified information about people on the register should be used unless specific consent has been given in the particular case by an inquirer for his or her name to be released to a relation.
Every register should be under the auspices of a clearly designated body. The auspicing body should be responsible for the maintenance and funding of the register, for assuring its continuity, and for aspects of privacy related to it. The auspicing body should be accountable to the families to which the register relates and to their doctors.

The auspicing body should ensure that the records in the register are managed according to the safeguards and conventions that apply to medical records generally. It should ensure that information in the register is used in accordance with these guidelines as they relate to confidentiality and with guidelines published by National Health and Medical Research Council in relation to research.

While doctors should be responsible for the use of information in the register, they will be assisted by other trained staff. Like everyone else concerned with handling cancer genetic information, those who staff registers must understand that they have ethical and legal obligations related to confidentiality and privacy; they should formally acknowledge these obligations when they are first employed.

Only specified register staff should have contact with the public regarding material kept on the genetic register. However, other staff may come into contact with interested individuals, their relatives and health professionals. They may not be able to avoid involvement in clinical and social matters with families. Staff likely to be involved in such personal contacts should be trained in some of the skills required in genetic counselling.

### 2.10 Conclusion

There is evidently a great deal to be considered by people who find themselves involved in the unfolding process of genetic risk assessment, genetic testing, and the consequences of these things. These people will be best served by their having been acquainted early in the process with as many as possible of the broader implications and outcomes of their decisions. It is important that the professionals involved ensure that the complexity of it all does not swamp such people. Once the need for a decision about having a genetic test has been established, individuals must be able to focus on the potentials for benefit and harm to them of having such a test. This way they can chart their courses in the light of as full an understanding of their whole situation as is feasible. Professionals involved have to be aware of the continual need to strike a balance between these requirements.

All health professionals who come to possess information in the course of assessing risk in a family will perceive a duty to act in the interests of the
individuals to whom the information relates. At times, the interests, or the expressed wishes, of all the members of a family will not coincide. Health professionals should never be reluctant to seek independent advice in such circumstances, for example from an institutional ethics committee, bearing in mind that they need always to be prepared to justify their decisions.
CHAPTER 3
EDUCATIONAL ISSUES

Education is vital to every aspect of cancer genetics. Education of the public and of health professionals about developments in the field of cancer genetics should be a priority.

Educational strategies regarding familial aspects of cancer should be planned and piloted as soon as possible. However, promotional and educational campaigns need to be linked to the services available, in order to avoid promoting services which do not exist or which are not capable of handling the demand. It is important to ensure that promotional activities do not increase anxiety levels in members of the public. The fact that the great majority of cancers are not inherited should be emphasised.

Planning and piloting of educational strategies should be immediate so that the human and material resources are in place.

In devising educational material the principles to consider are:

- the information which is to be disseminated;
- the target groups which must be reached;
- the suggested educational strategies for each target group; and
- the continuing evaluation of these strategies.

As education is an integral part of familial cancer research and establishment of services, all submissions for funding should include provision for educational research, resources and personnel.

3.1 Provision of information for health care professionals

Health professionals for whom education in the area of cancer genetics is essential include general practitioners, surgeons, oncologists, genetic counsellors, clinical geneticists, women’s health nurses and cancer screening (e.g. breast) clinic staff. These professionals will increasingly be asked for advice about a client’s cancer risk. Specific guidelines covering risk estimation, strategies for prevention and surveillance and genetic testing need to be developed for specific types of cancer.

How these guidelines apply to an individual will depend on the person’s family history of cancer. Since such a history evolves continually it must be updated on
a regular basis. For example, the diagnosis or death from cancer in additional family members may mean that information provided previously about risk and surveillance strategies should change.

Familial cancer registers have a role in the coordination of care, surveillance and education for those who are at high risk of having an inherited predisposition to cancer. In addition, they may provide a database for research and a means for informing high-risk individuals of advances in research. Professional awareness of these registers is an important educational focus.

<table>
<thead>
<tr>
<th>Guidelines — information for health care professionals</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Guidelines should be developed for health care professionals on risk estimation, prevention strategies, surveillance and genetic testing for specific types of cancer.</td>
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</tr>
<tr>
<td>An individual’s family history of cancer should be regularly updated to ensure that information given to that person is appropriate.</td>
<td>—</td>
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<tr>
<td>Professional awareness of familial cancer registers should be a focus of educational initiatives.</td>
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### 3.2 Provision of information for the public

#### 3.2.1 Coordination

Any information disseminated on familial aspects of cancer must be credible, specific and consistent. Consistency will best be achieved by a coordinated national approach, involving site-specific peak bodies (such as the NHMRC National Breast Cancer Centre). Education of the public and health care professionals should be coordinated and, where possible, professional education should preceed that of the public.

Organisations such as the Australian Cancer Network should collate the material currently available, including educational resources, research data and information on knowledge and attitudes regarding familial aspects of cancer.

<table>
<thead>
<tr>
<th>Guidelines — coordination of education</th>
<th>Level of evidence</th>
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<tr>
<td>Education about familial cancer should be coordinated nationally.</td>
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<tr>
<td>Education of the public and professionals should be coordinated.</td>
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</tr>
<tr>
<td>Educational resources, research data and information on knowledge and attitudes to familial cancer should be collated.</td>
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3.2.2 Determining what is needed

In order to devise effective educational programs, research should be conducted among the public and health care professionals regarding:

- current levels of knowledge about familial aspects of cancer;
- levels of misunderstanding and misinformation; and
- attitudes to genetic testing and demand for such tests.

There should be liaison with curriculum developers and the Science Teachers Association in each state and territory to understand resource requirements for both health and science teachers.

<table>
<thead>
<tr>
<th>Guidelines — determining what is needed</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Research should be undertaken into public and professional knowledge, misconceptions and attitudes regarding familial cancer and genetic testing.</td>
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<tr>
<td>Resource requirements for teachers should be determined.</td>
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3.2.3 Strategies for disseminating information

There is a need for information on what is currently known about familial aspects of cancer and what services are available. Also all literature disseminated to professionals should be accompanied by consumer versions.

Information can be provided in many different ways including written material, public meetings, telephone information services, videos, audiotapes and the Internet. Published material should be written in plain English and in community languages (where appropriate), and should be linguistically and culturally sensitive. Use of creative educational aids can help to increase understanding.

Educational strategies need to address gaps in community knowledge and correct misconceptions about the heritability of cancer. For example, the public should be informed, regularly and repeatedly, that the great majority of cancers are not inherited, although an inherited predisposition to most types of cancers does exist. Any educational program should be conducted so that it does not increase anxiety levels in the public.

The national, regional and local media can be useful in education, although it is important to recognise their limitations. Spokespeople should be trained to use the media effectively, and strategies for the education of media workers should be developed.
Educational programs should be evaluated prospectively for effectiveness, acceptability and cost-effectiveness. The results of evaluations should be published so that a national approach is achieved using evaluated strategies with a proven outcome.

<table>
<thead>
<tr>
<th>Guidelines — strategies for education</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Information should be produced regarding current knowledge of familial cancers and services available.</td>
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<tr>
<td>Consumer versions should accompany all material developed for professionals.</td>
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</tr>
<tr>
<td>Information should address gaps in knowledge and misconceptions, and should not increase public anxiety.</td>
<td>—</td>
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<tr>
<td>Strategies should be developed for effective use of the media.</td>
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<tr>
<td>Educational programs should be evaluated.</td>
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### 3.2.4 Researching a family history

The public, and particularly those individuals who are concerned about a family history of cancer, or who themselves have cancer, should be encouraged and assisted to research their family health history (NSWGES 1996). Two groups for whom drawing up a family health history may be important are as follows.

- Individuals in whom the development of a cancer may be prevented if they know of their risk and act appropriately. This group, which is likely to be quite small, includes those at risk of developing a cancer which can be prevented, or a cancer which can be managed more effectively if it is detected early and with more intensive screening than is offered to the population as a whole.

- Individuals who are very anxious about their risk of inherited cancer and may be reassured that their risk of developing cancer is no more than the average. At this stage, the demand is very small, but it could be expected to grow with increasing media coverage.

Resources that have been evaluated, such as the Family Health Guide, should be provided to assist individuals wishing to research their family health history (NSWGES 1996). It is important to recognise the social and geographic barriers that may place limitations on many people in attempting such research.

People who are concerned about their risk of inherited cancer after researching their family health history should be encouraged to consult their medical adviser. Identification of individuals who are at risk of having an inherited cancer is important, particularly if the knowledge could lead to a reduction in
cancer mortality through prevention and/or the adoption of strategies for early diagnosis and treatment.

<table>
<thead>
<tr>
<th>Guidelines — researching family history</th>
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<td>The public, particularly those concerned about their family history of cancer, or who have cancer, should be encouraged and assisted to research their family health history.</td>
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<td>People concerned about their risk of inherited cancer after researching their family health history should be encouraged to consult their medical adviser.</td>
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CHAPTER 4

RESEARCH

The field of clinical cancer genetics, although in its infancy, holds the promise of making a major impact on cancer prevention and early detection by identifying specifically those individuals who are at high risk due to their genetic constitution. Research is urgently required at all levels to provide evidence on which to base rational counselling and clinical management of these individuals.

Australia presents unique challenges and opportunities in cancer genetics research. The population of 18 million, although geographically dispersed, is well documented for cancer incidence and racial origin and, in contrast to that of comparable nations, well educated and supportive of medical research. The relevant research community is relatively small and potentially cohesive.

The low frequency of major cancer gene mutations demands a nationally coordinated effort to ensure that worthwhile information is generated from planned studies. Australia cannot base major decisions and expenditures in clinical cancer genetics solely on data from other countries. For example, the incidence of breast cancer in the United States is approximately one-third higher than that of Australia, and the patterns of mutations in melanoma predisposition genes are quite different between the two countries.

4.1 Priority areas for research

Research is urgently needed in the following areas:

1. Determination of the frequency, type, penetrance and phenotype of mutations in cancer predisposition genes in the Australian population.

2. Analysis of the effect of modifier genes on cancer predisposition genes.

3. Determination of the relationship between modifiable environmental and lifestyle risk factors and the effect of mutations in cancer predisposition genes (such as the effects of exogenous oestrogens on the expression of BRCA1 and BRCA2 gene mutations).

4. Clarification of the psychological impact of genetic testing for cancer and determination of optimal modes of counselling for the multicultural Australian community.
5. Evaluation of client expectations and satisfaction with the familial cancer clinic.

6. Evaluation of whether genetic counselling/testing alters surveillance and lifestyle factors such that mortality and morbidity from cancer are reduced.

7. Technological improvements in the efficiency of molecular testing of cancer predisposition gene mutations.

8. Clinical trials of the efficacy and effectiveness of surveillance, screening and intervention strategies on high-risk groups, through which incidence, tumour characteristics, morbidity, mortality and cost-effectiveness can be established.

4.2 Principles for research

- Research in cancer genetics should be conducted according to the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999c).

- Research proposals should have appropriate multidisciplinary participation from relevant stakeholders.

- Research designed to clarify aspects of the relationship between the genetic, environmental and lifestyle causes of human cancer may best be conducted on a coordinated national level. This would provide the best prospects for a rapid and unequivocal outcome, help avoid duplication of effort, prevent wastage of scarce resources, and secure the privacy and cooperation of high-risk families.

- Individuals and families with cancer predisposition gene mutations in the Australian population might be registered, on a voluntary basis, allowing rapid analysis of distribution, phenotype and penetrance for the benefit of the health of all Australians. Registration must provide security against any breach of personal privacy or human rights. Molecular data entered on such registries should be generated by accredited cancer genetics laboratories. Any research proposals that may lead to the discovery in an individual of genetic mutations predisposing to cancer should take into account the implications for testing of presymptomatic at-risk family members, the manner in which this would be carried out and budgetary implications. Such testing should be conducted in an accredited diagnostic laboratory through accredited familial cancer services and should include provision for re-testing of presymptomatic individuals (and family members) who consent to diagnostic testing.
<table>
<thead>
<tr>
<th>Guidelines — research principles</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>The Australian Cancer Network should notify funding bodies of the special concerns and requirements relating to proposals in the field of cancer genetics, particularly the need for a coordinated national approach by investigators.</td>
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<tr>
<td>The Australian Cancer Network should initiate formation of national consortia for research into heritable cancers, such as the Kathleen Cuningham Foundation National Consortium for Research on Familial Breast Cancer (kConFab), recognising the particularly urgent need for evidence on which to base the rational surveillance and screening of carriers of mutations in cancer susceptibility genes.</td>
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<tr>
<td>National symposia should be initiated to ensure the rapid dissemination of advances in the technology of cancer gene mutation analysis.</td>
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<tr>
<td>Collaboration with international research groups may be important for the rarer familial cancers or for studies requiring large numbers of participants.</td>
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CHAPTER 5
LABORATORY STANDARDS

The standards of Australian diagnostic laboratories have been governed by accreditation procedures for many years. The procedures were initially developed for common diagnostic tests where the indication for the test, its interpretation and the appropriate clinical response to the test result were well defined. In this setting, the accreditation process concentrated on the performance of the specific assay rather than the other dimensions of the investigative process.

With the introduction of molecular genetic testing in cancer, there is a need for the highest standard of care in this evolving laboratory discipline. In contrast to the majority of other laboratory investigations, the indications for such studies, their interpretation and the appropriate clinical response to the test result are usually not well defined. In view of the novel nature of these investigations, the Australian Cancer Network has taken a relatively broad view of laboratory accreditation.

These guidelines define:

- the minimum activity level appropriate for a laboratory offering diagnostic molecular genetic tests in cancer;
- the minimum standard of training and experience for the person supervising such a laboratory;
- the continuing assessment and quality assurance procedures that are deemed necessary for such a laboratory;
- the minimum acceptable standards of laboratory processes and procedures;
- the liaison required between such a laboratory and the clinical service counselling people about familial aspects of cancer; and
- a process for the implementation, review, and regulation of these guidelines.

During the current evolutionary phase of molecular genetic testing in cancer, these tests will usually be performed in publicly funded laboratories in teaching hospitals. The choice of technique for these studies is likely to change over the next few years. For these reasons, the laboratory is the focus of these guidelines, rather than specific techniques. Once a consensus has been achieved regarding the choice of technique for analysis of a particular gene, it may be appropriate for such studies to be carried out in the private sector, provided they are linked
to appropriate counselling services. At that stage, the accreditation process would need to be modified to target specific investigations.

**Key points — purpose of guidelines**

These guidelines are designed to establish a minimum standard of care in relation to the identification of mutations that may be inherited and are associated with an increased susceptibility to cancer. Tests of people with cancer that are designed to indicate diagnosis, prognosis, or management are not considered here.

The assessment of specimen handling and safety issues is covered by the National Association of Testing Authorities (NATA), and is not addressed in these guidelines.

### 5.1 Accreditation

The Australian Cancer Network, Human Genetics Society of Australasia and Royal College of Pathologists of Australasia should distribute these guidelines to all laboratories currently involved in molecular genetic testing in cancer. Also these bodies should make a joint submission to the National Association of Testing Authorities (NATA) that compliance with these guidelines be a prerequisite for accreditation of a diagnostic molecular genetics laboratory offering tests related to familial cancer. The Australian Cancer Network should act as the host organisation for regular review of these guidelines in collaboration with the Human Genetics Society of Australasia, Royal Australasian College of Physicians, Royal Australasian College of Surgeons, Royal College of Pathologists of Australasia, and Clinical Oncology Society of Australia.

<table>
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<tr>
<th>Guideline — laboratory accreditation</th>
<th>Level of evidence</th>
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<tr>
<td>A submission should be made to NATA that compliance with these guidelines be a prerequisite for accreditation of a diagnostic molecular genetics laboratory offering tests related to familial cancer.</td>
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### 5.2 Minimum appropriate activity level

We do not know precisely who is carrying out what genetic tests in familial cancer, and with what resources, in Australia at present.
A survey of laboratories should be undertaken to determine what genes are being studied, the methods being used, and the personnel and expertise in cancer genetic testing available throughout Australia.

For the foreseeable future, none of the genetic tests in cancer will be routine, the research base for these studies will be limited, and the sample throughput will be small. It would be unwise to dilute this throughput and the associated experience among many laboratories. Minimum throughput criteria have been established for cytogenetics laboratories to ensure that a laboratory maintains the requisite skills (HGSA 1994). The benefits of centralisation versus development of local expertise and autonomy are difficult to resolve. Rapid advances and changes in methods of genetic analysis compound the situation.

When offering presymptomatic detection of an identified mutation, a laboratory should be able to issue a report within four weeks of the receipt of a sample. The staffing level in a laboratory should be determined by the sample throughput and the time required to issue a report.

In each State and Territory, the coordination of laboratories involved in research, development and clinical testing will be essential.

Once a method has been established in a laboratory, the laboratory should handle at least 20 DNA samples per year for each gene being analysed for mutations. This would include initial mutation identification in probands and presymptomatic screening in family members. Mutation detection in rare disorders (eg von Hippel–Lindau syndrome) should not be subject to this requirement.

### 5.3 Minimum standard of training and expertise

Because molecular genetics is a new and rapidly evolving discipline, its practitioners have a wide variety of training and expertise. At present, there are no guidelines in place regarding the necessary training and accreditation for individuals supervising molecular genetic studies. Such guidelines have been issued by the American College of Medical Genetics (Murphy et al 1992, ACMG 1994), and are being considered by the Human Genetics Society of Australasia and the Royal College of Pathologists of Australasia. The
commitment of these bodies to developing training and accreditation guidelines in molecular genetics is noted.

<table>
<thead>
<tr>
<th>Guidelines — experience and training</th>
<th>Level of evidence</th>
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<tr>
<td>The person supervising genetic testing should have appropriate training and expertise in clinical molecular genetics. In the current absence of an accreditation program, the laboratory supervisor should have a medical degree or PhD with the equivalent of at least three years’ full-time postgraduate experience in the application of human molecular genetics in clinical medicine.</td>
<td>—</td>
</tr>
<tr>
<td>The Human Genetics Society of Australasia and the Royal College of Pathologists of Australasia should ensure compatibility and (as appropriate) reciprocity between their training and accreditation programs.</td>
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5.4 **Continuing assessment and quality assurance procedures**

Genetic testing in cancer involves the use of novel and evolving techniques to provide information that may be the basis of major life decisions. There is clearly a need for a comprehensive quality assurance program.
Guideline — quality assurance

All laboratories should be involved in a relevant quality assurance program, which should be administered by a body representing the expertise of both the Royal College of Pathologists of Australasia and the Human Genetics Society of Australasia. An Australian quality assurance program should be developed which addresses the following issues:

- diseases and techniques;
- source and form of test samples (human genomic DNA, genomic DNA from cell lines, or PCR-amplified alleles);
- provision of samples;
- sample preparation;
- distribution of samples;
- collation and scoring of responses;
- frequency of quality assurance program;
- cost of the quality assurance program; and
- infrastructure for quality assurance program.

Where there is insufficient demand in Australia to warrant creating a quality assurance program for a specific gene, a laboratory should seek to join a quality assurance program established overseas. A register of quality assurance programs that may be suitable should be established by the Royal College of Pathologists of Australasia/ Human Genetics Society of Australasia.

