The demand for genetic services by women with a family history of breast cancer has increased exponentially over the last few years. It is important that risks to women are accurately assessed and that processes are in place for appropriate counselling and management. The classification of risk into average, moderate, and high, depending upon the assessed lifetime risk of breast cancer, allows for the management of moderate risk women within cancer units and high risk women within the regional genetic centres. Management of high risk women includes discussion of options including screening, chemoprevention, and preventive surgery. The majority of these options are still unproven in the long term and continuing research is needed for their evaluation. Mutation screening and predictive testing are now a reality for a minority of families, allowing for a more informed basis for decisions regarding management options.

**BACKGROUND**

Breast cancer is the most common form of cancer affecting women. One in 10-12 women will develop the disease in their lifetime in the UK. Every year 39 000 women develop the disease in England and Wales and as a result 13 000 will die (Cancer Research Campaign Statistics).

Women at risk of breast cancer may be classified into average (population) risk, moderate risk (two to three times the population risk), and high risk (greater than three times the population risk). This paper will concentrate on risk assessment and management of the last group, those women at high risk of developing breast cancer.

There is some evidence that women with inherited breast cancer have a worse prognosis than a control population. This is on the background of an already poor record of survival within the UK as compared to the rest of Europe and the USA. It is important, therefore, that a high risk population of women is identified and optimal management, either by screening or prevention, is offered.

Various referrals are in place to ensure that appropriate referrals are seen within the regional genetics centre. Within the north west region of England, nurse led clinics are being established within cancer units to triage high risk women and refer them into the regional genetics centre.

Moderate risk women should be offered annual mammography between 35 and 50 years within the cancer units.

**RISK FACTORS**

**Family history**

The presence of a significant family history is the most important risk factor for the development of breast cancer. About 4-5% of breast cancer is thought to result from inheritance of a dominant cancer predisposing gene. While hereditary factors may play a part in a proportion of the rest, these are harder to evaluate. Except in very rare cases such as Cowden syndrome, there are no phenotypic clues that help to identify those who carry pathogenic mutations. Evaluation of the pedigree is therefore necessary to assess the likelihood that the predisposing gene is present within a family. Inheritance of a germline mutation or the deletion of a predisposing gene results in early onset, and frequently contralateral, breast cancer. Certain gene mutations also confer an increased susceptibility to other malignancies, such as ovary and sarcomas. Multiple primary cancers in one person, or related early onset cancers in a pedigree, are highly suggestive of a predisposing gene. To illustrate the importance of age, it is thought that over 25% of breast cancer under 30 years is the result of a mutation in a cancer predisposing gene.

The important features in a family history are therefore:

- Age at onset.
- Bilateral disease.
- Multiple cases in the family (particularly on one side).
- Other related early onset tumours.
- Number of unaffected subjects (large families are more informative).

<table>
<thead>
<tr>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche (&lt;12 years)</td>
</tr>
<tr>
<td>Late first pregnancy (after 28 years)</td>
</tr>
<tr>
<td>Current use of the OCP and for 10 years after nulliparity</td>
</tr>
<tr>
<td>Late menopause</td>
</tr>
<tr>
<td>Prolonged use of HRT (particularly combined therapy)</td>
</tr>
<tr>
<td>Significant weight gain in adult life</td>
</tr>
<tr>
<td>Proliferative breast disease on biopsy (not benign disease such as a fibroadenoma)</td>
</tr>
</tbody>
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**Table 1 Factors associated with an increased risk of breast cancer**
Hormonal and reproductive risk factors

The incidence of breast cancer within the general population is increasing, and this may in part be related to the increasing use of exogenous hormones. Hormonal and reproductive factors have long been recognised to be important in the development of breast cancer.

It has been shown that prolonged exposure to endogenous oestrogens is an adverse risk factor for breast cancer. Breast cancer is, therefore, very uncommon in Turner syndrome, as these women rarely ovulate. Early menarche, as it prolongs exposure to oestrogens, increases the risk of breast cancer11 as does late menopause.12

Exogenous oestrogens, either the combined oral contraceptive (COC) or hormone replacement therapy (HRT), also confer increased risks of breast cancer. The oestrogen element of the COC, although suppressing ovulation, will still stimulate the breast cells, although the extent of this increased risk is still controversial. A meta-analysis suggested that both during current use of the COC and 10 years post use there may be a 24% increase in risk of breast cancer.13

