Clinical practice guidelines

Familial aspects of cancer: a guide to clinical practice

Endorsed November 1999

NHMRC
National Health and Medical Research Council
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>
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<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

| 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. | — |
| 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\(^3\). | — |
| General practitioners and other health care professionals should consider for referral individuals and families they consider to be at high risk of familial cancer. | — |

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 (Struewing 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>
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### 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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<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>
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<tr>
<td>• no confirmed family history of breast cancer; or</td>
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<td>• one first-degree relative diagnosed with breast cancer at age 50 or older; or</td>
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<td>• one second-degree relative diagnosed with breast cancer at any age; or</td>
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<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>
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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.
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%.
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).

### 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 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).

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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 (Streuwing et al 1995). In premenopausal women prophylactic oophorectomy may reduce the risk of breast cancer (Streuwing 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 with 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 cancer (Mandel et al 1993, Kronborg et al 1996, Hardcastle et al 1996).
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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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).

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.

### 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).
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>
<td>—</td>
</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...
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)**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>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.</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Genetic testing should proceed only in the context of genetic counselling.</td>
<td>—</td>
</tr>
</tbody>
</table>

### 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)**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>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.</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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>
<td>—</td>
</tr>
<tr>
<td></td>
<td>In families known to have a proximal 5' mutation, surveillance should be based on colonoscopy rather than sigmoidoscopy.</td>
<td>—</td>
</tr>
</tbody>
</table>
7.2.3 Prophylactic colectomy


<table>
<thead>
<tr>
<th>Guidelines — prophylactic colectomy in FAP</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>III</td>
</tr>
<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></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

<table>
<thead>
<tr>
<th>Guideline — sulindac prophylaxis in FAP</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulindac chemoprevention should be considered in FAP patients with rectal adenomas after ileorectal anastomosis and/ or with duodenal adenomas.</td>
<td>II</td>
</tr>
</tbody>
</table>

#### 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.

<table>
<thead>
<tr>
<th>Guidelines — surveillance of stomach and duodenum</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance of the upper gastrointestinal tract should be considered once colonic polyposis has been diagnosed.</td>
<td>—</td>
</tr>
<tr>
<td>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.</td>
<td>—</td>
</tr>
<tr>
<td>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.</td>
<td>—</td>
</tr>
</tbody>
</table>

#### 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 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
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).

Guideline — surgery (HNPCC)

<table>
<thead>
<tr>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
</tr>
</tbody>
</table>

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.

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>
</tr>
</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$^a$</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>

$^a$ 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).
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).

<table>
<thead>
<tr>
<th>Guideline — surveillance (moderately increased risk of colorectal cancer)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>For those at three- to six-fold increased risk of colorectal cancer, the following should be considered:</td>
<td>III</td>
</tr>
<tr>
<td>• 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</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
</tbody>
</table>

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, whole grain 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>
</tr>
<tr>
<td>• tobacco should be avoided; and</td>
<td></td>
</tr>
<tr>
<td>• physical activity should be incorporated into daily routine.</td>
<td></td>
</tr>
</tbody>
</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>
<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 (eg 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>
</table>
| 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 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>
</table>
| 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. | — |

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)  

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)

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>
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<tr>
<td>— onset of ovarian cancer before the age of 50,</td>
<td></td>
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<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>
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</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 (Struwing 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 (Struwing 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>
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</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.
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 (CGHFB 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 p16INK4a (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/p16A 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 ultrason (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>
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<tr>
<td>• use of sun-protective clothing and hats;</td>
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<tr>
<td>• use of 15+ or stronger sunscreens;</td>
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</tr>
<tr>
<td>• avoidance of peak ultraviolet (UV) conditions; and</td>
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</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\(^{4A}\) 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.

<table>
<thead>
<tr>
<th>Guidelines — management (high melanoma risk) (contd)</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>—</td>
</tr>
</tbody>
</table>

### 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, 10q, 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.

### Guideline — individuals (high prostate cancer risk)

<table>
<thead>
<tr>
<th>Guideline</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>
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).
Penetration 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

Professor Richard Kefford Department of Medicine, Westmead Hospital, NSW (Chair)

Dr Judy Kirk Familial Cancer Service, Westmead Hospital, NSW

Professor Bruce Armstrong Director, Cancer Research and Registers Division, Cancer Council, NSW

Dr Kristine Barlow-Stewart NSW Genetics Education Program, NSW

Professor Robert Burton Anti-Cancer Council of Victoria, Vic

Dr Georgia Chenevix-Trench Queensland Institute of Medical Research, Qld

Dr John Collins Royal Melbourne Hospital, Vic

Associate Professor Michael Friedlander Department of Medical Oncology, Prince of Wales Hospital, NSW