5.5 Processes and procedures

5.5.1 Choice of technique

The sensitivity of each method of mutation detection varies and the choice of technique will be a compromise based on a number of factors. It could be argued that, in a service setting, the choice of technique should not be left to the laboratory, as there may be a financial temptation to use a cheap but less sensitive test. Within the next few years it may be necessary to specify which test is appropriate, or even approved, for the analysis of a specific gene.
<table>
<thead>
<tr>
<th>Guidelines — laboratory techniques</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Laboratories should be encouraged to use the most accurate method for identifying mutations in a specific gene. A mechanism for determining which methods are recommended for specific analyses should be established.</td>
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</tr>
<tr>
<td>If no specific mutation has been identified in a given family, the laboratory should be committed to retesting the DNA sample of an affected family member at a later date as relevant new techniques or information become available.</td>
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5.5.2 Control samples

It will be essential that each laboratory assess the sensitivity and specificity of its methods. The control samples would ideally be a resource shared between laboratories to reduce the time and cost involved for each laboratory and to ensure consistency between laboratories.

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<thead>
<tr>
<th>Guideline — registry of control DNA samples</th>
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<tbody>
<tr>
<td>A bank or registry of control DNA samples should be established as part of the quality assurance program.</td>
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</tbody>
</table>

5.5.3 DNA storage

Research and service laboratories may accumulate DNA samples from more than one member of the same family. Once a mutation (or lack of it) has been defined in a sample, some would argue that the sample can be discarded and freezer space conserved. The contrary view is that cancer is a disease in which a number of genes are involved, and there is always the possibility that analysis of another gene at some stage in the future may yield crucial information concerning the risk of cancer in the consultand. In the current developmental phase of genetic testing in cancer, all laboratories should retain DNA samples under the guidelines recommended by the Human Genetics Society of Australasia (HGSA 1996; Ad Hoc Committee on DNA Technology, American Society of Human Genetics 1988; Yates et al 1989).
5.5.4 Reporting of results

A report issued by a laboratory should include more than just the molecular data. The rapid development of information and methods in molecular genetics requires laboratories to have a major role in interpreting the molecular data for referring practitioners. The guidelines of the American College of Medical Genetics and those distributed by the Clinical Molecular Genetics Society in the United Kingdom (Mountford R, pers.comm.) include similar detailed requirements for reporting results. A report of test results should include a statement regarding the possibility of inaccuracy, for example due to nonpaternity or incorrect diagnosis (King et al 1993).

<table>
<thead>
<tr>
<th>Guideline — reporting of test results</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Each report should contain:</td>
<td>—</td>
</tr>
<tr>
<td>• collection date and identifying information;</td>
<td></td>
</tr>
<tr>
<td>• indication for testing;</td>
<td></td>
</tr>
<tr>
<td>• method used (including unpublished modifications);</td>
<td></td>
</tr>
<tr>
<td>• molecular data;</td>
<td></td>
</tr>
<tr>
<td>• interpretation of the raw data in clear and concise text which is appropriate for an accredited counsellor who is not a geneticist;</td>
<td></td>
</tr>
<tr>
<td>• details of further tests or information that may be required; and</td>
<td></td>
</tr>
<tr>
<td>• a statement regarding the possibility of inaccuracy due to nonpaternity, incorrect diagnosis etc.</td>
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</tbody>
</table>

5.6 Liaison between laboratories and counselling services

Cancer is common, and the public demand for cancer genetic testing will be high. There may be a temptation for a research or service laboratory (in the public or private sector) to perform genetic tests in familial cancer without
adequate evaluation or provision of appropriate pre- and post-test counselling. This is unacceptable.

Subject to appropriate legal and ethical guidelines, particularly in relation to confidentiality, a laboratory should be required to maintain close liaison with State/Territory cancer registries and other registers of individuals and families with a genetic predisposition to cancer.

<table>
<thead>
<tr>
<th>Guideline — liaison with counselling services</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular genetic tests in familial cancer should be performed only within the context of a comprehensive counselling and follow-up program. This precludes a private or public sector laboratory providing a stand-alone testing service, and should also preclude ‘mail order tests’ not associated with a counselling service. It does not preclude a private laboratory from developing a close affiliation with a comprehensive counselling program and performing these investigations. Any proposal to include genetic testing in cancer on the Medicare schedule should explicitly include this requirement for affiliation with a counselling service.</td>
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</tbody>
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PART 2

ISSUES RELATING TO SPECIFIC CANCERS
CHAPTER 6

BREAST CANCER

Breast cancer is the commonest cause of death from cancer in Australian women. Approximately one in 11 Australian women develop the disease before the age of 75 years. Between 1 and 5% of all breast cancer, and a higher proportion of early onset cases, is due to the autosomal dominant inheritance of highly penetrant mutations in one of a small number of cancer-related genes (see Table 6.1). Carriers of these mutations have a high lifetime risk, perhaps up to 80%, of developing breast cancer.

Table 6.1 Known genes responsible for hereditary breast cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Proportion of inherited breast cancer</th>
<th>Frequency of gene mutations in population</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>17q</td>
<td>~60%</td>
<td>~1/1000</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13q</td>
<td>~20%</td>
<td>~1/1000</td>
</tr>
<tr>
<td>Tp53</td>
<td>17p</td>
<td>&lt;1%</td>
<td>~1/10,000</td>
</tr>
</tbody>
</table>

Source: Easton (1993a)

BRCA1 is the best studied of the principal breast cancer-related genes. Of women with a mutated BRCA1 gene, clinical disease may develop in about 50% by age 50 and 80% by age 70, based on data from large extended breast cancer kindreds. The risk of ovarian cancer in carriers is thought to be up to 20% by age 50 and 60% by age 70 (Easton et al 1995). There is also limited evidence that carriers may have an increased risk of colon cancer and that male carriers may have an increased risk of prostate cancer (Ford et al 1994). However, there is considerable uncertainty in these estimates of risk, and they may need to be modified when population-based studies are published.

Genetic testing for mutations in BRCA1 and BRCA2 is available in most familial cancer services in Australia, but is expensive and difficult. Current mutation detection techniques identify 70% or more of the errors thought to be present in a gene.

A positive test result in an affected individual in a breast cancer family defines the causative mutation in the family. It also allows for subsequent predictive genetic testing for unaffected adult family members who may be at risk.

A negative test result does not rule out the presence of a disease-associated mutation, since mutations may be missed, or they may be present in other, as
yet unknown, genes. However if a mutation has already been found in the family, then a negative test result means that the individual involved does not carry the high-risk gene mutation.

Much remains to be learnt about the frequency and pattern of mutations in the Australian population, their penetrance and phenotype, and the effect on their expression of modifier genes and environmental risk factors. These questions are a major priority for Australian medical research.

Breast cancer due to constitutional mutations in Tp53 occurs in the Li-Fraumeni syndrome (Lynch et al 1994). There is a possibility that breast cancer may also be associated with constitutional mutations in the ATM (ataxia telangiectasia mutated) gene. Both are considered below.

### 6.1 Family history

The presence of a family history of breast cancer is an important and well-established risk factor for breast cancer, but it is important to recognise that this could be due to genetic and/or environmental factors shared by family members (Hopper and Carlin 1992).

Cohort studies (not influenced by recall bias) have shown that having a mother or sister with breast cancer increases a woman’s risk of breast cancer 1.5- to 2.0-fold (Colditz et al 1993, Sellers et al 1994). This increased risk is greater if, in an affected relative, the cancer occurred at a young age (such as before the age of 50 years) or was bilateral. The increased risk associated with having an affected second-degree relative is less, being 1.2- to 1.5-fold. Having a first-degree female relative with ovarian cancer increases a woman’s risk of breast cancer by 1.2- to 1.5-fold.

People’s knowledge of their family cancer history can often be inaccurate (Phillips et al 1991). The dynamic nature of events in families requires a system of regular pedigree updates. The family history should include both maternal and paternal sides of the family, as transmission through the male line should be considered. Familial cancer services can clarify risks by taking into account specific details of the family history, verifying diagnoses and maintaining periodic review of pedigrees.
### Guidelines — family history of breast cancer

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioners and other primary health care providers should take a family history, and update it regularly. Taking a family history involves asking about any cancer in all first- and second-degree relatives, male or female, on both the maternal and paternal sides of the family. Attempts should be made to verify all reports of all cancers. The Family Health Tree Guide(^2) may assist in completing a family history chart.</td>
<td>—</td>
</tr>
<tr>
<td>General practitioners and other health professionals who are unsure about the appropriate management associated with an individual’s family history should seek advice from a familial cancer service(^3).</td>
<td>—</td>
</tr>
<tr>
<td>General practitioners and other health care professionals should consider for referral individuals and families they consider to be at high risk of familial cancer.</td>
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</table>

### 6.2 Predicting risk based on family history

The estimation of risk of breast cancer based on analysis of family history by use of existing data (obtained largely from United States studies) requires modification in the Australian setting.

There are published tables available for estimating risk of breast cancer, based on the current age and family history of the subject, including the age of onset of cancer in relatives of particular types (such as mother and/or sister/s). These are typically based on data collected in the United States (Claus et al 1994, Gail et al 1989).

The underlying lifetime risk of breast cancer, however, is about one-third higher in white women living in the United States than in Australia (McCredie et al 1995). In other words, the average risk for Australian women is about 75% that of United States women. Furthermore, past case-control studies, which relied on self-reporting of family history without validation, may have over-estimated the increased risk due to having affected relatives.

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\(2\) NSWGES (1996), available from NSW Genetics Education Program (see Appendix D).

\(3\) A list of familial cancer services is available from the NHMRC National Breast Cancer Centre (see Appendix D).
Breast cancer is common, and by chance alone there will be many families with two or more cases of breast cancer. In Australia, the cumulative risk of breast cancer is about 9% (1 in 11) by age 75 years (AIHW and AACR 1998; Kricker and Jelfs 1996). Therefore, if a woman has five female relatives who have lived to at least 75 years, by chance alone the probability that at least one of these will have had breast cancer is 37%.

Highly penetrant, dominantly inherited genetic alterations, such as those seen in BRCA1 and BRCA2, probably account for only a small proportion of breast cancer (less than 5%), and hence for a small proportion of families in which breast cancer cases cluster. Family history is not a well-defined term, and cannot be used alone to unambiguously identify families in which high-risk genetic mutations are causing cancers.

Segregation analyses, which provide only weak evidence, predict that 1–5% of breast cancer could be attributed to an autosomal dominant, highly penetrant gene mutation. This proportion is likely to be higher in women under the age of 40 years. These estimates are not precise because they rely on assumptions and mathematical models applied to data in which genetic testing has not been applied (Claus et al 1990). Until all breast cancer-related genes are cloned and studied in population-based samples, this proportion will not be known with certainty. It may also vary from population to population, so local data is required to assess the impact of genetic factors on breast cancer in the Australian community.

**Key point — breast cancer risk based on family history**

Australian women should be informed that a family history for breast cancer does not necessarily imply the presence in their family of an inherited genetic alteration that predisposes to breast cancer. Because such mutations are rare, yet breast cancer is a common disease, chance alone will account for many families having two or more members affected by breast cancer.
6.3 Genes associated with breast cancer

Constitutional, or germline, mutations in specific genes are associated with a high risk of breast cancer in carriers. This risk may be up to 80% by the age of 75 years in the approximately 1 in 500 to 1 in 1000 women who carry such a mutation. Some mutations, such as 185delAG and 5382insC in BRCA1, as well as 6174delT in BRCA2, are each carried by about 1% of individuals of Ashkenazi Jewish descent (Struwing et al 1997).

Female carriers of mutations in BRCA1 also have an increased risk of ovarian cancer. Affected women who carry certain constitutional mutations in this gene have a high risk of developing a second primary breast or ovarian cancer.

Male and female carriers of mutations in BRCA2 are at a substantially increased risk of breast cancer. Female carriers may also have an increased risk of ovarian cancer.

The Li–Fraumeni syndrome is a rare, dominantly inherited condition, characterised by paediatric bone or soft tissue sarcoma, early onset breast cancer, and other tumours (such as brain, leukaemia, lung, larynx and adrenal). A germline mutation in the Tp53 gene has been identified in more than half the families with this syndrome (Malkin et al 1990).

Mutation carriers in the Tp53 gene are at high risk of soft tissue sarcomas while young and have an increased risk of breast cancer at a young adult age (Malkin et al 1990). About 1 in 10,000 women have inherited a defective copy of the Tp53 gene.

The 0.5–1% of women who have inherited one mutated copy of the gene for the recessive childhood condition ataxia telangiectasia (ATM) (Savitsky et al 1995) may be at a three-fold or greater increased risk of breast cancer (Athma et al 1996), although this is the subject of controversy (FitzGerald et al 1997).

Finally, there may be other genes, as yet undiscovered, which are associated with an increased risk of cancer.

In total, germline mutations in high-risk genes may be the direct cause of about 1–5% of all breast cancer, and perhaps a higher proportion of early onset breast cancer.

Mutations in BRCA1 (Miki et al 1994) and BRCA2 (Wooster et al 1995) have been detected in the large extended kindreds studied as part of the International Breast Cancer Linkage Consortium, mostly in those families which contain four or more affected relatives (Easton et al 1993a). The vast majority of breast cancer-dense families in which there was also one or more relative with ovarian cancer were linked to BRCA1 (Easton et al 1993a). Breast cancer-dense families
in which there was also male breast cancer have been linked to BRCA2 (Wooster et al 1995). In population-based studies, some women with breast cancer, but without a relevant family history, have also been found to carry germline BRCA1 or BRCA2 mutations (Langston et al 1996).

The age-specific risks for carriers of deleterious mutations in BRCA1 and BRCA2 have generally been estimated from linkage data, and are not precise, having large confidence intervals (Ford et al 1994, Easton et al 1993a). These estimates could be too high, as the families studied are likely to be those in which the most highly penetrant mutations are being inherited (Ford et al 1998). Information on the risk of breast cancer associated with ATM is also based on indirect methods (Athma et al 1996). All estimates of the proportion of women with a mutated copy of these genes are approximate (Easton et al 1993b, Ford et al 1995a).

Key points — genetic predisposition to breast cancer

Although some genes have been discovered that, when inherited in an altered form, confer a high lifetime risk of breast cancer, only between 1 in 500 and 1 in 1000 women have a high risk due to having inherited a mutation in one of these genes. In women of Ashkenazi Jewish descent, however, up to 1 in 50 may have inherited a high-risk mutation.

Knowledge about genetic predisposition is preliminary. Precise and accurate risk estimates for mutation carriers are not yet established. There may be other as yet undiscovered genes which confer an increased risk of breast cancer, but there is still much uncertainty in this area and further research is required to clarify these issues.

6.4 Testing of genes associated with breast cancer

Although it is now technically possible to detect constitutional alterations in breast cancer-associated genes, genetic testing requires specialised laboratory techniques and is expensive and time consuming, especially if it aims to cover all possible genetic mutations. Currently, only a few Australian laboratories can conduct this specialised testing, and 100% mutation detection is not yet available. Genetic testing should only be offered with pre- and post-test counselling, conducted in conjunction with a specialist genetics service for breast cancer.

More than 100 different genetic alterations are known, and for some of these alterations, the effect on risk of breast cancer is unknown. Because there are several genes associated with breast cancer, testing for alterations in one gene alone is not sufficient.
Familial cancer services make use of tables which allow estimates to be made of those women who are most likely to have mutations, based on the family history of breast cancer (Ford et al 1995a). The process of genetic testing for a family usually begins with the analysis of breast cancer genes of an affected individual.

Detection of a genetic alteration in an affected person is technically difficult, but if a mutation is found, it may have major implications for that person. It also allows for further (usually simple) genetic testing of adult, unaffected relatives. Family members found not to carry that mutation may be reassured that they are at the population risk, and cannot pass the mutation to their children. They can avoid unnecessary screening. Family members found to carry the particular mutation can be advised regarding methods of prevention and early detection.

Failure to detect a genetic alteration in an affected person does not automatically imply a low or reduced risk of developing breast cancer for their relatives.

<table>
<thead>
<tr>
<th>Guideline — genetic testing for breast cancer</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing should only be offered with pre- and post-test counselling, conducted in conjunction with a specialist genetics service for breast cancer. Individuals undergoing testing should be made aware of the limitations of genetic tests for breast cancer.</td>
<td>—</td>
</tr>
</tbody>
</table>

**Key points — genetic testing for breast cancer**

- **There are limitations to genetic testing.** Although it is now possible to conduct some genetic tests, there is no single or simple genetic test for breast cancer.

- **Genetic testing is under development.** Genetic testing for breast cancer genes is difficult and is still in a stage of research and development.

- **Negative genetic tests require informed interpretation.** Failure to detect a genetic alteration does not automatically imply a low or reduced risk of developing breast cancer. Negative genetic tests are meaningful only when the genetic alteration in the family is already known and an individual family member is found not to carry that specific high-risk alteration in her or his constitutional DNA.

- **Genetic testing may be of assistance in highly selected families.** When a particular mutation has been detected in an affected family member, the testing of relatives for the presence or absence of that mutation is technically straightforward.
6.5 Categorisation of risk based on family history

For the purposes of advising women about their risk of breast cancer based on family history, it is useful to divide Australian women into three broad categories. One group comprises women with no family history, or a weak family history. These women are at average or slightly above average risk. Another group is women with a very strong family history of breast cancer, which suggests that there may be a cancer predisposing gene mutation present in the family. If this is the case, on average, half the female members will be at high risk. Between these two extremes is a group comprised of women at a moderately increased risk.

6.5.1 Women at or slightly above average risk

The great majority of women do not have a family history of breast cancer. Of those women who do have a family history, the majority have only one affected relative who was either affected at a late age, or was not a first-degree relative. Their lifetime risk (to age 75) of developing breast cancer is between 9 and 12%, compared to the population average of about 9%. These two groups of women are either at or slightly above average risk, and constitute at least 95% of the population. This estimate is based on limited Australian data, and should be updated when more information is available.

<table>
<thead>
<tr>
<th>Key points — average/ slightly increased breast cancer risk</th>
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</thead>
<tbody>
<tr>
<td>The following women should be advised that they are either at average or slightly above average risk of breast cancer. This group covers about 95% of the population, and consists of women with either:</td>
</tr>
<tr>
<td>• no confirmed family history of breast cancer; or</td>
</tr>
<tr>
<td>• one first-degree relative diagnosed with breast cancer at age 50 or older; or</td>
</tr>
<tr>
<td>• one second-degree relative diagnosed with breast cancer at any age; or</td>
</tr>
<tr>
<td>• two first- or second-degree relatives diagnosed with breast cancer, at age 50 or older, but on different sides of the family.</td>
</tr>
<tr>
<td>Women in this group should be reassured that their chances of not developing breast cancer are greater than 90%. They should, however, be made aware of the current best practice for the early detection of breast cancer.</td>
</tr>
</tbody>
</table>
### Guidelines — management (average/ slightly increased breast cancer risk)

| The initial step in the management of women at average or slightly above average risk of breast cancer must be to exclude malignancy by physical examination. Thereafter, early detection should be emphasised. | — |
| — | — |
| A woman who is considered on the basis of family history to be at average or slightly above average risk of breast cancer should be advised to: | — |
| • maintain breast awareness (Miller 1997); | — |
| • visit her general practitioner promptly if she notices any breast changes; and | — |
| • attend for mammographic screening every second year from the age of 50 years (Kerlikowske et al 1995). | I |

### 6.5.2 Women at a moderately increased risk

For a small proportion of women, perhaps fewer than 4% of the population, the number of affected relatives, their ages at diagnosis, and the types of cancers sustained in the family suggest a lifetime risk of cancer between 12 and 25%. There is a small chance that within these families there are dominantly inherited genetic alterations conferring a high risk of breast cancer. There may be inherited genetic alterations associated with a moderate risk. These women should be considered to be at a moderately increased risk.