HRT is a further area of controversy. Long term treatment (>10 years) after the menopause is associated with a significant increase in risk. However, shorter treatments may still be associated with risk to those with a family history.11 In a large meta-analysis the risk appeared to increase cumulatively by 1-2% per year, but disappear within five years of cessation.11 It is becoming clear that the risk from combined oestrogen/progesterone HRT is greater than for oestrogen only.14

The age at first pregnancy influences the relative risk of breast cancer as pregnancy transforms breast parenchymal cells into a more stable state, resulting in less proliferation in the second half of the menstrual cycle. As a result, early first pregnancy offers some protection, while women having their first child over the age of 30 have double the risk of women delivering their first child under the age of 20.15

It is important to emphasise that these hormonal factors will in most cases alter risks only marginally, and even at the extremes only by a factor of two.15 Many women who have most of the unfavourable factors will not develop breast cancer and some, particularly if they have a germline mutation, will develop the disease despite favourable reproductive and hormonal factors. Hormonal and reproductive factors will have a noticeable effect on an 80% penetrant gene, other than to accelerate or delay the onset of breast cancer. Although studies do suggest an increase in risk in family history cases associated with these factors, this may simply represent an earlier expression of the gene. Generally, therefore, risk estimates are between 40% (50% probability of inheriting an 80% penetrant gene mutation) and 8-10% (population risk of breast cancer), although lower risks are occasionally given. Higher risks are only applicable when a woman at 40% genetic risk is shown to have a germline mutation, to have inherited a high risk allele, or to have proliferative breast disease.15

The modification of such a person’s risk is only likely with the demonstration or exclusion of a known family mutation.

When considering a woman with a family history of breast cancer, it is also important to be aware of any family history of ovarian cancer. Families with strong histories of both breast and ovarian cancer are likely to have mutations in BRCA1 or BRCA2. A risk figure for ovarian cancer can then be calculated based on the probability of either a BRCA1/2 mutation (see later).

RISK ESTIMATION

There are few families where it is possible to be sure of dominant inheritance. However, the breast cancer linkage consortium data (BCLC) suggest that in families with four or more cases of early onset or bilateral breast cancer, the risk of an unaffected woman inheriting a mutation in a predisposing gene is close to 50%. Epidemiological studies have shown that approximately 80% of mutation carriers in known predisposing genes (BRCA1 and BRCA2) develop breast cancer in their lifetime. Therefore, unless there is significant family history on both sides of the family, the maximum risk counselled to an unaffected woman is 40-45% (including population risk). Breast cancer genes may be paternally inherited and a dominant history on the paternal side of the family would give at least a 20% additional lifetime risk to his daughters (probability of a mutation of 25% multiplied by 80% risk of developing breast cancer).

In the absence of a dominant family history, risk estimation is based on large epidemiological studies. These show a 1.5-3 fold increased risk with a family history of a single affected relative.1 One of the risks then increases with the increasing number of affected relatives. These risks also increase with the decreasing age at diagnosis of the affected relatives, so that an unaffected woman with a first degree relative diagnosed with breast cancer at 35 years has a higher lifetime risk than a woman with a first degree relative diagnosed at 45 years. In the UK, risk estimation is based mainly in the Claus data set.5 However, in the USA the Gail model of risk estimation is widely used. This model is based on data from the Breast Cancer Detection and Demonstration Project (BCDDP) and combines factors including family history, breast biopsy data, and hormonal factors.26 27 Refinement of the model resulted in the production of graphs for the estimation of a person’s risk of breast cancer.28 One of the limitations of the Gail model may be the variation in the effect of hormonal factors on differing genetic backgrounds.

As well as these data sets allowing the estimation of risks, specific computer programs are available, including Cyrillic29 for the estimation of risk and BRCA PRO for the estimation of the likelihood of a BRCA1/2 mutation. These programs take into consideration varying permutations of age of onset of diagnosis, number of affected and unaffected women, and hormonal factors, and as a consequence different programs will result in different risk estimations.30 Geneticists should be able to assess risk from a pedigree without the use of a computer program in order to ensure that results from the program are within the correct “ball park”.

It is important to differentiate between lifetime and age specific risks. For example, some studies quote a nine-fold or greater risk associated with bilateral disease in a mother or proliferative breast disease in a first degree relative.31 2 If one then uses these risks and multiplies them on a lifetime incidence of 1 in 10, the estimated risk of developing a malignancy then becomes very high. As the population risks include both high and low risk subjects, it is not possible simply to multiply with the relative risks from these studies. For example, the relative risk of breast cancer in a woman with atypical ductal hyperplasia is halved if she remains disease free for 10 years.32 Therefore the increase in risk is time specific and not cumulative.