Dr Mark Frydenberg Urological Society of Australasia, NSW

Mr Clive Glover representative of health consumers, NSW

Dr Eric Haan South Australian Clinical Genetics Service, SA

Associate Professor John Hopper Department of Public Health and Community Medicine, University of Melbourne, Vic

Professor Jeremy Jass Department of Pathology, Royal Brisbane Hospital, Qld

Dr David Koorey Department of Gastroenterology, Royal Prince Alfred Hospital, NSW

Professor Sally Redman NHMRC National Breast Cancer Centre, NSW

Emeritus Professor Tom Reeve Australian Cancer Network, NSW

Professor Bruce Robinson Kolling Institute, Royal North Shore Hospital, NSW
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<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.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rodney Sinclair</td>
<td>University of Melbourne, VIC</td>
</tr>
<tr>
<td>Dr Michael Stanford</td>
<td>Royal Melbourne Hospital, VIC</td>
</tr>
<tr>
<td>Ms Vanessa Lambert</td>
<td>Highgate, SA</td>
</tr>
<tr>
<td>Ms Elizabeth Percival</td>
<td>Royal College of Nursing, ACT</td>
</tr>
<tr>
<td>Ms Melba Mensh</td>
<td>Diabetes Education Centre, Royal Newcastle Hospital, NSW</td>
</tr>
<tr>
<td>Ms Marilyn Gendek</td>
<td>Australian Nursing Council Inc, ACT</td>
</tr>
<tr>
<td>Dr R F Broadbent</td>
<td>Royal Australian and New Zealand College of Psychiatrists, VIC</td>
</tr>
</tbody>
</table>

### Second stage consultation

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>R C Bennett</td>
<td>Royal Australasian College of Surgeons, VIC</td>
</tr>
<tr>
<td>Judy Kirk</td>
<td>Familial Cancer Service, Westmead Hospital, NSW</td>
</tr>
<tr>
<td>Ian Alexander</td>
<td>The Royal Australasian College of Physicians, NSW</td>
</tr>
<tr>
<td>D J Koorey</td>
<td>Royal Prince Alfred Hospital and University of Sydney, NSW</td>
</tr>
<tr>
<td>Caroline Lorbach</td>
<td>Donor Conception Support Group, NSW</td>
</tr>
<tr>
<td>Mary Byrne RSC</td>
<td>Plunkett Centre for Ethics in Health Care, St Vincent’s Hospital, NSW</td>
</tr>
<tr>
<td>Stephanie Hooper</td>
<td>The Royal Australian College of General Practitioners, NSW</td>
</tr>
<tr>
<td>Brian Conway</td>
<td>Commonwealth Department of Health and Aged Care, ACT</td>
</tr>
<tr>
<td>Judy Lumby</td>
<td>The New South Wales College of Nursing, NSW</td>
</tr>
<tr>
<td>Elizabeth Percival</td>
<td>Royal College of Nursing, Australia, ACT</td>
</tr>
<tr>
<td>Melvyn Korman</td>
<td>Monash Medical Centre, VIC</td>
</tr>
<tr>
<td>Terry Bolin</td>
<td>Prince of Wales Hospital, NSW</td>
</tr>
<tr>
<td>Ian Walpole</td>
<td>Genetic Services of Western Australia, WA</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(s)</th>
<th>Chromosome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon, duodenum, perianpillary</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 Medullary thyroid carcinoma</td>
<td>Medullary carcinoma of the thyroid, phaeochromocytoma</td>
<td>Dominant</td>
<td>MEN2A/RET, RET</td>
<td>10q</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>Dominant</td>
<td>RB1</td>
<td>13q</td>
</tr>
<tr>
<td>Naevoid 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>
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<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 (e.g., familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), Peutz–Jeghers syndrome); breast and ovarian cancer; and syndromes with cancer as a feature (e.g., 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 Counselling 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
  - 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**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes associated with cancer:</td>
<td>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.</td>
</tr>
<tr>
<td>Mutation:</td>
<td>Change in the normal DNA code which may cause disease.</td>
</tr>
<tr>
<td>Cancer predisposition gene mutation:</td>
<td>Changed DNA code which gives rise to an increased risk of certain cancers.</td>
</tr>
<tr>
<td>DNA (deoxyribonucleic acid):</td>
<td>The chemical compound of which the genes are made.</td>
</tr>
<tr>
<td>RNA (ribonucleic acid):</td>
<td>The chemical message from the genes.</td>
</tr>
</tbody>
</table>