#### Key points — moderate risk of breast cancer

Fewer than 4% of women are at a moderately increased risk (12–25% lifetime risk). This group includes women with:

- one or two first-degree relatives diagnosed with breast cancer before the age of 50 (without the additional features of the potentially high-risk group described below); or
- two first- or second-degree relatives on the same side of the family, diagnosed with breast or ovarian cancer (without the additional features of women at potentially high risk described below).

Women in this group should be advised that their chances of not developing breast cancer are 75 to 90%.
### Guidelines — management (moderate risk of breast cancer)

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>The initial step in the management of a woman at moderately increased risk must be to exclude malignancy by physical examination. Thereafter, early detection should be emphasised. Women in this group should be advised to:</td>
<td>—</td>
</tr>
<tr>
<td>• maintain breast awareness (Miller 1997);</td>
<td>—</td>
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<tr>
<td>• at the very least, attend for second yearly mammographic screening from the age of 50 years — additional surveillance, such as mammogram from a younger age or more frequently, should be considered on an individual basis, as evidence about optimal strategies in this group does not currently exist (Kerlikowske et al 1995); and</td>
<td>I</td>
</tr>
<tr>
<td>• visit her general practitioner promptly with any breast changes.</td>
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</table>

These women may also be advised to attend annually for clinical breast examination from the age of 40 years.

Women in this category may need more precise risk assessment. If this is the case, it is recommended that the treating doctor consult specialist cancer or genetic services for advice and formulate an appropriate counselling and management plan (see Appendix D).

Possible participation in a relevant approved clinical trial for the prevention of breast cancer should be discussed. The tamoxifen chemoprevention trial for women who have an increased risk of developing breast cancer is ongoing in Australia through the Australian and New Zealand Breast Cancer Trials Group (see Appendix D) (Fisher et al 1998).

### 6.5.3 Women at a potentially high risk

For a very small proportion of women, the number of affected blood relatives, their ages at diagnosis, and the types of cancers suggest that it is more likely than not that there is a dominantly-inherited gene mutation associated with a high risk of cancer running in their family.

The lifetime risk of breast cancer for a woman chosen at random from these families is between 25 and 50%. It may be as high as 80% if she has inherited a high-risk mutation, or it may be as low as 9% if she has not. Overall, less than 1% of the population are at potentially high risk because of their family history.
# Key points — high risk of breast cancer

The following women should be advised that they have a potentially high risk of developing breast cancer, and perhaps other cancers. This group covers less than 1% of the population, and consists of women who have:

- breast or ovarian cancer diagnosed in three or more first- or second-degree relatives on the same side of the family; or

- two or more first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, plus one or more of the following features (on the same side of the family)
  - bilaterality
  - onset of breast cancer before the age of 40
  - onset of ovarian cancer before the age of 50
  - breast and ovarian cancer in one individual
  - Jewish ancestry
  - breast cancer in a male relative; or

- one first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 or younger; or

- a demonstrated germline mutation in a high-risk breast cancer-associated gene such as BRCA1, BRCA2 or TP53 by genetic testing.

Women in this group should be advised that although potentially at high risk, the majority of women in this group will not get breast cancer.

There is a paucity of data on which to base the management of women at a potentially high risk, so precise protocols remain controversial. The following evidence is used as a basis for best practice.

## Breast self-examination

The increased risk of early onset breast cancer, and anecdotal reports of the failure of mammography to detect breast cancer in carriers of BRCA1 mutations, may make breast self-examination, or maintaining ‘breast awareness’, of greater value in high-risk women than in women of average risk (Evans et al 1992).

## Clinical breast examination

Clinical breast examination can detect breast cancers that are palpable. It can detect some cancers that are not detectable by mammography, or may detect interval cancers between regular mammographic screenings. There has been no randomised controlled trial examining the effect of clinical breast examination alone on breast cancer mortality, though evidence from North American studies supports the value of including clinical breast examination as a component of breast screening programs (Clarke et al 1998). In the Breast Cancer Detection
Demonstration Project, 6.2% of tumours were detected by clinical examination alone (NCI and ACS 1979). Clinical breast examination may be an important adjunct in screening for breast cancer in young, high-risk women for whom there is some doubt about the sensitivity of mammography.

**Mammographic screening**
The efficacy of mammographic screening in young, potentially high-risk women remains controversial. One study in women aged 40–49 gave a positive predictive value\(^4\) of 0.13 (95% CI 0.05–0.21) for women with a positive family history of breast cancer, compared with 0.04 (95% CI 0.02–0.06) for women without a family history of breast cancer (Kerlikowske et al 1993). Anecdotal reports document both success and failure of mammography to detect breast cancer in carriers of BRCA1 mutations (Evans et al 1992).

No data are available on radiation risk in carriers of BRCA1 or BRCA2 mutations. Increased risk could theoretically result from radiation sensitivity, particularly in ATM and Tp53 heterozygotes, or from the cumulative effect of imaging. Magnetic resonance imaging for breast cancer screening for Tp53 heterozygotes is currently under investigation.

**Prophylactic mastectomy and oophorectomy**
Women found to carry a mutation in BRCA1 or BRCA2 are at increased risk of both breast and ovarian cancer. Statistical models estimate that 30-year-old women who carry BRCA1 or BRCA2 mutations may gain three to five years of life expectancy from prophylactic mastectomy and from 0.5 to 1.5 years of life expectancy from prophylactic oophorectomy, depending on their cumulative risk of cancer. Gains in life expectancy decline with age at the time of prophylactic surgery and are minimal for 60-year-old women. Among 30-year-old women, this model predicts that oophorectomy may be delayed 10 years with little reduction in life expectancy (Schrag et al 1997), and it is usually offered after the age of 35 or when child bearing is complete.

Breast cancer has been reported after prophylactic simple mastectomy (Mies 1993), usually of the subcutaneous form (Pennisi and Capozzi 1989). Breast tissue may be present in the axilla and abdominal wall (Goldman and Goldwyn 1973). Surgery does not obliterate the risk of breast cancer, nor reduce the need for careful, ongoing surveillance, but a recent retrospective study has suggested that prophylactic mastectomy reduces significantly the risk of breast cancer in women with a strong family history (Hartmann et al 1999). Prophylactic oophorectomy in premenopausal women may reduce the risk of breast cancer (Streuwing et al 1995).

\(^4\) positive predictive value (PPV) = number of cancers detected per abnormal examination.
Almost no data exist on the effect of prophylactic mastectomy on anxiety in high-risk women. In a small series of women undergoing prophylactic mastectomy, performed in the context of an experienced familial cancer service with an appropriately intense counselling program, more than 70% were satisfied with their decision in follow-up surveys (Stefanek 1995, Stefanek et al 1995).

Primary peritoneal carcinoma may occur despite prophylactic oophorectomy (Tobacman et al 1982), with the rates of such malignancies in two studies being 11% (Nguyen et al 1994) and 2% (Piver et al 1993). Together, these reports nonetheless suggest a protective effect of prophylactic oophorectomy, although this evidence is not statistically significant (Strewing et al 1995). In premenopausal women prophylactic oophorectomy may reduce the risk of breast cancer (Strewing et al 1995). Following prophylactic oophorectomy, indefinite follow-up using annual CA125 measurement is appropriate. For further information, see Chapter 8.

**Screening for ovarian cancer**

Screening strategies using CA125 level and ultrasound can detect ovarian cancer preclinically. Screening for ovarian cancer has not been shown to reduce mortality in unselected patients. The optimum frequency of screening is also unclear (NIH Consensus Development Panel on Ovarian Cancer 1995). When used alone, CA125 measurement lacks both sensitivity and specificity. In premenopausal women, specificity is only 94.5% (Einhorn et al 1992).

Transvaginal ultrasound enables assessment of ovarian size and morphology. Ovarian enlargement and solid and cystic morphology may raise the index of suspicion for neoplasia.

Ovarian tumours are characterised by a lower than average impedance to blood flow, which may be detected by colour flow Doppler. The sensitivity and specificity of the technique has been reported as 96.4 and 99.8% respectively (Jacobs et al 1993). The addition of transvaginal ultrasound to CA125 measurement increases specificity to close to 100%, and gives a positive predictive value of 27% (Einhorn et al 1992, Kramer et al 1993). For further information, see Chapter 8.

**Oral contraceptive use and hormone replacement therapy**

A recent meta-analysis showed a 20% increase in risk of breast cancer for all women while taking, or within 10 years of ceasing to take, oral contraceptives (CGHFBC 1996). After cessation, that risk abated over the next decade. There is no evidence from this large study that the effect of taking oral contraceptives is any different in women with a family history of breast cancer, although women at very high risk, such as those carrying BRCA1 or BRCA2 mutations have not yet been studied adequately. Similarly, in users of hormone replacement therapy, the relative risk of having breast cancer diagnosed
increased by 2.3% for each year of use. Although the risk of having breast
cancer diagnosed is increased in women using hormone replacement therapy,
and increases with increasing duration of use, the effect largely disappears about
five years after cessation of therapy (CGHFBC 1997).

Cohort and cross-sectional studies have suggested that oral contraceptives are
protective against ovarian cancer (Lee et al 1987), and there is now some
evidence from a case-control study that use of the oral contraceptive pill may
reduce risk of ovarian cancer in women with a pathogenic mutation in either
BRCA1 or BRCA2 (Narod et al 1998).

The possible increased risk of breast cancer associated with use of hormone
replacement therapy in women without a family history of breast cancer appears
to be outweighed, in terms of mortality and morbidity on a population basis, by
beneficial effects on cardiovascular disease and osteoporosis (Evans et al 1992).

The effects of hormone replacement therapy on breast cancer risk for women
at a potentially high genetic risk are not known, so advice concerning the use of
hormone replacement therapy needs to be individualised.

**Screening for colorectal cancer in individuals with mutations in BRCA1 and
BRCA2**

There is no reliable evidence that men or women carrying mutations in the
BRCA1 gene are at increased risk of colorectal cancer (Ford et al 1994). A
program of annual faecal occult blood testing directed at middle-aged and
elderly people in the general population reduces mortality from colorectal
Guidelines — management (high risk of breast cancer)

For women at a potentially high risk whose DNA status is unknown, the initial step must be to exclude malignancy by physical examination. Thereafter, early detection should be emphasised. Women in this group should be advised to:

- maintain breast awareness (Miller 1997);
- attend for 6 to 12 monthly clinical breast examination (Clarke et al 1998);
- report to her general practitioner promptly with any breast changes;
- attend for annual mammographic screening (and possibly ultrasound) commencing at age 40, and consider starting five years earlier than the age at diagnosis of the youngest breast cancer case in the family, whichever is earlier (Kerlikowske et al 1995; Burke et al 1997a);
- attend a cancer specialist for further advice about surveillance, screening and management of breast and ovarian cancers;
- attend a familial cancer service for specialist genetic services, advice and counselling; if they wish to clarify the genetic risk for themselves or family members; and
- discuss possible participation in relevant approved clinical trials for the prevention of breast cancer such as the International Breast Cancer Intervention Study tamoxifen prevention trial (Fisher et al 1998).\(^5\)

Consideration should also be given to screening for ovarian cancer (see Chapter 8).

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\(^5\) For a list of specialist genetics services for breast cancer, contact the NHMRC National Breast Cancer Centre (see Appendix D).

\(^6\) Contact the Australian and New Zealand Breast Cancer Trials Group (see Appendix D).
For women shown by genetic testing to carry a high-risk mutation, in addition to the above, consideration should be given to advising women:

- to attend for annual transvaginal pelvic ultrasonography, preferably with colour Doppler measurements, commencing at age 25 to 30, or at least five years earlier than the age at diagnosis of the youngest ovarian cancer case in the family, whichever is earlier. Annual CA125 may be appropriate as an additional screening test after the menopause;
- that prudence suggests it would be wise to avoid high alcohol intake, to avoid long-term use (more than 10 years) of oral contraceptives, and to avoid long-term use of hormone replacement therapy unless there are severe menopausal symptoms, or a personal or family history of cardiovascular disease or osteoporosis; and
- that prophylactic surgery (such as total bilateral mastectomy or oophorectomy) may be an option in some highly selected individuals, but only after extensive counselling (Burke et al 1997a).

<table>
<thead>
<tr>
<th>Guidelines — management (high risk of breast cancer) (contd)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>For women shown by genetic testing to carry a high-risk mutation, in addition to the above, consideration should be given to advising women:</td>
<td>—</td>
</tr>
</tbody>
</table>

### 6.5.4 Women at high risk who have already had breast cancer

Some women who have already been diagnosed with breast cancer may be identified as belonging to a family potentially carrying a high-risk genetic alteration. Affected women in families with high-risk features need special management. For women known or strongly suspected of carrying a high-risk mutation, the risk of contralateral breast cancer approached 60%, and the risk of ovarian cancer was also increased in a study by Ford et al (1994).
Where DNA status is unknown, women at high risk who have already had breast cancer should be advised:

- to continue regular clinical surveillance as determined by the cancer specialist;
- to maintain breast awareness;
- to report to her general practitioner or cancer specialist promptly with any breast changes;
- to attend for annual mammographic screening (and possibly ultrasonography);
- that if they wish to clarify the genetic risk for themselves or their family, they should attend a familial cancer service for specialist genetic services, advice and counselling;
- to attend for annual transvaginal pelvic ultrasonography, preferably with colour Doppler, commencing at age 25 to 30, or at least five years earlier than the age at diagnosis of the youngest affected case of cancer in the family, whichever is earlier. Annual CA125 measurement may be appropriate as an additional screening test after the menopause; and
- that the degree of surveillance for ovarian cancer may be reduced by laparoscopic oophorectomy, which may also offer a survival benefit as adjuvant therapy for stage II breast cancer. Following oophorectomy, indefinite follow-up using annual CA125 measurement is appropriate.

Women shown by genetic testing to carry a high-risk mutation should be advised according to the guideline for management of women at high risk of breast cancer.

<table>
<thead>
<tr>
<th>Guidelines — management (history of breast cancer)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where DNA status is unknown, women at high risk who have already had breast cancer should be advised:</td>
<td>—</td>
</tr>
<tr>
<td>• to continue regular clinical surveillance as determined by the cancer specialist;</td>
<td></td>
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<tr>
<td>• to maintain breast awareness;</td>
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<tr>
<td>• to report to her general practitioner or cancer specialist promptly with any breast changes;</td>
<td></td>
</tr>
<tr>
<td>• to attend for annual mammographic screening (and possibly ultrasonography);</td>
<td></td>
</tr>
<tr>
<td>• that if they wish to clarify the genetic risk for themselves or their family, they should attend a familial cancer service for specialist genetic services, advice and counselling;</td>
<td></td>
</tr>
<tr>
<td>• to attend for annual transvaginal pelvic ultrasonography, preferably with colour Doppler, commencing at age 25 to 30, or at least five years earlier than the age at diagnosis of the youngest affected case of cancer in the family, whichever is earlier. Annual CA125 measurement may be appropriate as an additional screening test after the menopause; and</td>
<td>I</td>
</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>

### 6.6 Updating information and maintaining best practice among health professionals

The state of knowledge and the technology as it applies to genetic and familial aspects of breast cancer are rapidly changing. Therefore, general practitioners and other professional carers of women will not necessarily be properly informed about current knowledge and best practice, and need to be continually educated and updated.

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7 For a list of specialist genetics services for breast cancer currently operating, contact the NHMRC National Breast Cancer Centre (see Appendix D).
6.7 Collection of relevant Australian data

There is a paucity of data on Australian women which address issues such as risk due to different levels of family history, the proportion of Australian women with different levels of family history, the number actively seeking advice from professionals, and the level of understanding and knowledge about genetic and familial issues.

Some relevant data have been collected in a population-based survey being conducted by the NHMRC National Breast Cancer Centre. Support from NHMRC and other funding organisations in collecting population-based and other information should be encouraged. Further information is being obtained from epidemiological research studies being conducted in Australia.

6.8 Links with research

Genetic counselling and genetic testing are expensive, and need to be linked with scientific research. Moves to rationalise genetic testing within Australia, conducted in conjunction with genetic counselling, have commenced through the Kathleen Cuningham Foundation National Consortium for Research on Familial Breast Cancer (kConFab).

A network of breast cancer family clinics linked with genetic testing laboratories and nationally coordinated research groups should be established and supported.
6.9 National database of breast cancer families

A register of high-risk families can be used to assist in the clinical management and prevention of cancer, and to facilitate scientific research. Australian families at high risk of breast cancer may contain members from several states and territories, and there may be families linked with one another, suggesting that a national database may eventually be useful.

In order to facilitate the work of kConFab, and to facilitate clinical management of genetically high-risk families, consideration may eventually be given to establishing a national database, with common software and database management for breast cancer family clinics.

<table>
<thead>
<tr>
<th>Guideline — national database of breast cancer families</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A national database of families at high risk of breast cancer may be established to facilitate clinical treatment, counselling and research. The database could be based on a common protocol for collecting genetic and epidemiological information, and maintained in accordance with the NHMRC Guidelines for Genetic Registers and Associated Genetic Material (NHMRC 1999b) and Section 14 (Epidemiological Research) in the National Statement on Ethical Conduct in Research Involving Humans (NHMRC 1999c).</td>
<td>—</td>
</tr>
</tbody>
</table>

6.10 Breast cancer family clinics and genetic testing facilities

Few family cancer clinics are established in Australia, and currently these are restricted to major cities and are under-resourced. Only minimal testing facilities are in place, and comprehensive testing of high-risk breast cancer-related genes is not available on a service basis.

Mutation screening and tests for protein truncating mutations are being performed in a few laboratories across the country. These activities, however, are in an early stage of development and are currently funded mainly through research grants only.

Given that in the order of 100,000 women in Australia may belong to the ‘moderately increased risk’ category, and 10,000 to the ‘potentially at high risk’ category, clearly there are not yet sufficient resources to cope with anything but a small proportion. Broad public announcements encouraging women to attend these clinics are likely to result in clinics being unable to handle the demand, given that currently they are heavily booked. The impact on demand at local breast cancer family clinic(s) from the distribution of information about familial
aspects of breast cancer to general practitioners is being monitored by the NHMRC National Breast Cancer Centre.