Perhaps the best way to assess risk is to consider the strongest risk factor, which in our view is family history. If first line risk is assessed on this basis then minor adjustments can be made for other factors. It is arguable whether these hormonal and reproductive factors will have a noticeable effect on an 80% penetrant gene, other than to accelerate or delay the onset of breast cancer. Although studies do suggest an increase in risk in family history cases associated with these factors, this may simply represent an earlier expression of the gene. Generally, therefore, risk estimates are between 40% (50% probability of inheriting an 80% penetrant gene mutation) and 8-10% (population risk of breast cancer), although lower risks are occasionally given. Higher risks are only applicable when a woman at 40% genetic risk is shown to have a germline mutation, to have inherited a high risk allele, or to have proliferative breast disease.32 The modification of such a person’s risk is only likely with the demonstration or exclusion of a known family mutation.

When considering a woman with a family history of breast cancer, it is also important to be aware of any family history of ovarian cancer. Families with strong histories of both breast and ovarian cancer are likely to have mutations in BRCA1 or BRCA2. A risk figure for ovarian cancer can then be calculated based on the probability of either a BRCA1/2 mutation (see later).

COMMUNICATION OF RISK

Within the genetic counselling process, risk is an important and difficult concept to impart. A woman’s perception of risk may vary depending on her own life experiences.31 The way in which risks are expressed may also impinge upon comprehension, with some patients preferring risks communicated as gambling odds.32 Often the patient’s agenda may be to
ascertain whether or not they are eligible for a screening pro-
gramme, and the actual risk figure becomes irrelevant.

Some women find the concept of lifetime risk and remain-
ing risk useful, especially if they are approaching the age of 50.
For example, an unaffected woman from a young onset breast
breast family may have a lifetime risk of breast cancer of 40%.
However, if she is 60 years old, her probability of being a
mutation carrier is only 25% (>60% mutation carriers would
have developed the disease by this age) and therefore her
remaining risk of developing breast cancer related to an
inherited gene mutation is 20%. This is in addition to her
population risk. This reflects the gradual equalisation of risk
to population after 60 years in those with a strong family history.
It is important to try to express the stage at which risk is
present (in old age in the general population) and how much
risk remains. Some women may prefer to know their risk per
year. In a dominant family this may approximate to 1% per
year from the late twenties for someone at 50% risk of inher-
itating the gene.

As with other genetic conditions, the communication of risk
should be appropriate to the levels of comprehension of the
patient.

MANAGEMENT OF HIGH RISK WOMEN

Early detection
Breast self-examination (BSE) has been advocated to increase
breast awareness within the population. Early studies suggested
that BSE was useful in the early detection of breast
cancer, although later studies have suggested that it unduly
raises anxiety without a definite benefit with regard to survival.
Currently, we discuss BSE as an adjuvant to a mam-
mographic screening programme, with open access to the
family history clinic in the event of an abnormality being
detected.

Clinical breast examination has been shown to be useful in
the detection of breast cancer. Indeed, a recent study in
women aged 50-59 years showed that clinical examination
was as sensitive as mammograms alone. The detection rate of
malignancies increased with the use of both mammograms
and clinical breast examination.

Ultrasound scanning of the breast is usually used as an
adjunct to the diagnosis of a palpable lump or further deline-
ation of a mammographic abnormality. A recent consensus has
suggested that, in the general population, ultrasound
scanning has a high false positive rate and therefore should
not be used. However, there is still debate about the use of
ultrasound to screen within a subgroup of women at increased
risk. In practice, ultrasound may be used for screening in very
young women (less than 30 years) with a very early onset
family history.

Mammographic screening has been shown to be useful in
the early detection of breast cancer and confers a survival
advantage. However, mammography is problematical in
young women as the young breast is denser than a postmeno-
pausal breast, resulting in greater difficulties with interpret-
ation. Although the first evidence for a significant survival
advantage is now emerging for the general population under
50 years, the frequency of disease is probably too low to
justify population screening on economic grounds. The group
of women at high risk owing to their family history is,
however, a subgroup of the population in whom screening is
probably advantageous. Our own work has shown that impal-
pable small lesions are detected in the 35-49 year age high risk
group and that similar detection rates to the NHS Breast
Screening Programme are thus attainable. European
recommendations suggest that mammograms should be
offered on an annual basis to moderate and high risk women
from the age of 35 years. These recommendations are based on
empirical data.

This advantage may, however, be confined to those women
at moderate risk of breast cancer. Recent data have suggested
that the benefit to carriers of mutations in BRCA1/2 may not be
as great owing to the aggressive nature of tumours within this
group.