<table>
<thead>
<tr>
<th>Guideline — appropriate facilities</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health professionals and cancer organisations should not promote family cancer clinics or genetic testing until appropriate facilities are established.</td>
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</tr>
</tbody>
</table>

**Key point — seeking medical advice**

People in all breast cancer risk categories should be encouraged to seek medical advice promptly if they develop breast symptoms or signs. In families where breast cancer is common, family members should be encouraged to seek advice promptly if they develop symptoms or signs, which could be related to any cancers.
CHAPTER 7

COLORECTAL CANCER

Colorectal cancer is the second most common cause of cancer death in Australia. The lifetime risk to age 74 is 1 in 18 for men and 1 in 23 for women (Giles et al 1996). There are almost 10,000 new cases and 4500 deaths from the disease each year (Jelfs et al 1994). Studies have shown that 15–20% of people with colorectal cancer have a first-degree relative affected by the disease (St John et al 1993, Winawer et al 1997).

7.1 Genes associated with colorectal cancer

The three main clinical entities with proved or suspected hereditary predisposition to colorectal (or bowel) cancer are:

- familial adenomatous polyposis (FAP);
- hereditary nonpolyposis colorectal cancer (HNPCC); and
- familial clustering of the common form of colorectal cancer.

Although FAP and HNPCC are relatively uncommon, the two syndromes have special significance because of their major contribution to colorectal cancer diagnosed before 50 years of age.

7.1.1 Familial adenomatous polyposis

FAP is characterised by the early onset of multiple (>100) adenomatous colorectal polyps. These generally appear in the teenage years and, if left untreated, inevitably progress to carcinoma and early death (Rhodes and Bradburn 1992).

FAP accounts for less than 1% of all colorectal cancer. Recent estimates from several international registers indicate a figure of around 0.2%, the low figure being attributed to improved management of FAP families and prevention of colorectal cancer through prophylactic colectomy. The incidence without such intensive surveillance may be higher. Based on these data there are likely to be more than 2000 affected or at-risk members of FAP families in Australia (Järvinen 1992).

Traditional management strategies have involved regular sigmoidoscopic examination of at-risk family members, with prophylactic colectomy recommended when polyps appear (Rhodes and Bradburn 1992). Although this approach has significantly reduced colorectal cancer mortality in FAP (Järvinen...
1992), compliance with sigmoidoscopic screening has been imperfect and potentially preventable cancer deaths continue to occur.

A mutation of the adenomatous polyposis coli (APC) gene is responsible for the great majority of cases of FAP (see Appendix C). The cloning of this gene (Groden et al 1991, Kinzler et al 1991) now permits the identification of gene mutation carriers before they develop clinical features or symptoms. Family members who do not have the mutated copy of the gene can be reassured, and need not undergo sigmoidoscopic surveillance (Lynch and Lynch 1995).

Improved surveillance compliance among those shown to carry the mutated gene would be expected from confirmation of their carrier status.

APC is a large gene spanning 15 exons (Groden et al 1991, Kinzler et al 1991). Mutations in different families are scattered throughout the gene. Fortunately, most mutations produce a premature stop codon resulting in an abnormally shortened protein product. Such mutations can be readily identified in the laboratory using a protein truncation test (Powell et al 1993, van der Luijt et al 1994). FAP, therefore, is usually amenable to molecular genetic diagnosis.

7.1.2 Hereditary nonpolyposis colorectal cancer

HNPCC is another distinct clinicopathological entity with a known genetic basis (Lynch and Smyrk 1996). From a clinical viewpoint, an 'HNPCC family' is loosely defined as one in which there are multiple cases of colorectal cancer and/or certain other genetically related cancers (such as cancers of the endometrium, ovary, small intestine, renal pelvis and ureter) across two or more generations, characterised by early age of onset (Lynch and Smyrk 1996, Watson and Lynch 1993). Most of the colorectal cancers are located in the proximal two-thirds of the colon (ie proximal to the splenic flexure) (Lynch and Smyrk 1996). Special pathological features of HNPCC include the presence of small numbers of adenomas in the large bowel, a tendency for adenomas to be large and villous, an excess of mucinous cancer and poorly differentiated cancer, the presence of tumour-infiltrating lymphocytes and rapid evolution of cancer (Jass et al 1994a,b).

Estimates of the contribution of HNPCC to all colorectal cancers have been as high as 15%, but more recent estimates range between 1 and 4% (Lynch and Smyrk 1996). It is difficult to estimate the number of affected and at-risk members of HNPCC families in Australia, but the figure could be five times greater than for FAP, depending on the definition of 'HNPCC family'. Accurate calculations must await diagnosis based on genetic testing.

Alterations in the DNA code of one of at least four genes (see Appendix C) predispose, at least in part, to this syndrome (Fishel et al 1993, Leach et al 1993, Bronner et al 1994, Papadopoulos et al 1994, Nicolaides et al 1994). These
genes encode a ‘mismatch repair’ system which, when functioning normally, helps to prevent the accumulation of DNA mutations throughout the genome. When a mismatch repair gene is defective, the cell is liable to accumulate mutations at a faster rate than normal, and this state is detectable by assaying for replication errors in tumour DNA. Replication error is most easily detected in microsatellite repeat sequences (microsatellite instability, or MSI).

Advances in this area have been rapid in the past four years. However, at present, molecular genetic diagnosis in these families is difficult because mutations in any one of the four mismatch repair genes, or even other as yet undiscovered genes, might be responsible for HNPCC in a particular family, and a range of mutations occurs in each gene. Nevertheless, molecular genetic diagnosis is already possible in more than 50% of suspected HNPCC families (Liu et al 1996). Further refinements, making such diagnosis technically simpler, can be anticipated. This will be a major advance in the management of these families because there is no consistent premalignant clinical marker of the disease (such as polyposis in FAP). Molecular genetic diagnosis of affected individuals allows therapeutic interventions before cancer develops in mismatch repair gene mutation carriers (Lynch and Smyrk 1996).

The number of mutations identified in the mismatch repair genes involved in HNPCC is steadily increasing (180 mutations reported to the International Collaborative Group on HNPCC up to June 1997). In all but a few reported cases, mutations occur in just two of the four mismatch repair genes (hMSH2 and hMLH1) (Liu et al 1996).

7.1.3 Familial clustering of the common form of colorectal cancer

Relatives of patients with common colorectal cancer (ie colorectal cancer in non-FAP and nonHNPCC families) themselves have an increased risk for colorectal cancer (St John et al 1993, Rozen et al 1987, Slattery and Kerber 1994, Goldgar et al 1994, Fuchs et al 1994). In 15–20% of all cases of colorectal cancer, at least one first-degree relative is also affected (St John et al 1993).

While much of this familial clustering may be due to chance, a proportion is likely to be due to inheritance of low penetrance, dominant genetic mutations (Cannon-Albright et al 1988). However, if such mutations exist, the genes responsible have not yet been identified (Lewis et al 1996).

7.2 Familial adenomatous polyposis

7.2.1 Genetic testing

Genetic testing permits identification of presymptomatic APC mutation carriers and prevents unnecessary sigmoidoscopic screening in noncarriers (Groden

### Guidelines — genetic testing (FAP families)

| In familial adenomatous polyposis (FAP) families where the family-specific genetic mutation has been identified, genetic testing should be offered to all at-risk relatives. | III |
| Such testing should be offered when sigmoidoscopic surveillance is due to commence. This is usually between the ages of 10 and 15, depending on family details and dynamics. Testing in children younger than 10 should be performed only under exceptional circumstances. | — |
| Genetic testing should proceed only in the context of genetic counselling. | — |

### 7.2.2 Surveillance of the large bowel

Sigmoidoscopic surveillance and prophylactic surgery reduce the incidence and mortality of colorectal cancer in FAP (Järvinen 1992, Vasen et al 1990). In individuals with untreated FAP, colorectal cancer invariably occurs by the sixth decade (Rhodes and Bradburn 1992, Järvinen 1992, Vasen et al 1990). In the uncommon atypical (‘attenuated’) form of FAP, some family members have relatively few (<100) adenomas and an uneven distribution of adenomas around the large bowel (Leppert et al 1990, Evans et al 1993). Atypical FAP is associated with mutations at the proximal (or 5’) end of the gene, in which case, surveillance should be based on colonoscopy rather than sigmoidoscopy (Giardiello et al 1996).

### Guidelines — surveillance (FAP families)

| In familial adenomatous polyposis (FAP) families, yearly or second-yearly flexible sigmoidoscopy should commence from the age of 10–15 years in known mutation carriers and in at-risk family members of unknown genetic status. In known mutation carriers, yearly or second-yearly sigmoidoscopy should be continued until polyposis develops. | III |
| In family members of unknown genetic status, this should change to third-yearly sigmoidoscopy at age 35, then to colorectal cancer screening as recommended for the general population at age 55. | — |
| In families known to have a proximal 5’ mutation, surveillance should be based on colonoscopy rather than sigmoidoscopy. | — |
7.2.3 Prophylactic colectomy


**Guidelines — prophylactic colectomy in FAP**

<table>
<thead>
<tr>
<th>Prophylactic surgery should be considered for all patients with FAP on the basis of the sigmoidoscopic finding of multiple adenomas in those with an identified adenomatous polyposis coli mutation, positive family history of FAP, or typical FAP phenotype.</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery may consist of total colectomy and ileorectal anastomosis, or restorative proctocolectomy.</td>
<td>III</td>
</tr>
<tr>
<td>After ileorectal anastomosis, sigmoidoscopy should be performed each 6–12 months with removal or destruction of polyps. It should be performed six-monthly from the age of 45.</td>
<td>III</td>
</tr>
<tr>
<td>Proctectomy (with or without pouch construction) should be performed if polyps are not controllable or when cancer intervenes.</td>
<td>III</td>
</tr>
<tr>
<td>Proctectomy with pouch construction should be considered at age 40–50 in all patients with ileorectal anastomosis.</td>
<td>III</td>
</tr>
</tbody>
</table>

7.2.4 Chemoprevention

Sulindac reduces rectal adenomas after ileorectal anastomosis and may reduce duodenal adenomas (Giardiello et al 1993). However, protection against cancer development is not established, and routine use is not recommended for all patients with FAP (Niv and Fraser 1994).

The risks and benefits of sulindac therapy should be discussed with patients who have residual adenomas. Endoscopic surveillance should be continued.
Guideline — sulindac prophylaxis in FAP

Sulindac chemoprevention should be considered in FAP patients with rectal adenomas after ileorectal anastomosis and/or with duodenal adenomas.  

Level of evidence

II

7.2.5 Surveillance of the stomach and duodenum

Duodenal or ampullary adenomas occur in more than 90% of APC-mutation carriers by the sixth decade. Eight per cent develop duodenal or periampullary cancer (Offerhaus et al 1992). Gastric polyps are common, but most are not adenomas. There are no published data on which to judge the optimal frequency of surveillance for upper gastrointestinal malignancy nor has a survival advantage from upper gastrointestinal screening for FAP been demonstrated. The nominated guidelines are the most common international practice.

Guidelines — surveillance of stomach and duodenum

Surveillance of the upper gastrointestinal tract should be considered once colonic polyposis has been diagnosed.  

Level of evidence

—

Upper gastrointestinal endoscopy should be considered before proceeding with prophylactic colectomy to allow any large gastric or duodenal adenomas to be removed during surgery. Then annual or biennial upper gastrointestinal endoscopy should be continued if adenomas are present.

The management of patients with identified adenomas is controversial, ranging from simple observation, particularly for those with just small polyps, to surgical removal of large or malignant polyps, or to endoscopic destruction of all identified polyps.  

—

7.2.6 Surveillance for tumours at other sites

Other tumours associated with FAP include desmoid tumours arising within the abdomen or in the abdominal wall, papillary carcinoma of the thyroid, hepatoblastoma and primary brain tumours (Rhodes and Bradburn 1992). Ongoing research is examining whether particular APC mutations are associated with an increased risk for these tumours. Management protocols for surveillance for these tumours have not yet been developed because of the small number of reported cases and lack of evidence that surveillance would affect outcome.
7.3 Hereditary nonpolyposis colorectal cancer

7.3.1 Identification of at-risk family members

In at least half of all families with suspected HNPCC, the underlying abnormality is a germline mutation of one of the mismatch repair genes (Fishel et al 1993, Leach et al 1993, Bronner et al 1994, Papadopoulos et al 1994, Nicolaides et al 1994). The Amsterdam criteria provide a clinical definition for identification of HNPCC (Vasen et al 1991). However the original criteria failed to take into account family size or occurrence of syndrome cancers other than colorectal cancer (Lynch et al 1993). The modified Amsterdam criteria now take other cancers into account.

Demonstration that a tumour has is MSI increases the likelihood that mismatch repair genes are involved (Jass et al 1996), although a number of sporadic tumours are also found to have MSI (Liu et al 1995). In young patients without a family history, this may be an index of the presence of spontaneous mutation in germline mismatch repair genes (Liu et al 1995). Genetic testing for the mismatch repair genes is in the early stage of clinical application (Lynch et al 1993). Most families with mismatch repair gene involvement have mutations in hMSH2 or hMLH1 (Liu et al 1996).

About 70% of published mutations may be detected by protein truncation testing (Liu et al 1996). Identification of a specific mutation in a family can be followed by diagnostic testing of other family members. The penetrance of mismatch repair gene mutations for all forms of cancer is 70–90% in both men and women. In men, penetrance for colorectal cancer is 80–90% but in women, reported levels of penetrance for colorectal cancer range from 30 to 80% (Vasen et al 1996, Dunlop et al 1997).

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8 The modified Amsterdam criteria for HNPCC are that there should be at least three relatives with an HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter or renal pelvis), and all of the other following criteria should be present:

• one case a first-degree relative to the other two
• at least two successive generations affected
• at least one case diagnosed before the age of 50
• exclusion of FAP
The modified Amsterdam criteria can be applied to identify families with suspected hereditary nonpolyposis colorectal cancer (HNPCC), but the limitations of these criteria should be recognised, as there are some families with HNPCC where the family history does not meet the criteria.

The identification of colorectal cancers and other syndrome cancers with microsatellite instability will help identify families with mismatch repair gene mutations.

In HNPCC families where a specific mutation has been identified, genetic testing should be offered to all at-risk relatives.

Genetic testing should be offered when endoscopic surveillance is due to commence — either at age 25, or five years earlier than the age of the youngest affected relative, whichever comes first. The precise age will depend on family details and dynamics. Genetic testing should proceed only in the context of genetic counselling.

### 7.3.2 Surveillance

Carriers of mismatch repair gene mutations have a 70–90% lifetime risk of developing any cancer (Vasen et al 1996, Dunlop et al 1997). Women who are carriers of mismatch repair gene mutations have lifetime risk of up to 40% for endometrial cancer and a risk for ovarian cancer of 10% or higher (Vasen et al 1996). Carriers of mismatch repair gene mutations also have an increased risk for cancer of the stomach, urinary tract, small intestine, pancreas and biliary tree (Watson and Lynch 1993, Mecklin and Järvinen 1991).


Recommendations for the interval between surveillance colonoscopies range from yearly to once every three years, but yearly or every two years in known mutation carriers (Vasen et al 1995, Burke et al 1997b).

There is a paucity of published data on which to judge best practice for surveillance of cancers other than colorectal cancer in this group (Burke et al 1997b). Recommendations will be influenced by a family’s history of cancer at these sites, knowledge of genetic status, and likely compliance with surveillance protocols. The risks and benefits of such surveillance should be considered.
For individuals at risk of hereditary nonpolyposis colorectal cancer (HNPCC), second-yearly colonoscopy is recommended from the age of 25, or five years earlier than the age of the youngest affected relative, whichever comes first. Annual colonoscopy should be considered in known mutation carriers.

Faecal occult blood testing may be offered in intervening years, and to those with poor compliance for colonoscopy.

For individuals at risk of HNPCC there are options for surveillance at other sites, usually from age 25–35, which may include:

- annual transvaginal ultrasonography, preferably with colour flow Doppler imaging, together with endometrial sampling;
- annual check of CA125 level (after the menopause);
- second-yearly upper gastrointestinal endoscopy; and
- annual urinalysis and cytology.

### 7.3.3 Surgery

In HNPCC, metachronous primary colorectal cancers are common (Lynch and Smyrk 1996, Ponz de Leon et al 1993). Two-thirds of cancers occur proximal to the splenic flexure (Lynch and Smyrk 1996). Total colectomy with ileorectal anastomosis or restorative proctocolectomy should be considered as the primary surgical option for large colorectal cancer in HNPCC (Burke et al 1997b).

### 7.3.4 Prophylactic surgery

Surgery would involve total colectomy with ileorectal anastomosis, or possibly restorative proctocolectomy. Consideration should also be given to total hysterectomy and bilateral salpingo-oophorectomy at the time of colectomy in those women who have completed their families. Annual sigmoidoscopy should be performed on any residual large bowel.

<table>
<thead>
<tr>
<th>Guideline — prophylactic surgery (HNPCC)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The option of prophylactic surgery rather than surveillance for hereditary nonpolyposis colorectal cancer (HNPCC) should be discussed with known mutation carriers.</td>
<td>—</td>
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</tbody>
</table>

### 7.4 Familial clustering of the common form of colorectal cancer

#### 7.4.1 Identification of high-risk individuals by family history

Family history of colorectal cancer or adenomas, especially before the age of 55, confers an increased risk of colorectal cancer (St John et al 1993, Rozen et al 1987, Slattery and Kerber 1994, Goldgar et al 1994, Fuchs et al 1994, Winawer et al 1996). Table 7.1, which refers to people who do not fulfil the modified Amsterdam criteria for HNPCC, aims to quantify that risk.

#### Table 7.1 Quantifying risk of colorectal cancer based on family history

<table>
<thead>
<tr>
<th>Family history</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>One first-degree relative with colorectal cancer diagnosed at age 55 or over</td>
<td>two-fold</td>
</tr>
<tr>
<td>One first-degree relative with colorectal cancer diagnosed under 55</td>
<td>three- to six-fold</td>
</tr>
<tr>
<td>Two first-degree relatives with colorectal cancer diagnosed at any age</td>
<td>three- to six-fold</td>
</tr>
</tbody>
</table>

* There is no consistent evidence for elevated risk of other cancers in these individuals, who have familial clustering of colorectal cancer but do not fulfil the modified Amsterdam criteria for HNPCC (St John et al 1993).
### Guideline — identification of colorectal cancer risk

<table>
<thead>
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<th>Level of evidence</th>
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Where there is a family history of colorectal cancer, a full and detailed family medical history, including the ages of onset of all cancers in the family, can be used to help determine the most appropriate management of this group.

### 7.4.2 Surveillance for those with moderately increased risk

There is good evidence that a program of annual faecal occult blood testing directed at middle-aged and elderly people in the general population reduces mortality from colorectal cancer (Mandel et al 1993, Kronborg et al 1996, Hardcastle et al 1996). The use of colonoscopic surveillance appears prudent in those at a three- to six-fold increased risk despite the absence of published mortality data, but the optimal frequency and age of commencement has not been established. Flexible sigmoidoscopy plus double contrast barium enema is an acceptable alternative to colonoscopy if the latter is unavailable (Selby et al 1992).

### Guideline — surveillance (moderately increased risk of colorectal cancer)

<table>
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<th>Level of evidence</th>
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<td>III</td>
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For those at three- to six-fold increased risk of colorectal cancer, the following should be considered:

- annual faecal occult blood testing starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Colonoscopic follow-up (or flexible sigmoidoscopy plus double contrast barium enema if colonoscopy is unavailable) is necessary for those with a positive faecal occult blood test; and
- colonoscopy every five years starting at age 50, or at an age 10 years younger than the age of first diagnosis of colorectal cancer in the family, whichever comes first. Flexible sigmoidoscopy plus double contrast barium enema is an acceptable alternative to colonoscopy if the latter is unavailable.

### 7.4.3 Surveillance for those at slightly above average risk

In this group, the risk of colorectal cancer is only marginally higher than the general population (St John et al 1993, Slattery and Kerber 1994, Goldgar et al 1994, Fuchs et al 1994, Dunlop and Campbell 1997). There is a paucity of data on which to judge best practice. Some clinicians advise colonoscopic surveillance, but several careful audits of colonoscopy have revealed a low yield
of significant lesions (Grossman and Milos 1988, McConnell et al 1990). It should be noted that the report on colorectal cancer screening (AHTAC 1997) suggests that individuals with a two-fold increased risk should be managed in the same way as the general population and AHTAC have recommended a program for the introduction of population screening using faecal occult blood testing from the age of 50 for average-risk individuals. Thus, for those at two-fold increased risk of colorectal cancer, faecal occult blood testing should be offered annually from the age of 50 (Mandel et al 1993, Kronborg et al 1996, Hardcastle et al 1996). The present document does not aim to address screening for those without a family history.

<table>
<thead>
<tr>
<th>Guideline — surveillance (at slightly above average risk of colorectal cancer)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>For those at two-fold increased risk of colorectal cancer, the following are advised:</td>
<td></td>
</tr>
<tr>
<td>• faecal occult blood testing should be offered annually from the age of 50.</td>
<td>I</td>
</tr>
<tr>
<td>• sigmoidoscopy (preferably flexible) should be considered every five years from the age of 50 (Selby et al 1992).</td>
<td>III</td>
</tr>
</tbody>
</table>

7.5 Other polyposis syndromes

Peutz–Jeghers syndrome (mucocutaneous pigmentation together with multiple hamartomatous polyps) and juvenile polyposis (multiple gastrointestinal juvenile polyps) are other polyposis syndromes that impose an increased risk for colorectal cancer and for some other cancers. Such patients and their families should be referred to a family cancer clinic for investigation and advice regarding management (Phillips et al 1994).

<table>
<thead>
<tr>
<th>Guideline — surveillance (non-FAP polyposis syndromes)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Peutz–Jeghers syndrome or juvenile polyposis should be encouraged to seek medical advice promptly if they develop rectal bleeding or other symptoms suggestive of colorectal cancer.</td>
<td>—</td>
</tr>
</tbody>
</table>

7.6 Primary prevention of colorectal cancer

7.6.1 Environmental risk factors

Interaction between environmental and genetic factors may affect the level of risk and age of occurrence of colorectal cancer in those with genetic predisposition to the disease (Shike et al 1990, Thun et al 1992). Although data remain inconclusive concerning the effectiveness of intervention strategies, the
World Health Organization has adopted guidelines for primary prevention (Winawer et al 1995). Australian studies showed that a low-fat diet supplemented with wheatbran reduces the risk of adenoma growth (MacLennan et al 1995).

<table>
<thead>
<tr>
<th>Guideline — primary prevention of colorectal cancer</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The World Health Organization guidelines for primary prevention of colorectal cancer should be made known to all individuals with elevated risk on the basis of family history. They are:</td>
<td>III</td>
</tr>
<tr>
<td>• fat consumption to be less than 20% of total calories;</td>
<td></td>
</tr>
<tr>
<td>• a balanced diet should be consumed, containing five to eight servings of fruit, vegetables, wholegrain cereals (especially wheatbran) and breads in order to provide adequate fibre, vitamins and other components with anticarcinogenic effects;</td>
<td></td>
</tr>
<tr>
<td>• fibre intake should exceed 25 grams/day;</td>
<td></td>
</tr>
<tr>
<td>• obesity should be avoided;</td>
<td></td>
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<tr>
<td>• tobacco should be avoided; and</td>
<td></td>
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<tr>
<td>• physical activity should be incorporated into daily routine.</td>
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</table>

7.6.2 Chemoprevention

In cohort studies, aspirin usage of 350 mg every second day for 10–20 years resulted in a reduction in the incidence of colorectal cancer (Giovannucci et al 1994, 1995). Published, relatively short-term, randomised controlled trials have not shown reduction in risk for cancer at this or other dosages (Gann et al 1993). There are certain risks associated with aspirin use, including an increase in risk for acute gastrointestinal haemorrhage (Weil et al 1995).

<table>
<thead>
<tr>
<th>Guideline — aspirin prophylaxis for colorectal cancer</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical attendants should discuss the risks and benefits associated with aspirin prophylaxis with those at high risk of colorectal cancer.</td>
<td>II</td>
</tr>
</tbody>
</table>

7.6.3 Genetic registers for hereditary colorectal cancer families

Registers for hereditary colorectal cancer can play an important role in reducing the incidence of, and mortality from, colorectal cancer in the population at high genetic risk (Vasen et al 1990, Spigelman and Thomson 1994, Goldberg et al 1995). Registers act as a central repository and clearing house of information for families with hereditary colorectal cancer. Their unique role allows the linking of...
disparate individuals or family units, so that effective, coordinated care can be offered through the treating clinicians.

By working closely with family cancer clinics, treating clinicians and other registers throughout Australia (see Appendix D), registers can assist in the identification, tracing and guidance of individuals at high genetic risk, the maintenance of recommended surveillance programs and the efficient utilisation of genetic testing. Registers are also a source of up-to-date information on hereditary colorectal cancer syndromes and can facilitate and undertake ethical research on hereditary colorectal cancer. All registers in Australia communicate and collaborate with the international bodies for FAP and HNPCC: the Leeds Castle Polyposis Group in the United Kingdom and the International Collaborative Group for Hereditary Non-Polyposis Colorectal Cancer (see Appendix D).

<table>
<thead>
<tr>
<th>Guideline — genetic registers (colorectal cancer)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should notify consenting patients with an hereditary colorectal cancer syndrome (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz–Jeghers syndrome, juvenile polyposis etc) to the appropriate State or Territory register. Such registers should conform to the NHMRC Guidelines for Genetic Registers and Associated Genetic Material (NHMRC 1999b).</td>
<td>III</td>
</tr>
</tbody>
</table>
CHAPTER 8

OVARIAN CANCER

Epithelial ovarian cancer is the leading cause of death from gynaecological malignancy. About 1 in 100 Australian women develop ovarian cancer during their lifetime (to age 75) (Kricker and Jelfs 1996). Ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women, with the median age at diagnosis being 63 years.

Although the survival rate of women with early-stage ovarian cancer is higher than for those with advanced disease, the majority of women are diagnosed with advanced disease (NIH Consensus Development Panel on Ovarian Cancer 1995). Between 1 and 5% of all ovarian cancer, and a higher proportion of early onset cases, are thought to be due to the autosomal dominant inheritance of mutations in one of a small number of ovarian cancer-related genes (Stratton 1996) (see Table 8.1). Carriers of mutations in such genes have an increased risk of ovarian cancer. Some of these genes are also associated with an increased risk of female breast cancer, while others are associated with an increased risk of other cancers, such as male breast cancer and cancer involving other organs.

Table 8.1 Known genes responsible for hereditary ovarian cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Risk of other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast/ovarian cancer</td>
<td>BRCA1</td>
<td>17q</td>
<td>Female breast, prostate</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>13q</td>
<td>Female breast, male breast, prostate, pancreas</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer (HNPCC)</td>
<td>DNA mismatch repair genes</td>
<td>Various</td>
<td>Colorectal, other gastrointestinal, endometrial, renal tract</td>
</tr>
</tbody>
</table>

Two main hereditary ovarian cancer syndromes have been identified and these account for only a small percentage of all cases of ovarian cancer. They are:

- hereditary breast/ovarian cancer syndrome, which is characterised by susceptibility to both breast and ovarian cancer (see Chapter 6), and sometimes other cancers (Table 8.1); and

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9 This chapter is underpinned by a consensus statement prepared by the Royal Australian College of Obstetricians and Gynaecologists' Working Party on Familial Ovarian Cancer, under the chairmanship of Dr Robert Rome.
• hereditary nonpolyposis colorectal cancer syndrome (HNPCC), which includes early onset colorectal cancer and an increased risk of extracolonic cancers, including cancer of the uterus and ovaries (see Chapter 7).

8.1 Genes associated with ovarian cancer

Constitutional (germline) mutations in specific genes are associated, in carriers, with an increased risk of ovarian cancer. The risk depends on the gene involved, and there is evidence that different mutations in the same gene may cause different risks of certain cancers.

The BRCA1 and BRCA2 breast/ovarian cancer susceptibility genes have been well-studied because of their major role in the genetic predisposition to breast cancer (see Chapter 6). Carriers of a germline mutation in either BRCA1 or BRCA2 are also at some increased risk of ovarian cancer (Ford et al 1998). However, much remains to be learnt about the frequency of BRCA1 and BRCA2 mutations in the Australian population, their penetrance and phenotype and the effect on their expression of modifier genes and/or environmental risk factors.

Female carriers of germline mutations in BRCA1 have an estimated lifetime risk of ovarian cancer which may be as high as 60% (Easton et al 1995). There is some evidence that mutations in the 3' end of the gene are associated with a lower risk of ovarian cancer (Gayther et al 1995). Mutations of the BRCA2 gene may also predispose to ovarian cancer, but the cumulative risk by age 70 appears to be less than 10% (Wooster et al 1994). Between 1 in 500 and 1 in 1000 unaffected women may carry a germline mutation in one of these genes. Some mutations, such as 185delAG and 5382insC in BRCA1, as well as 6174delT in BRCA2, are each carried by about 1% of individuals of Ashkenazi Jewish descent. Although each of these mutations is associated with an increased risk of ovarian cancer, the estimated risk falls below previous estimates based on subjects from high-risk families (Struwing et al 1997).

In families with HNPCC due to a germline mutation in one of the DNA mismatch repair genes, carriers of a mutation have a 70–90% lifetime risk of developing any cancer. Women who are carriers of mismatch repair gene mutations have a lifetime risk of up to 40% for endometrial cancer and a risk for ovarian cancer of 10% or higher (Vasen et al 1996) (see Chapter 8).

All of the above risks for carriers of deleterious mutations in ovarian cancer-related genes are estimates and have large confidence intervals. These risk figures could eventually prove to be over-estimates, since they are mostly derived from selected families, where the penetrance of the gene mutation may be particularly high.
Finally, there may be other genes, as yet undiscovered, which are associated with an increased risk of ovarian cancer.

### 8.2 Testing of genes associated with ovarian cancer

Although it is now technically possible to detect constitutional alterations in ovarian cancer-associated genes, genetic testing requires specialised laboratory techniques and is expensive and time consuming. It is possible that some genetic errors may not be detected using current technology.

Familial cancer clinics make a thorough assessment of the family history and determine the likelihood that a germline mutation in an ovarian cancer-related gene may be present. The process of genetic testing usually begins with the analysis of ovarian cancer-related genes of an affected family member. Detection of a genetic alteration in an affected family member allows for further predictive genetic testing of adult, unaffected relatives.

Genetic testing should only be offered with pre- and post-test counselling, conducted in conjunction with a specialist genetics service for breast/ovarian cancer. The potential harms, benefits and limitations of genetic testing have been discussed in other chapters (see Chapter 2).

### 8.3 Family history

The presence of a family history of ovarian cancer is an important risk factor for ovarian cancer (Nguyen et al 1994). Similarly, a family history of breast cancer or other cancers associated with HNPCC may increase the risk of ovarian cancer and other cancers in a family member.

Epidemiological data (case-control studies) have documented a two- to 20-fold increase in risk of ovarian cancer associated with a family history of ovarian cancer (Nguyen et al 1994, Kerlikowske et al 1992). The risk increases with the number of affected first-degree relatives. The lifetime risk of ovarian cancer for women with a single relative with ovarian cancer may approach 5% (a two- to four-fold increase compared to the general population), while for a woman with a single relative with breast cancer, it is less than 2% (Goldgar et al 1994). The lifetime risk for women with two first-degree relatives with ovarian cancer has been estimated to range between 7 and 20% (Foulkes and Narod 1997). It should be noted that estimates of risk for women with various combinations of more than one affected relative are often based on small numbers, and should be interpreted with caution.
In estimating risk of ovarian cancer based on family history, it is essential to take an accurate family history, and update it regularly. Taking a family history involves asking about all first- and second-degree relatives, both male and female, with or without cancer, on both the maternal and paternal sides of the family. Attempts should be made to verify all reports of cancer.

8.4 Predicting risk based on family history

For the purpose of advising women about their risk of ovarian cancer, it is useful to divide women into three broad categories.

The first category comprises women with no family history, or a weak family history, who are at low risk.

The second category includes women with a family history which may include two relatives with ovarian cancer on the same side of the family, but without the additional features which may indicate potentially high risk.

In the third category are women with a strong family history of ovarian and/or breast cancer, occurring in a number of different generations, on one side of the family. There may be additional features in potentially high-risk families, including early age at diagnosis, the presence of breast and ovarian cancer in one individual, bilateral breast cancer or male breast cancer in the family. This history suggests that there is likely to be, within the family, a dominantly inherited mutation in a gene such as BRCA1 or BRCA2, which confers a high risk of breast cancer and an increased risk of ovarian cancer. The third category also includes women from families with a suspected germline mutation in one of the mismatch repair genes (e.g., HNPCC). Women from families in which the presence of an ovarian cancer-associated gene mutation has been established belong to the third category, since they are at potentially high risk.

For each of these risk categories, the family history of ovarian cancer should not be considered in isolation. A family history of breast cancer and of some other types of cancer should also be taken into account and, if present, referral to a specialist cancer genetics service may be appropriate. People in all of the above risk categories should be encouraged to seek medical advice promptly if they develop symptoms or signs which could be related to any cancers. Women of any age found to have a pelvic mass should be referred for specialist opinion.

8.4.1 Women at low risk

The majority of women do not have a family history of breast or ovarian cancer. For those who do have a family history, most have only one relative who was affected by breast or ovarian cancer, diagnosed at a later age, or who
was not a first-degree relative. Their lifetime risk of ovarian cancer is about two- to four-fold that of the general female population, but less than 5%.

<table>
<thead>
<tr>
<th>Guideline — identification (at or slightly above average ovarian cancer risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following women should be advised that they are either at or only slightly above the average risk of ovarian cancer. This group covers over 99% of the population, and consists of women with:</td>
<td>—</td>
</tr>
<tr>
<td>• no confirmed family history of ovarian cancer; or</td>
<td></td>
</tr>
<tr>
<td>• one first-degree relative diagnosed with ovarian cancer at age 50 or older; or</td>
<td></td>
</tr>
<tr>
<td>• one second-degree relative diagnosed with ovarian cancer at any age; or</td>
<td></td>
</tr>
<tr>
<td>• two first- or second-degree relatives diagnosed with ovarian cancer, at age 50 or older, but on different sides of the family.</td>
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</table>

Management of women at low risk

Women in this group should be reassured that their chances of not developing ovarian cancer are greater than 95%. For the majority of women in this group, the lifetime risk of ovarian cancer is about 1%, the same as for most women in the community. Women in this category should, however, be made aware of the current best practice for the prevention of cancers in the general population (see Section 6.6). Screening the general population for epithelial ovarian cancer cannot be justified on the basis of its prevalence and the sensitivity of the available tests (NIH Consensus Development Panel on Ovarian Cancer 1995).

<table>
<thead>
<tr>
<th>Guideline — management (at or slightly above average ovarian cancer risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women at low risk of ovarian cancer should be:</td>
<td>—</td>
</tr>
<tr>
<td>• reassured that their chances of not developing ovarian cancer are greater than 95%;</td>
<td></td>
</tr>
<tr>
<td>• made aware of the current best practice for the prevention of cancers in the general population.</td>
<td></td>
</tr>
</tbody>
</table>

8.4.2 Women at a moderately increased risk

For a small proportion of women, the number of affected relatives and their ages at diagnosis may suggest an increased lifetime risk of ovarian cancer. The risk of ovarian cancer for a woman who has two first-degree relatives affected by ovarian cancer has been estimated to range from 7 to 20% (Foulkes and Narod 1997), but the exact risks are imprecise.
**Guideline — identification (moderately increased ovarian cancer risk)**

<table>
<thead>
<tr>
<th>Level of evidence</th>
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</table>

A small number of women (less than 1%) are at a moderately increased risk of ovarian cancer. This group comprises women with:

- one first-degree relative diagnosed with ovarian cancer before the age of 50 (but without the additional features of the potentially high-risk group — see below); or
- two first- or second-degree relatives, on the same side of the family, diagnosed with ovarian cancer (but without the additional features of the potentially high-risk group — see below).

**Management of women at moderately increased risk**

Women in this category may need more precise risk assessment. It is recommended that the treating doctor consult specialist cancer or genetic services for advice and an appropriate counselling and management program. The efficacy of ovarian cancer screening is unproven (Mackey and Creasman 1995). While surveillance of women at moderately increased risk or potentially high risk may be appropriate (see next section), women should be aware of the limitations of surveillance.

**Guideline — management (moderately increased ovarian cancer risk)**

<table>
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<tr>
<th>Level of evidence</th>
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</table>

Women with moderately increased risk of ovarian cancer should be informed that:

- there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality from ovarian cancer in women at risk;
- unnecessary intervention can sometimes result after a false positive test; and
- interval cancers can develop between tests.

Methods that may be considered as screening tools include tumour markers, specifically CA125, and transvaginal ultrasonography as well as colour Doppler imaging.

**8.4.3 Women at potentially high risk**

For a very small proportion of women, the number of affected blood relatives, their ages at diagnosis and the types of cancers occurring suggest that there is a substantial chance that there is a dominantly inherited gene mutation associated
with a high risk of cancer running in their family. As a group, the lifetime risk of ovarian cancer for women from these families is substantially increased.

For some women the risk may be as high as 60% if it is found that she has inherited a high-risk mutation in a gene such as BRCA1. For others, it may be as low as 1% if it is found that she has not inherited the high-risk mutation running in her family. Overall, much less than 1% of the population are at a potentially high risk because of their family history.

<table>
<thead>
<tr>
<th>Guideline — identification (potentially high ovarian cancer risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following women should be advised that they have a potentially high risk of developing ovarian cancer and perhaps other cancers. This group includes much less than 1% of the population, and comprises women who have:</td>
<td>—</td>
</tr>
<tr>
<td>• breast or ovarian cancer diagnosed in three or more first- or second-degree relatives on the same side of the family; or</td>
<td></td>
</tr>
<tr>
<td>• two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, plus one or more of the following features (on the same side of the family):</td>
<td></td>
</tr>
<tr>
<td>– onset of ovarian cancer before the age of 50,</td>
<td></td>
</tr>
<tr>
<td>– onset of breast cancer before the age of 40,</td>
<td></td>
</tr>
<tr>
<td>– breast and ovarian cancer in one individual,</td>
<td></td>
</tr>
<tr>
<td>– Jewish ancestry,</td>
<td></td>
</tr>
<tr>
<td>– breast cancer in a male relative; or</td>
<td></td>
</tr>
<tr>
<td>• three or more first- or second-degree relatives on the same side of the family with cancers including early onset colorectal cancer (age less than 50 at diagnosis) in particular, but also with endometrial cancer, ovarian cancer, gastric cancer, colorectal cancer or cancers involving the renal tract— features consistent with hereditary nonpolyposis colorectal cancer; or</td>
<td></td>
</tr>
<tr>
<td>• a member of a family with a demonstrated germline mutation in a high-risk ovarian cancer-associated gene such as BRCA1, BRCA2 or one of the DNA mismatch repair genes.</td>
<td></td>
</tr>
</tbody>
</table>

Women in this group should be advised that, although potentially at high risk, the majority will not get ovarian cancer. The identification of a germline mutation in one of the ovarian cancer susceptibility genes, however, is associated with a high risk of cancer.
Management of women at potentially high risk

There is a paucity of data on which to base the management of women at a moderately increased or potentially high risk of ovarian cancer, so precise protocols remain controversial. Women from families with the breast/ovarian cancer syndrome or site-specific ovarian cancer syndrome should be considered at increased risk of breast cancer (see Chapter 6). Women from families with suspected HNPCC require screening for gastrointestinal and endometrial cancers, as well as screening for ovarian cancer (see Chapter 7).

Screening the general female population for ovarian cancer has not been shown to reduce mortality (Mackey and Creasman 1995). The optimal frequency of screening is also unclear. Vaginal bimanual pelvic examination, although simple, is not specific or sensitive enough to detect ovarian cancer, and is not recommended as a screening method (Grover and Quinn 1995).

CA125 is a tumour marker associated with ovarian cancer. Serum levels of this marker are elevated in about 80% of women with epithelial ovarian cancer. However, CA125 is increased in only 25–50% of patients with Stage 1 ovarian cancer (Friedlander and Tucker 1997). Benign conditions such as fibroids, endometriosis, pelvic inflammatory disease and pregnancy can elevate the CA125 level substantially. These conditions are more common in premenopausal women, making false positive results more common in this group. Other malignancies can be associated with an elevated CA125 level, especially if there has been spread involving the pleural and peritoneal surfaces. Physiological fluctuations of CA125 occur during the menstrual cycle. When used alone, CA125 measurement lacks both sensitivity and specificity. In premenopausal women, specificity is only 94.5% (Einhorn et al 1992). CA125 is not generally recommended as a surveillance test in premenopausal women. Nevertheless, many premenopausal women do have this test and are then referred for management. The trend of the CA125 level is important, and a persistent upward trend over an observation period of two to three months is of concern, and more likely to be associated with neoplasia.

Transvaginal ultrasound enables assessment of ovarian size and morphology. Ovarian enlargement and solid and cystic morphology raises the index of suspicion for neoplasia.

Ovarian tumours are also characterised by a lower than average impedance to blood flow, which may be detected by colour flow Doppler. The sensitivity and specificity of the technique has been reported as 96.4 and 99.8% respectively (Jacobs et al 1993). The addition of transvaginal ultrasound to CA125 measurement increases specificity close to 100%, and gives a positive predictive value of 27% (Einhorn et al 1992, Kramer et al 1993).

Prophylactic surgery (bilateral oophorectomy) can be considered as an option in woman at potentially high risk of ovarian cancer, usually from the age of 30 to
35 years, or when child-bearing has been completed. Oophorectomy may reduce the risk of breast cancer (Strueming et al 1995). Prophylactic hysterectomy may be appropriate for women with HNPCC.

Primary peritoneal carcinoma may occur despite prophylactic oophorectomy (Tobacman et al 1982), with the rates of such malignancies in two studies being 11% (Nguyen et al 1994) and 2% (Piver et al 1993). Together, these reports suggest a protective effect of prophylactic oophorectomy, although this evidence is not statistically significant (Strueming et al 1995). Following prophylactic oophorectomy, indefinite follow-up using annual CA125 measurement is appropriate.

<table>
<thead>
<tr>
<th>Guidelines — management (potentially high ovarian cancer risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>For women at potentially high risk of ovarian cancer, whose ovarian cancer-associated gene status is unknown, the initial step must be to exclude malignancy. Thereafter, early detection should be emphasised.</td>
<td>—</td>
</tr>
</tbody>
</table>

Women in this category should be advised:

- that there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality of ovarian cancer in women at risk;
- that unnecessary intervention can sometimes result after a false positive test and that interval cancers can develop between tests;
- to attend for annual transvaginal pelvic ultrasonography, preferably with colour flow Doppler, commencing at age 25 to 30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier;
- that annual CA125 measurement may be appropriate as an additional screening test after menopause; and
- that prophylactic surgery (bilateral oophorectomy) may be offered as an option in some highly selected individuals, after extensive counselling.
Guidelines — management (potentially high ovarian cancer risk) (contd)

<table>
<thead>
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<th>Level of evidence</th>
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</table>

In women at potentially high risk of ovarian cancer who have been shown by genetic testing to carry a high-risk mutation in a gene that predisposes to ovarian cancer, the first step is to exclude cancer. Following that, consideration should be given to advising women:

- to attend for annual transvaginal pelvic ultrasonography, preferably with colour flow Doppler, commencing at age 25 to 30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier;
- that annual CA125 measurement may be appropriate as an additional screening test after menopause; and
- that prophylactic surgery (bilateral oophorectomy) could be considered as an option, usually from the age of 30 to 35 years or when their child-bearing has been completed. This may also reduce the risk of breast cancer. Women with HNPCC may also consider prophylactic hysterectomy.

### 8.5 Prevention of ovarian cancer

Epidemiological studies have shown that the use of the oral contraceptive pill may reduce the incidence of ovarian cancer (Lee et al 1987), and there is now some evidence from a case-control study that the use of the oral contraceptive pill may reduce risk of ovarian cancer in women with pathogenic mutations in the BRCA1 and BRCA2 genes (Narod et al 1998). Long-term use of the oral contraceptive pill is associated with a slightly increased risk of breast cancer for all women while taking, or within 10 years of ceasing to take, the oral contraceptive (CGHFBC 1996). There is no evidence that the effect of taking the oral contraceptive is any different in women with a family history of breast cancer, although women at very high risk, such as those carrying BRCA1 or BRCA2 mutations, have not yet been studied adequately.

### 8.6 Conclusion

The state of knowledge and technology as it applies to genetic and familial aspects of ovarian cancer are changing rapidly. The need for updating information, collection of relevant Australian data and links to research are as relevant to this field as they are to breast cancer (see Chapter 6).
CHAPTER 9
OTHER CANCERS

9.1 Melanoma

After sun exposure, number of moles and skin phenotype, family history is the next major risk factor for developing melanoma. People with one affected first-degree relative have a two- to three-fold increased lifetime risk of developing the disease.

About 5% of melanoma in Australia is thought to be due to dominantly inherited mutations in melanoma-related genes (Kraehn et al 1995). Markers for the presence of such genetic predisposition include having a number of individuals with melanoma in different generations on one side of the family, early age of onset (in the third or even second decade), the presence of multiple primary melanomas and, in some but not all families, the presence of multiple atypical (dysplastic) naevi. These naevi display unevenness of pigmentation, may be red-brown, have indistinct irregular margins, are asymmetrical and are often larger than 5 millimetres in diameter.

Many of these familial clusters will be due to chance or shared environmental influences, but heterogeneity analyses have shown that, at a minimum, 2% of all Australians with melanoma are members of genuine high-risk kindreds (Aitken et al 1994), potentially resulting from inheritance of uncommon but highly penetrant, dominantly inherited mutations in melanoma-associated genes.

Two genes in which mutations predispose a person to hereditary melanoma have recently been identified. The first, CDKN2A, (cyclin dependent kinase inhibitor 2A) which codes for the protein p16\(^{INK4a}\) (often referred to as p16), has been found to be mutated in about one-third of Australian hereditary melanoma families (Holland et al 1995, Walker et al 1995). The second gene, CDK4 (cyclin dependent kinase 4), appears to be a much rarer cause of the disease and mutations have not yet been identified in the Australian population (Zuo et al 1996). These genes normally play a fundamental role in regulating cellular proliferation. The manner in which they interact with ultraviolet radiation has not been determined.

Mutations have been described in all three exons of the CDKN2A gene. There appears to be a predominance of exon 1 mutations in Australian families, but few, if any, 'hot-spots' which would permit rapid screening (Holland et al 1995, Walker et al 1995). Although the gene is small, mutation detection remains a laborious procedure, and genetic testing is therefore in a developmental stage. It
is currently impossible to guarantee to an individual that their CDKN2A gene is normal, except in the context of excluding a known inherited mutation from a particular member of a defined pedigree.

9.1.1 Clinical features of hereditary melanoma kindreds

In kindreds which suggest strongly a dominant inheritance of melanoma, the risk of developing melanoma is about 6% by age 18, rising to 85% by age 48 (Goldstein et al 1994).

There is a suggested pattern of anticipation in the age of onset of melanoma in successive generations. This means that in a younger generation, melanoma may occur 11–16 years earlier than it did in the previous generation (Goldstein et al 1994). This may be due to a combination of genetic and environmental factors, in addition to the effects of family awareness and increased surveillance.

Melanoma occurring in childhood, although rare, may be a marker of a genetic predisposition. Children with a family history of melanoma and the presence of multiple dysplastic or atypical naevi are at high risk of developing melanoma at an early age (Novakovic et al 1995).

The sites of melanoma in hereditary melanoma kindreds follow the same distribution as noninherited cases — they occur predominantly on the back and arms in men, and on the legs and back in women (Barnhill et al 1992). There is a tendency for the melanomas from hereditary melanoma families to be thinner, possibly due to earlier diagnosis. Nodular melanomas and acral lentiginous melanomas are not often seen in the familial context (Ford et al 1995b).

In those with multiple atypical (dysplastic) naevi, at least one-third of melanomas develop de novo, rather than arising from existing naevi (Kelly, forthcoming).

9.1.2 Identification of individuals at high risk

Indications that individuals may be carriers of high-risk mutations in melanoma-associated genes include the presence of one or more of the following:

- multiple cases of melanoma on the same side of the family. There is no clear association with other cancers (Greene et al 1987), although certain rare families show an association with inherited ocular melanoma, and others with pancreatic carcinoma (Gruis et al 1995);

- early age of onset (median age of onset is 33 years compared to 60 years for melanoma in the general population, and 9% occur before the age of 20, compared with 2% of all melanomas) (Goldstein et al 1994);
• multiple primary melanomas in the same individual (Tucker and Bale 1988, Moseley et al 1979); and/or

• the presence of multiple atypical naevi, often distributed over both sun-exposed and nonexposed skin surfaces. These naevi may be distinguished by the presence of unevenness of pigmentation, red-brown colour, indistinct irregular margins, asymmetry, and size often greater than 5 millimetres in diameter. When there are large numbers of these atypical naevi the term ‘dysplastic naevus syndrome’ (DNS) (Greene et al 1985), or ‘familial atypical multiple mole–melanoma syndrome’ (FAMMM) is sometimes applied. Only about one-third of Australian hereditary melanoma families display this skin phenotype (Holland et al 1995). Most DNS–melanoma kindreds seem to show linkage to chromosome 9p, and many have been shown to have mutations in CDKN2A/p16 (Gruis et al 1995, Hussusian et al 1994).

9.1.3 Management of individuals at high risk

Traditionally, all members of such families have been enrolled in intensive skin surveillance programs, which include:

• whole-body photography, which may be used as a baseline (Kelly et al 1997);

• skin and scalp examination by a dermatologist at six-monthly or annual intervals;

• skin surface microscopy (epiluminescence microscopy) (Kenet et al 1993, Menzies et al 1996); and

• a low threshold for the excision biopsy of any suspicious lesions (Greene et al 1987).

The detection of a specific CDKN2A/p16 mutation in an affected family member has already been used for predictive genetic testing in an Australian family (Kefford RF, pers. comm.). The major value in such testing of unaffected family members is to detect those relatives who do not carry gene mutations, so they may be spared intensive and constant skin surveillance, and the anxiety associated with it. The results of predictive testing should be given only in association with pre- and post-test counselling.

Certain families carrying CDKN2A/p16 mutations have a high incidence of pancreatic adenocarcinoma. Although there is no reliable screening method for early operable pancreatic carcinoma at present, on an experimental basis, endoscopic ultrasound (Stevens and Lightdale 1998) and positron emission tomographic (PET) scanning (Friess et al 1995) may be useful in such high-risk kindreds.
Individuals at high risk should be educated about sun protection and self-examination. For example, they should be aware of the ABCD rules — note any change of area, border irregularity, colour change or diameter of skin lesion > 0.5 cm (McGovern and Litaker 1992). In one study, the specificity and sensitivity of self-reporting of cutaneous risk factors for melanoma were 83–95% and 68–88% respectively (Gruber et al 1993).

<table>
<thead>
<tr>
<th>Guidelines — management (high melanoma risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given current gaps in knowledge about the expression of melanoma susceptibility genes in the population, genetic testing cannot be used as a guide to clinical practice of prevention and surveillance. All individuals deemed to be at high risk of melanoma should be managed with the same attention to the measures given below.</td>
<td>—</td>
</tr>
<tr>
<td>For families with a high genetic risk of melanoma, parents should be educated about sun protection and examination for young infants and children, including:</td>
<td>—</td>
</tr>
<tr>
<td>• use of sun-protective clothing and hats;</td>
<td></td>
</tr>
<tr>
<td>• use of 15+ or stronger sunscreens;</td>
<td></td>
</tr>
<tr>
<td>• avoidance of peak ultraviolet (UV) conditions; and</td>
<td></td>
</tr>
<tr>
<td>• ABCD rules— note any change of area, border irregularity, colour change, or diameter of skin lesion &gt; 0.5 cm.</td>
<td></td>
</tr>
<tr>
<td>Commencing at age 10 years, management of should include:</td>
<td>—</td>
</tr>
<tr>
<td>• education of the individual and parent/ partner/ family member in skin examination, the hallmarks of suspicion in pigmented skin lesions (ABCD rules), and the importance of reporting new naevi or change in existing naevi;</td>
<td></td>
</tr>
<tr>
<td>• three-monthly self-examination and examination by parent/ partner/ family member;</td>
<td></td>
</tr>
<tr>
<td>• six-monthly dermatological examination until competent in self-surveillance, then annually;</td>
<td></td>
</tr>
<tr>
<td>• annual examination should include adequate examination of the scalp;</td>
<td></td>
</tr>
<tr>
<td>• skin-surface microscopy (epiluminescence microscopy) may be helpful;</td>
<td></td>
</tr>
<tr>
<td>• a careful initial extended family history is imperative, including the ages and verified histological diagnoses of all family members with cancer. The pedigree should be revised annually;</td>
<td></td>
</tr>
<tr>
<td>• baseline full-skin surface photography and close-up photography of selected lesions may be helpful for the detection of new lesions and change in existing lesions; and</td>
<td></td>
</tr>
<tr>
<td>• excision biopsy of suspicious skin lesions.</td>
<td></td>
</tr>
</tbody>
</table>
For families with a genetic predisposition to melanoma, screening and surveillance guidelines for the general population should be adhered to, with the following possible special considerations:

- melanoma in the context of the Li-Fraumeni syndrome, the hallmark for which is the presence of sarcoma in the pedigree. Screening should be conducted in accordance with guidelines for this condition;
- presence of a strong family history of pancreatic cancer. Certain families carrying CDKN2A/\(p16\) mutations have a high incidence of pancreatic adenocarcinoma. At present there is no reliable screening method for early, operable, pancreatic carcinoma. However, on an experimental basis, at-risk individuals in such kindreds, where there is a demonstrable family history of pancreatic tumours, may be advised to undergo endoscopic ultrasound, perhaps on an annual basis from an age five years earlier than the earliest case of pancreatic carcinoma in the family. Positron emission tomographic (PET) scanning is a highly sensitive, noninvasive, technique, the cost-effectiveness of which may warrant further investigation in very high-risk cohorts; and
- where ocular melanoma has occurred in the family annual fundoscopy after adequate mydriasis is recommended, although is of unproved efficacy.

### 9.2 Prostate cancer

Prostate cancer is the most common cancer in men in the western world and, with colorectal cancer, the second highest cause of cancer death in men. Its recorded incidence is increasing. Men who develop prostate cancer are usually over the age of 65.

Prostate cancer presents in two forms:

- indolent disease, which is slow growing and unlikely to affect the length and quality of life; and
- an aggressive form, which almost invariably metastasises, particularly to bone, and usually results in the death of the patient.

Recently, there has been an increase in the incidence of the disease. Deaths from prostate cancer have also increased, although to a lesser extent (McCredie et al 1996).
Numerous studies in Europe and the United States have provided evidence of familial clustering of prostate cancer, indicating that family history is a major risk factor for this disease. Male first-degree relatives of men with prostate cancer have at least a two-fold increased risk of prostate cancer. The incidence is further increased in families with two or more members affected, and the disease occurs earlier (Lesko et al 1996).

Several research groups are working on trying to discover genes associated with prostate cancer, focusing particularly on regions located on chromosome 8p, 10g, 16q and 17q, which are frequently lost in prostate cancers (Gao et al 1995). Recently, a genome-wide scan has provided evidence of linkage to chromosome 1q at a susceptibility locus HPC1 (Smith et al 1996). Male carriers of a mutation in the BRCA1 gene may have a three-fold increased risk of prostate cancer (Ford et al 1994).

There is currently considerable debate over early detection of prostate cancer using digital examination, rectal ultrasound and testing for prostate specific antigen (PSA) levels. The natural history of the indolent form of the disease may warrant no other management than observation. However, attempts to detect early operable disease could be warranted in family members where two or more are affected by prostate cancer at a younger age, since it is in these families that aggressive disease tends to occur in younger men. The advent of genetic testing in such high-risk groups may improve such targeted, invasive clinical investigation. A committee of the National Health and Medical Research Council is addressing the issue of screening.

<table>
<thead>
<tr>
<th>Guideline — individuals (high prostate cancer risk)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history is a risk factor for prostate cancer. Recording of the family history may be used to identify men at high risk. It is anticipated that genetic testing may eventually be used to accurately identify high-risk men who may benefit from targeted screening.</td>
<td>—</td>
</tr>
</tbody>
</table>

### 9.3 Multiple endocrine neoplasia type 2

Medullary thyroid carcinoma (MTC) is a rare malignancy that accounts for 5–10% of all thyroid cancers. About 75% of all MTCs are not inherited, while the remaining 25% of MTCs occur in three well-defined, dominantly inherited syndromes.

When only MTCs occur in a family, the condition is known as familial medullary thyroid carcinoma (FMTC), when they occur in conjunction with phaeochromocytomas and parathyroid disease in the same family, the syndrome is defined as multiple endocrine neoplasia type 2A (MEN2A). If, in addition,
mucosal neuromas, a marfanoid body habitus and ganglioneuromas of the intestinal tract are present in the same individual, then the condition is known as MEN2B.

Point mutations in the RET proto-oncogene on chromosome 10 have been identified in both inherited and noninherited forms of MTC (Marsh et al 1996a). Germline mutations are found in the majority of MEN2 and FMTC families, while somatic mutations, confined to tumour tissue, are identified in noninherited MTC.

In the majority of FMTC and MEN2A families studied, germline point mutations are found tightly clustered in five regions of the RET gene. Germline mutations in one of these five regions have been identified in 97% of MEN2A patients and 86% of FMTC patients. Other germline mutations are far less frequent. There is a small number of MEN2A and FMTC families in which a RET mutation has not yet been identified.

Currently, the best approach to the assessment of a newly diagnosed person with MTC is shown in Figure 9.1 (Learoyd et al 1995). In families where there is clear evidence of familial MTC, the family will require genetic counselling, and genomic DNA from an affected family member should be analysed for the presence of one of the described germline mutations in RET. Once the causative germline mutation has been identified, other family members can be tested to determine whether they carry the same RET germline mutation. Such predictive genetic testing requires pre- and post-test genetic counselling, so that the implications of test results will be understood.

Patients with RET germline mutations have a lifetime risk of about 80% of developing MTC and, depending on the specific mutation, a risk of up to 50% of developing phaeochromocytoma. They also have a 20% risk of hyperparathyroidism.

<table>
<thead>
<tr>
<th>Guideline — management (RET mutation)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>For individuals with a RET germline mutation, screening for phaeochromocytoma should be performed annually, or whenever symptoms suggest, with urine catecholamine and metanephrine measurements. Screening for hyperparathyroidism should be performed annually by measuring serum ionised calcium (or total calcium corrected for albumin), phosphate and parathyroid hormone levels.</td>
<td>—</td>
</tr>
</tbody>
</table>
New patient with medullary thyroid carcinoma

Assess clinical features/family history

RET germline mutation studies (2 samples)

- mutation positive
  - confirms familial nature of the disorder
  - management and surveillance for the proband
  - genetic counselling and testing for first-degree relatives
  - mutation positive
    - thyroidectomy if >6 years old
  - mutation negative
    - reassurance

- mutation negative
  - familial disease unlikely
  - no further surveillance
  - mutation negative
  - surveillance

**Figure 9.1** Ideal approach to assessment of patient with medullary thyroid carcinoma

Presymptomatic genetic testing for RET mutations should be discussed with parents of children at 50% risk of having inherited FMTC/MEN2. Prophylactic thyroidectomy should be offered to those children shown to carry a mutation or at very high risk on the basis of a family linkage study. Pentagastrin screening is an alternative, but experience has shown that MTC detected in this way is associated with lymph node involvement in 50% of cases (Marsh et al 1996b).
Penetrance of C-cell hyperplasia, the precursor of carcinoma, approaches 100% by 30 years of age. The Fifth International Multiple Endocrine Neoplasia Workshop held in Stockholm in 1994 recommended that thyroidectomy should be performed in RET mutation carriers when they reach six years of age (Eng et al 1996). It would be anticipated that the availability of genetic testing should dramatically improve the ability to identify early C-cell abnormalities and reduce morbidity and mortality from MTC.

9.4 Rare cancers

A number of individuals and families with rare cancer syndromes are seen by geneticists for diagnosis and counselling. Syndromes including Li–Fraumeni (Strong et al 1992), von Hippel–Lindau (Maher et al 1995), neurofibromatosis, nevoid basal cell carcinoma, ataxia telangiectasia, retinoblastoma, Wilms’ tumour and other rarer familial cancers also cause a small number of patients to present to geneticists and familial cancer services (see Appendix D).

<table>
<thead>
<tr>
<th>Guideline — management of families with a history of a rare cancer syndrome</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families with a history consistent with one of the rare familial cancer syndromes require counselling. In some cases, they will be candidates for genetic testing. Such testing may be available only with the cooperation of research laboratories.</td>
<td>—</td>
</tr>
</tbody>
</table>
APPENDIXES
APPENDIX A

MEMBERSHIP OF THE AUSTRALIAN CANCER NETWORK CANCER GENETICS WORKING PARTY

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Richard Kefford</td>
<td>Department of Medicine, Westmead Hospital, NSW (Chair)</td>
</tr>
<tr>
<td>Dr Judy Kirk</td>
<td>Familial Cancer Service, Westmead Hospital, NSW</td>
</tr>
<tr>
<td>Professor Bruce Armstrong</td>
<td>Director, Cancer Research and Registers Division, Cancer Council, NSW</td>
</tr>
<tr>
<td>Dr Kristine Barlow-Stewart</td>
<td>NSW Genetics Education Program, NSW</td>
</tr>
<tr>
<td>Professor Robert Burton</td>
<td>Anti-Cancer Council of Victoria, Vic</td>
</tr>
<tr>
<td>Dr Georgia Chenevix-Trench</td>
<td>Queensland Institute of Medical Research, Qld</td>
</tr>
<tr>
<td>Dr John Collins</td>
<td>Royal Melbourne Hospital, Vic</td>
</tr>
<tr>
<td>Associate Professor Michael Friedlander</td>
<td>Department of Medical Oncology, Prince of Wales Hospital, NSW</td>
</tr>
<tr>
<td>Dr Mark Frydenberg</td>
<td>Urological Society of Australasia, NSW</td>
</tr>
<tr>
<td>Mr Clive Glover</td>
<td>representative of health consumers, NSW</td>
</tr>
<tr>
<td>Dr Eric Haan</td>
<td>South Australian Clinical Genetics Service, SA</td>
</tr>
<tr>
<td>Associate Professor John Hopper</td>
<td>Department of Public Health and Community Medicine, University of Melbourne, Vic</td>
</tr>
<tr>
<td>Professor Jeremy Jass</td>
<td>Department of Pathology, Royal Brisbane Hospital, Qld</td>
</tr>
<tr>
<td>Dr David Koorey</td>
<td>Department of Gastroenterology, Royal Prince Alfred Hospital, NSW</td>
</tr>
<tr>
<td>Professor Sally Redman</td>
<td>NHMRC National Breast Cancer Centre, NSW</td>
</tr>
<tr>
<td>Emeritus Professor Tom Reeve</td>
<td>Australian Cancer Network, NSW</td>
</tr>
<tr>
<td>Professor Bruce Robinson</td>
<td>Kolling Institute, Royal North Shore Hospital, NSW</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dr Robert Rome</td>
<td>Royal Australian College of Obstetricians and Gynaecologists, Vic</td>
</tr>
<tr>
<td>Professor Joe Sambrook</td>
<td>Peter MacCallum Cancer Institute, Vic</td>
</tr>
<tr>
<td>Professor Joseph Shepherd</td>
<td>Department of Surgery, Royal Hobart Hospital, Tas</td>
</tr>
<tr>
<td>Ms Meryl Smith</td>
<td>Familial Cancer Service, Westmead Hospital, NSW</td>
</tr>
<tr>
<td>Professor Allan Spigelman</td>
<td>Division of Surgery, John Hunter Hospital, NSW</td>
</tr>
<tr>
<td>Dr James St John</td>
<td>Department of Gastroenterology, Royal Melbourne Hospital, Vic</td>
</tr>
<tr>
<td>Dr Graeme Suthers</td>
<td>South Australian Clinical Genetics Service, Women’s and Children’s Hospital, SA</td>
</tr>
<tr>
<td>Dr Katherine Tucker</td>
<td>Hereditary Cancer Clinic, Prince of Wales Hospital, NSW</td>
</tr>
<tr>
<td>Dr Ian Walpole</td>
<td>Department of Medical Genetics, Princess Margaret Hospital, WA</td>
</tr>
<tr>
<td>Professor Robert Williamson</td>
<td>Murdoch Institute, Royal Children’s Hospital, Vic</td>
</tr>
</tbody>
</table>
APPENDIX B

GUIDELINE DEVELOPMENT PROCESS

The National Health and Medical Research Council (NHMRC) has identified four primary reasons why guidelines may be needed. These are:

- the size of the health burden
- the cost of the health burden
- variations in practice
- the existence of available evidence.¹

In view of this, the Australian Cancer Network (ACN), after wide consultation, initiated a process to develop guidelines on the familial aspects of cancer. The process followed is in accordance with the guidelines of the NHMRC. A Cancer Genetics Working Party was established to oversee the project.

An extensive process of consultation was undertaken to involve the many medical, paramedical and consumer disciplines associated with the treatment of cancer. The groups involved include:

- Department of Medicine, Westmead Hospital
- Familial Cancer Service, Westmead Hospital
- Cancer Council of NSW
- NSW Genetics Education Program
- Anti-Cancer Council of Victoria
- Queensland Institute of Medical Research
- Royal Melbourne Hospital
- Department of Medical Oncology, Prince of Wales Hospital
- Urological Society of Australasia
- Health Consumers NSW
- South Australian Clinical Genetics Service
- Department of Public Health and Community Medicine, University of Melbourne
- Department of Pathology, Royal Brisbane Hospital
- Department of Gastroenterology, Royal Prince Alfred Hospital
- NHMRC National Breast Cancer Centre
- Kolling Institute, Royal North Shore Hospital
- Royal Australian College of Obstetricians and Gynaecologists
- Department of Surgery, Royal Hobart Hospital
- Division of Surgery, John Hunter Hospital
- Department of Gastroenterology, Royal Melbourne Hospital
- South Australian Clinical Genetics Service, Women’s and Children’s Hospital
The NHMRC legislative requirements for public consultation have also been fulfilled. The first stage of the NHMRC consultation process was carried out during the period 27 March 1998 to 8 May 1998. Consideration of the submissions informed the development of the second stage consultation draft.

Second stage consultation was held during the period 26 November 1998 to 15 January 1999.

The NHMRC Health Advisory Committee established a small expert working party to consider the submissions received. A list of submissions is provided below. Recommendations arising from deliberations of these submissions were referred to the ACN for action.

The document was revised in light of these recommendations and the final document was forwarded to the Health Advisory Committee to consider NHMRC endorsement. In accordance with Health Advisory Committee protocols, the draft was sent out for external review. The review indicated that some technical and editorial work was required. This was subsequently undertaken and the final document referred to the NHMRC for final endorsement.

These guidelines are evidence based. They are inclusive, not prescriptive. They aim to provide information on which decisions can be made, rather than dictate a specific form of treatment. They are the result of a comprehensive process involving the careful assessment of evidence.
Submissions received

First stage consultation

Dr Rodney Sinclair  
University of Melbourne, VIC

Dr Michael Stanford  
Royal Melbourne Hospital, VIC

Ms Vanessa Lambert  
Highgate, SA

Ms Elizabeth Percival  
Royal College of Nursing, ACT

Ms Melba Mensh  
Diabetes Education Centre, Royal Newcastle Hospital, NSW

Ms Marilyn Gendek  
Australian Nursing Council Inc, ACT

Dr R F Broadbent  
Royal Australian and New Zealand College of Psychiatrists, VIC

Second stage consultation

R C Bennett  
Royal Australasian College of Surgeons, VIC

Judy Kirk  
Familial Cancer Service, Westmead Hospital, NSW

Ian Alexander  
The Royal Australasian College of Physicians, NSW

D J Koorey  
Royal Prince Alfred Hospital and University of Sydney, NSW

Caroline Lorbach  
Donor Conception Support Group, NSW

Mary Byrne RSC  
Plunkett Centre for Ethics in Health Care, St Vincent’s Hospital, NSW

Stephanie Hooper  
The Royal Australian College of General Practitioners, NSW

Brian Conway  
Commonwealth Department of Health and Aged Care, ACT

Judy Lumby  
The New South Wales College of Nursing, NSW

Elizabeth Percival  
Royal College of Nursing, Australia, ACT

Melvyn Korman  
Monash Medical Centre, VIC

Terry Bolin  
Prince of Wales Hospital, NSW

Ian Walpole  
Genetic Services of Western Australia, WA
<table>
<thead>
<tr>
<th>Name</th>
<th>Organization/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ian Hammond</td>
<td>The Royal Australian College of Obstetricians and Gynaecologists, VIC</td>
</tr>
<tr>
<td>Donald Moss</td>
<td>Urological Society of Australasia</td>
</tr>
<tr>
<td>James St John</td>
<td>Australian Cancer Network Genetics Working Party</td>
</tr>
<tr>
<td>Gillian Rothwell</td>
<td>West Pennant Hills, NSW</td>
</tr>
<tr>
<td>Bruce Armstrong</td>
<td>NSW Cancer Council, NSW</td>
</tr>
<tr>
<td>Jane Halliday</td>
<td>Murdoch Institute for Research into Birth Defects, Royal Children’s Hospital, VIC</td>
</tr>
<tr>
<td>S Krul</td>
<td>The Royal Australian College of Medical Administrators, VIC</td>
</tr>
<tr>
<td>David W Kissane</td>
<td>Centre for Palliative Care, VIC</td>
</tr>
<tr>
<td>Colin Macleod</td>
<td>The Royal College of Pathologists of Australasia, NSW</td>
</tr>
<tr>
<td>Judy Uren</td>
<td>Australian Nursing Federation, VIC</td>
</tr>
<tr>
<td>Sandra Hacker</td>
<td>Australian Medical Association Limited, ACT</td>
</tr>
<tr>
<td>David Wong</td>
<td>Australian College of Dermatologists, NSW</td>
</tr>
<tr>
<td>Fran Boyle</td>
<td>Medical Oncology Group of Australia Inc, NSW</td>
</tr>
</tbody>
</table>
## APPENDIX C

### KNOWN CANCER PREDISPOSITION GENES

<table>
<thead>
<tr>
<th>Hereditary syndrome</th>
<th>Commonest cancers</th>
<th>Mode of inheritance</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon, duodenum, perianampillary</td>
<td>Dominant</td>
<td>APC</td>
<td>5q</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>Colon, endometrium, ovary, stomach, small bowel, renal tract, pancreas, biliary tract</td>
<td>Dominant</td>
<td>hMSH2, hMLH1, hMSH6, hPMS2</td>
<td>2p, 3p, 2p, 7p</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>Gastrointestinal tract, pancreas, ovary, testis, breast, uterus</td>
<td>Dominant</td>
<td>STK11</td>
<td>19p</td>
</tr>
<tr>
<td>Breast cancer, breast/ovarian cancer</td>
<td>Breast, ovary, prostate</td>
<td>Dominant</td>
<td>BRCA1, BRCA2</td>
<td>17q, 13q</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma, pancreas</td>
<td>Dominant</td>
<td>CDKN2A/p16, INK4A, CDK4</td>
<td>9p, 12q</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>Sarcoma, breast, brain, leukaemia, adrenocortical</td>
<td>Dominant</td>
<td>p53</td>
<td>17p</td>
</tr>
<tr>
<td>Neurofibromatosis I</td>
<td>Neurofibrosarcoma, phaeochromocytoma, optic glioma</td>
<td>Dominant</td>
<td>NF-1</td>
<td>17q</td>
</tr>
<tr>
<td>Von Hippel–Lindau syndrome</td>
<td>Haemangioblastoma of retina and central nervous system, renal cell carcinoma, phaeochromocytoma</td>
<td>Dominant</td>
<td>VHL</td>
<td>3p</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>Pancreatic islet, pituitary adenoma</td>
<td>Dominant</td>
<td>MEN1</td>
<td>11q</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2A and 2B</td>
<td>Medullary carcinoma of the thyroid, phaeochromocytoma</td>
<td>Dominant</td>
<td>MEN 2A/RET, RET</td>
<td>10q, 10q</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>Medullary carcinoma of the thyroid, phaeochromocytoma</td>
<td>Dominant</td>
<td>MEN 2A/RET, RET</td>
<td>10q, 10q</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>Dominant</td>
<td>RB1</td>
<td>13q</td>
</tr>
<tr>
<td>Nævoid basal cell carcinoma syndrome (Gorlin syndrome)</td>
<td>Basal cell carcinomas, gliomas</td>
<td>Dominant</td>
<td>PTCH</td>
<td>9q</td>
</tr>
<tr>
<td>Wilms' tumour</td>
<td>Nephroblastoma</td>
<td>Dominant</td>
<td>WT1</td>
<td>11p</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Leukaemia, lymphoma, breast, brain</td>
<td>Recessive</td>
<td>ATM</td>
<td>11q</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Skin, melanoma, leukaemia</td>
<td>Recessive</td>
<td>Various</td>
<td>Various</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Angiomyolipoma</td>
<td>Recessive</td>
<td>TSC2</td>
<td>16p</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Breast, thyroid, other</td>
<td>Dominant</td>
<td>PTEN</td>
<td>10q</td>
</tr>
<tr>
<td>Hereditary syndrome</td>
<td>Commonest cancers</td>
<td>Mode of inheritance</td>
<td>Gene</td>
<td>Chromosome</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------</td>
<td>---------------------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>Leukaemia, tongue, oesophagus, nephroblastoma, colon</td>
<td>Recessive</td>
<td>BLM</td>
<td>15q</td>
</tr>
<tr>
<td>Fanconi anaemia</td>
<td>Leukaemia, oesophagus, skin, hepatoma</td>
<td>Recessive</td>
<td>FAA, FAC</td>
<td>Various</td>
</tr>
</tbody>
</table>

This table is current at May 1999.
APPENDIX D

CONTACTS AND RESOURCES

Contacts within Australia

Anti-Cancer Council of Victoria  
1 Rathdowne Street  
Carlton VIC 3052  
Ph: (03) 9635 5000

Australian and New Zealand Breast Cancer Trials Group  
Ph: (02) 4921 1161

Human Genetics Society of Australasia  
145 Macquarie Street  
Sydney NSW 2000  
Ph: (02) 9256 5443

National Program for the Early Detection of Breast Cancer  
Ph: 13 20 50 (tollfree)

NHMRC National Breast Cancer Centre  
PO Box 572  
Kings Cross NSW 2011  
Ph: (02) 9334 1700  
Fax: (02) 9326 9329  
E-mail: directorate@nbcc.org.au

NSW Genetics Education Program  
Ph: (02) 9926 7324

Victorian Cancer Helpline  
Ph: (03) 131 120

Victorian State Familial Bowel Cancer Service  
Ph: (03) 9342 8423
FAP Registers in Australasia

New South Wales
The Registrar
NSW Hereditary Bowel Cancer Register
NSW State Cancer Council
PO Box 572
Kings Cross NSW 2011
Ph: (02) 9334 1817

Queensland
The Registrar
Queensland Familial Adenomatous Polyposis Register
Queensland Cancer Fund
553 Gregory Terrace
Fortitude Valley QLD 4006
Ph: (07) 3258 2228

South Australia
The Registrar
South Australia Familial Adenomatous Polyposis Register
Anti-Cancer Foundation
PO Box 929
Unley SA 5061
Ph: (08) 8291 4111

Victoria
The Registrar
ESSO Familial Polyposis Register for Victoria
1 Rathdowne Street
Carlton South VIC 3053
Ph: (03) 9279 1176

Western Australia
The Registrar
Familial Polyposis Registry
334 Rokeby Road
Subiaco WA 6008
Ph: (09) 346 2448

New Zealand
The Registrar
Familial Adenomatous Polyposis Register
Northern Regional Genetics Services
Private Bay 92024
Auckland 0800 476 123
New Zealand
Ph: 64 +9 307 4949 Ext. 5436
Family cancer clinics

Familial cancer clinics provide a comprehensive service to families with a history of various cancers including colorectal cancer (eg familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPPC), Peutz–Jeghers syndrome); breast and ovarian cancer; and syndromes with cancer as a feature (eg von Hippel–Lindau syndrome and multiple endocrine neoplasia). The clinics provide risk assessment, facilitate genetic testing (if appropriate) in association with genetic counselling, and provide guidance for cancer screening and prevention.

New South Wales (NSW)

Hereditary Cancer Clinic
Prince of Wales Hospital
High Street
Randwick NSW 2031
Ph: (02) 9382 2577
Fax: (02) 9382 2588

Department of Molecular and Clinical Genetics
Royal Prince Alfred Hospital
Camperdown NSW 2050
Ph: (02) 9515 5080
Fax: (02) 9515 7595

Clinical Genetic Counselling Service
St George Hospital
Kogarah NSW 2217
Ph: (02) 9350 2315
Fax: (02) 9350 3901

Familial Cancer Service
Department of Medicine
Westmead Hospital
Westmead NSW 2145
Ph: (02) 9845 5079
Fax: (02) 9687 2331

Concord Family Cancer Clinic
Medical Oncology Day Care Unit (MODCU), Admin 3
Concord Repatriation General Hospital
Concord NSW 2139
Ph: (02) 9767 6262
Fax: (02) 9767 7934

Dept of Clinical Genetics
Liverpool Health Service
PO Box 103
Liverpool NSW 2170
Ph: (02) 9828 4665
Fax: (02) 9828 4650

Hunter Family Cancer Service
Hunter Genetics
PO Box 84
Waratah NSW 2298
Ph: (02) 4985 3132
Fax: (02) 4985 3133

Other locations in NSW

For contact details of genetic counselling services in other areas of NSW which may also provide cancer genetics services, phone the NSW Genetics Education Program on (02) 9926 7324
ACT
Canberra Genetic Counseling Clinic
Canberra Hospital Woden ACT 2606
Ph: (02) 6244 4042
Fax: (02) 6244 3834

Victoria
Familial Cancer Clinic
Outpatients Breast Clinic
Austin Repatriation Hospital
Banksia Street
West Heidelberg VIC 3081
Ph: (03) 9496 5000
(pager number 3494)
Fax: (03) 9348 1391

Familial Cancer Genetics Unit
Victorian Clinical Genetic Services
Royal Children’s Hospital
10th Floor, Flemington Road
Parkville VIC 3052
Ph: (03) 8341 6201
Fax: (03) 8341 6390

Monash Genetics
Monash Medical Centre
246 Clayton Road
Clayton VIC 3168
Ph: (03) 9550 1111
Fax: (03) 9550 4124

Royal Melbourne Hospital Family Cancer Centre
Royal Melbourne Hospital
C/- RMH Post Office
VIC 3050

Bowel Cancer
Ph: (03) 9342 8423
Fax: (03) 9342 7848

Breast Cancer
Ph: (03) 9342 7151
Fax: (03) 9347 7508

All other enquiries
Ph: (03) 9342 7151
Fax: (03) 9347 7508

Familial Cancer Centre
Peter MacCallum Cancer Institute
St Andrew’s Place
East Melbourne VIC 3002
Ph: (03) 9656 1199
Fax: (03) 9656 1539

Western Australia
Genetic Services of Western Australia
King Edward Memorial Hospital
374 Bagot Road
Subiaco WA 6008
Ph: (08) 9340 1525
Fax: (08) 9340 1678

South Australia
Clinics held in various locations

Familial Cancer Unit
South Australia Clinical Genetics Service
Women’s and Children’s Hospital
North Adelaide SA 5006
Ph: (08) 8204 7375
Fax: (08) 8204 6088

Queensland
Queensland Clinical Genetics Service
Herston Hospital Complex
Herston QLD 4029
Ph: (07) 3253 1686
Fax: (07) 3253 1987

Brisbane North Breast Cancer Family Clinic
534 Hamilton Road
Chermside QLD 4032
Ph: (07) 3350 7411
Fax: (07) 3350 5102
Other relevant resources


_Ethical Aspects of Human Genetic Testing_— an Information Paper— to be published by the National Health and Medical Research Council in 2000.

Contacts overseas

_Leeds Castle Polyposis Group_ Administrative Headquarters The Polyposis Registry St Mark’s Hospital Northwick Park Watford Road, Harrow Middlesex HA1 3UJ United Kingdom Ph: 0011 44 181 2354270 Fax: 0015 44 181 2354278 Email: kneale@netcomuk.co.uk
APPENDIX E

A GUIDE FOR GENETIC TESTING CONSENT FORMS

Consent form for diagnostic testing

Analysis of genes associated with cancer

This form has been designed to ensure that your consent is on an informed basis. Please read and consider each section carefully.

Subject name _________________________________________
Address _________________________________________
Telephone _________________________________________
Date of Birth _________________________________________
ID _________________________________________

I understand and consent to the following:

• The collection of (cross out whatever does not apply): blood/ other tissue/ __________________ which will be used to obtain cells so that DNA and RNA can be extracted and stored for the agreed purposes below.

• The testing is completely voluntary and it is possible to withdraw from the testing process at any stage.

• The sample will be used for analysis of one or more of the genes involved in: (tick appropriate box)

  □ hereditary breast/ ovarian cancer

  □ hereditary colorectal cancer

  □ other hereditary cancer predisposition genes (specify)
• Alterations (mutations) in cancer predisposition genes cause a high, but not a certain, risk of cancer. The test may show the presence of a mutation in a cancer predisposition gene, but it cannot accurately predict the age of onset or type of cancer that may develop as a result.

• The test may not reveal all possible mutations that may occur in the genes tested, and it is possible that mutations in other unknown genes may be responsible for the inherited predisposition to cancer in a family.

• Test results of one individual can change the estimation of risk for other family members who have not requested testing.

• The test result may have implications for other members of the family and may affect the ability of myself and them to obtain some types of insurance.

• My own test result, and the fact that I have had a test, will not be revealed to any other person or organisation without my written consent (see below), except under subpoena.

• The result will be held by this centre and will be known by those participating in the provision of the test.

• I agree that the results of the test carried out on this sample may be revealed at any time (tick appropriate box) to:

  □ Any family member
  or
  □ Only the following individual(s)

  -----------------------------------------------

  □ My doctor(s) ----------------------------------

  □ No other individual

• In the event of my death, the test results may be made known to:

  -----------------------------------------------

• The details of the mutation causing cancer in the family may be made available to laboratories which have been asked to test other family members, provided that to do so would not reveal any person’s test result without their consent.
The sample will remain the property of the laboratory. It will be stored in good faith, but its viability for future use cannot be guaranteed.

- Counselling will be available for myself or other family members (if requested) after the test result has been given.

... ... ... ... ... ... ... ... ... ... (Doctor or other health professional) has explained to me and I understand the potential benefits and adverse consequences involved in testing and storage of this sample. I have had an opportunity to ask questions. I am satisfied with the explanation and answers to my questions.

Signature of test subject/guardian  Date

**Explanation of terms used in this consent form**

- **Genes associated with cancer:** Specific genes in which changes (mutations) have been associated with an increased risk of cancer. A genetic test involves analysis of one or more of those genes to determine whether a mutation is present.

- **Mutation:** Change in the normal DNA code which may cause disease.

- **Cancer predisposition gene mutation:** Changed DNA code which gives rise to an increased risk of certain cancers.

- **DNA (deoxyribonucleic acid):** The chemical compound of which the genes are made.

- **RNA (ribonucleic acid):** The chemical message from the genes.
### Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomatous polyposis coli gene</td>
<td>Germline mutations in this gene are associated with familial adenomatous polyposis.</td>
</tr>
<tr>
<td>Allele</td>
<td>One of two or more alternative DNA sequences at identical loci of homologous chromosomes.</td>
</tr>
<tr>
<td>Anticipation</td>
<td>The phenomenon of an earlier age of onset or more severe manifestation of an inherited disorder in successive generations.</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Pattern of inheritance whereby a chance that a mutant gene resulting in a genetic disorder is transmitted by a parent to his or her children is 50% in every pregnancy.</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Pattern of inheritance whereby a chance that a mutant gene resulting in a genetic disorder is transmitted by a parent to his or her children is 25% in every pregnancy.</td>
</tr>
<tr>
<td>Autosome</td>
<td>Any chromosome that is not a sex chromosome.</td>
</tr>
<tr>
<td>BRCA1, BRCA2</td>
<td>The first two genes discovered in which germline mutations predispose to breast cancer and ovarian cancer.</td>
</tr>
<tr>
<td>Carrier</td>
<td>A person who has both an abnormal (altered or mutated) and a normal copy of a pair of genes for a genetic disorder or characteristic. A carrier of a gene for a recessive disorder will almost always remain unaffected through life.</td>
</tr>
<tr>
<td>Chromosome</td>
<td>Threadlike structure containing DNA that carries genetic information arranged in a linear sequence. Humans have 46 chromosomes in all cells except germ cells (22 paired autosomes and one pair of sex chromosomes). One of each pair of homologous chromosomes is maternally derived, the other paternally derived. Chromosomes have a longer arm termed ‘q’ and a shorter arm termed ‘p’ joined at the centromere. The ends of the chromosome are the telomeres.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cloning</td>
<td>The identification of a precise DNA sequence of a specified gene.</td>
</tr>
<tr>
<td>Constitutional</td>
<td>See germline mutation.</td>
</tr>
<tr>
<td>Constitutional mutation</td>
<td>See germline mutation.</td>
</tr>
<tr>
<td>Consultand</td>
<td>The first person in a family to seek professional advice regarding his or her genetic status, or that of other family members.</td>
</tr>
<tr>
<td>DNA sequencing</td>
<td>Laboratory technique for determining the order of nucleotides in a target stretch of DNA. Although much of the procedure is now automated, it remains laborious and expensive.</td>
</tr>
<tr>
<td>Dominant</td>
<td>The form of inheritance in which a genetic disorder or characteristic is manifest when only one copy of the gene is faulty.</td>
</tr>
<tr>
<td>Exon</td>
<td>That region of a gene which codes for part of the ultimate protein molecule. Most genes have three or more exons, separated by noncoding regions, called introns.</td>
</tr>
<tr>
<td>Familial cancer</td>
<td>Cancer, the incidence of which is perceived by an individual to be increased over population risk within his or her kindred. It may be truly hereditary, an effect of common environmental risk, a chance clustering event, or a misperception based on the occurrence of common cancers in the same kindred.</td>
</tr>
<tr>
<td>Gene</td>
<td>The fundamental physical and functional unit of heredity consisting of a sequence of nucleotides, frequently coding for one polypeptide chain, in a particular stretch of DNA, occupying a specific position in the genome.</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>Group of tests performed to detect mutations in particular genes. DNA or RNA may be used, usually isolated (for convenience) from peripheral blood leukocytes. Broad screening tests for the presence of an altered nucleotide include heteroduplex analysis and single-stranded conformational polymorphism analysis. Specific known changes may be sought using allelespecific oligonucleotide hybridisation. Chemical and enzymic cleavage detect altered nucleotides. The final arbiter is DNA sequencing.</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Genome</td>
<td>The total genetic complement of an individual.</td>
</tr>
<tr>
<td>Genotype</td>
<td>The particular pair of alleles at a specified gene locus. One of these alleles is inherited from the father, the other from the mother.</td>
</tr>
<tr>
<td>Germline mutation</td>
<td>A mutation in the genetic material of the spermatocyte or oocyte, which can be transmitted on fertilisation to one’s offspring. When a germline mutation first occurs there will be no previous history of disease (or carriers) in the family. Once transmitted to offspring the mutation will be present in all of the offspring’s cells, including approximately half of his or her germ cells, and can be transmitted to subsequent generations.</td>
</tr>
<tr>
<td>Hereditary cancer</td>
<td>Cancer due to the inheritance of a germline mutation in a cancer susceptibility gene.</td>
</tr>
<tr>
<td>hMSH2 and hMLH1</td>
<td>Human DNA mismatch repair genes. Mutations in these genes give rise to hereditary nonpolyposis colorectal cancer. The nomenclature is derived from the yeast genes to which they show close DNA sequence homology.</td>
</tr>
<tr>
<td>Intron</td>
<td>That region contained within the physical boundaries of a gene that does not code for the ultimate protein molecule. Some intronic DNA is nonfunctional; other regions regulate gene expression.</td>
</tr>
<tr>
<td>Mapping</td>
<td>The precise location of a specific gene within the human genome.</td>
</tr>
<tr>
<td><strong>Microsatellite instability</strong></td>
<td>The genomic instability seen in tumours resulting from malfunction of the DNA mismatch repair. The instability (or replication error) is detected in tumour microsatellite repeat sequences using a molecular assay. The tumours from individuals who carry a germline mutation in one of the mismatch repair genes generally show microsatellite instability.</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td><strong>Mutation</strong></td>
<td>An alteration in the coding sequence of nucleotides in a particular gene.</td>
</tr>
<tr>
<td><strong>Nucleotide</strong></td>
<td>The building blocks of DNA, consisting of cytosine (C), adenosine (A), guanidine (G) and thymidine (T). In RNA, T is replaced by uridine (U). The order in which these building blocks are assembled provides the basis of the three-letter genetic code.</td>
</tr>
<tr>
<td><strong>Oncogene</strong></td>
<td>A gene which normally functions physiologically to promote cellular division, for example during embryogenesis and the normal processes of tissue repair and regeneration. Inappropriate expression of such genes, or alterations in their DNA sequence, may disturb this function, resulting in unrestrained cellular proliferation and cancer. Such changes are common in the genesis of haematological cancers and in tumour progression, but are only rarely the cause of inherited cancer.</td>
</tr>
<tr>
<td><strong>Penetrance</strong></td>
<td>The proportion of carriers of a genetic alteration who will manifest the effects of it. A highly penetrant mutation, for example, is one for which perhaps &gt;80% of carriers will develop the disease at some point in their lifetime. Penetrance will depend upon an individual's age and possibly other factors, including gender and environmental factors.</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>The physical characteristics, including disease manifestations, of an individual.</td>
</tr>
<tr>
<td><strong>Polymerase chain reaction</strong></td>
<td>A laboratory technique using a heat-stable bacterial DNA polymerase which allows many cycles of denaturing and renaturing to occur between a target piece of nucleic acid and specific manufactured primers, allowing a target stretch of nucleic acid to be amplified many times, thereby facilitating its accurate detection, quantitation and manipulation.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Polymorphism</td>
<td>The manner in which, at a particular site in DNA, variations occur in the nucleotide sequence between individuals in the population, producing multiple different detectable forms on DNA analysis. Usually these are located outside the coding regions of genes, or do not alter the amino acid sequence of coded polypeptides. They are usually not associated with an altered phenotype. Useful in gene mapping and DNA fingerprinting.</td>
</tr>
<tr>
<td>Polypeptide</td>
<td>Protein, composed of many amino acids, folded into a three-dimensional structure allowing performance of a specific function. The effector molecules of the information contained in genes.</td>
</tr>
<tr>
<td>Predictive testing</td>
<td>Genetic testing of a healthy person to determine if they have inherited a mutation which is known to account for their family history of cancer.</td>
</tr>
<tr>
<td>Proband</td>
<td>The first affected member who brings a particular kindred to medical genetic attention.</td>
</tr>
<tr>
<td>Protein truncation test</td>
<td>PCR-based test which enables expression of the gene, or portion of the gene, as its protein product. Since many mutations produce a shortened (truncated) protein, these mutations can be detected by the presence of this truncated protein product on gel electrophoresis.</td>
</tr>
<tr>
<td>Recessive</td>
<td>The form of inheritance where a genetic disorder or characteristic is manifest only when both copies of the gene are faulty.</td>
</tr>
<tr>
<td>Somatic</td>
<td>Pertaining to the differentiated tissues. Thus a somatic mutation is one present only in the DNA of a particular tissue, perhaps occurring during differentiation, whilst a germline mutation was present in the fertilised ovum and therefore passed on to all progeny cells.</td>
</tr>
<tr>
<td>Tumour suppressor (TS) gene</td>
<td>A gene which normally functions physiologically to produce a protein that prevents cellular division, usually by blocking a key biochemical step in the regulation of the cell cycle. If one copy of a TS gene is lost, the cell is usually unaffected. Loss of the remaining copy results in cancer. Many, but not all, cancer-associated genes are TS genes.</td>
</tr>
</tbody>
</table>
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD</td>
<td>area, border, colour, diameter</td>
</tr>
<tr>
<td>AHTAC</td>
<td>Australian Health Technology Advisory Committee</td>
</tr>
<tr>
<td>APC</td>
<td>adenomatous polyposis coli</td>
</tr>
<tr>
<td>ATM</td>
<td>ataxia telangiectasia mutated</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DNS</td>
<td>dysplastic naevus syndrome</td>
</tr>
<tr>
<td>FAMMM</td>
<td>familial atypical multiple mole-melanoma syndrome</td>
</tr>
<tr>
<td>FAP</td>
<td>familial adenomatous polyposis</td>
</tr>
<tr>
<td>FMTC</td>
<td>familial medullary thyroid carcinoma</td>
</tr>
<tr>
<td>HGSA</td>
<td>Human Genetics Society of Australasia</td>
</tr>
<tr>
<td>HNPCC</td>
<td>hereditary nonpolyposis colorectal cancer</td>
</tr>
<tr>
<td>kConFab</td>
<td>Kathleen Cuningham Foundation National Consortium for Research on Familial Breast Cancer</td>
</tr>
<tr>
<td>MEN</td>
<td>multiple endocrine neoplasia</td>
</tr>
<tr>
<td>MSI</td>
<td>microsatellite instability</td>
</tr>
<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
</tr>
<tr>
<td>NATA</td>
<td>National Association of Testing Authorities</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>TS</td>
<td>tumour suppressor</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
REFERENCES


Goldberg PA, Madden MV, du Toit E et al (1995). The outcome of familial
adenomatous polyposis in the absence of a polyposis registry. South African

based assessment of cancer risk in first-degree relatives of cancer probands.
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Goldman LD and Goldwyn RM (1973). Some anatomical considerations of

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and transmission of invasive melanoma in 23 families with cutaneous malignant
melanoma/dysplastic nevi. Journal of the National Cancer Institute,
86:1385–1390.

melanoma. The familial dysplastic nevus syndrome. New England Journal of
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dysplastic nevus syndrome: the risk of cancers other than melanoma. Journal of
the American Academy of Dermatology, 16:792–797.


suspected risk factors for colon cancer: 1 family history. Gastroenterology,
94:395–400.


Gruber SB, Roush GC and Barnhill RL (1993). Sensitivity and specificity of self
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of Preventive Medicine, 9:50–54.

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Frants RR (1995). CDKN2 explains part of the clinical phenotype in Dutch
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controlled trial of faecal occult blood screening for colorectal cancer. Lancet,
348:1472–1477.


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