Because of the (low) level of radiation associated with
mammography, and a small theoretical risk of inducing a
malignancy, there is concern regarding regular mammogra-
phy of TP53 and ATM mutation carriers. As BRCA2 has also
been implicated in DNA repair, there may also be some risk to
mutation carriers.

Magnetic resonance imaging (MRI) does not involve radia-
tion and may be more sensitive than mammography, especially
of the dense breast. MRI has also been shown to have high sensitivity in the detection of early breast cancer.
The high cost and scarcity of MRI scanners prevents the use of
MRI except for the very high risk groups; a trial offering
mammography to BRCA1/2 and TP53 mutation carriers only is
currently continuing within the UK and Australia. Recent
data from the USA comparing the use of MRI, mammography,
ultrasound, and clinical breast examination suggests that both
the sensitivity and specificity of MRI is greater than that of
mammography in BRCA1/2 mutation carriers.

Ovarian screening
Owing to the increased risk of ovarian cancer with BRCA1 and
BRCA2 mutations, families with either a proven mutation or
with a family history of breast and ovarian cancer (or multiple
ovarian cancer cases only) should be offered ovarian
screening. Within the UK a randomised trial is currently
under way to assess the efficacy of transvaginal ultrasound
and CA125 measurement as a screening tool. An additional
observational trial has been established for women at high
risk of ovarian cancer from the age of 35 years (UKFOCSS
trial).

PREVENTION OF BREAST CANCER

Hormonal manipulation
It has been suggested that manipulation of hormonal/
reproductive factors may reduce the risks of breast cancer.
These include:

- Plan family early.
- Avoid COC and HRT.
- Good diet.

Many women at their first attendance at a family history
clinic will already have started a family and may have already
used oral contraception, so that alteration of these factors
becomes impossible. However, discussions regarding contra-
ception and HRT are useful in certain cases. It has been
suggested that the use of the COC will reduce the risk of ovar-
ian cancer in BRCA1 mutation carriers by up to 60%. However,
this may also decrease the age of onset of breast cancer
(unpublished data). Careful discussions in order to
ensure that the patients are aware of all the pros and cons of
hormonal treatment and/or manipulation are needed.

Chemoprevention
The use of hormonal manipulation via the use of medication
has been suggested as a preventive measure in breast cancer.
It has long been recognised that removing the effect of oestro-
genon on the breast is a useful adjunct to treatment of breast
cancer, and has therefore been postulated as a preventative
measure. The identification of a group of women at high risk
provides the possibility of obtaining sufficient events (devel-
oment of breast cancer) in order to assess chemopreventive
agents. A number of large collaborative trials are currently
continuing.

Tamoxifen has been shown to reduce the risk of contra-
lateral breast cancer in women with a previous breast
primary and a large American study has shown a reduction
in risk of breast cancer in asymptomatic women (at increased lifetime risk) by 40-50%.49 It is well tolerated, although hot flushes and other menopausal symptoms are common and there are increased risks of thromboembolic events and endometrial cancer.44 Tamoxifen also has a beneficial effect on bone density. However, two smaller studies did not show reduction in breast cancer risk.50 51 The most recent results from IBIS (International Breast Intervention Study)52 have shown a 33% risk reduction with the use of Tamoxifen (68 breast cancers v 101). There remains, however, concern over the increased risk of endometrial malignancy and thromboembolic events associated with the use of Tamoxifen. Therefore, while Tamoxifen is currently licensed and recommended for prevention within the USA, its use as a preventive agent is still being assessed in the UK. A new high risk trial, RAZOR, is being piloted in the UK and Australia involving suppressing the ovaries with Zoladex (GnRH agonist) and protecting the bones (and breasts) withRaloxifene. Variations of this are being undertaken in the USA and mainland Europe. Other studies under way include the administration of retinoids in Italy and the trials comparing Tamoxifen with Raloxifene in America. Recruitment to these trials of high risk women within the UK has been disappointing and this may be because of a reluctance to be randomised to placebo.53

Preventive surgery
Prophylactic mastectomy is now an option for women at high risk of breast cancer. The group to whom this surgery is offered varies with each centre,54 but is now accepted as an option for BRCA1/2 and TP53 mutation carriers. If removal of breast tissue is incomplete, such as with sparing of the nipple, then a residual risk of breast cancer remains.55 None of the different surgical procedures will completely remove all breast tissue, and therefore there will always be a (small) residual risk of breast malignancy. It is also important to emphasise that aesthetically this is not a cosmetic procedure. Both of these issues need to be discussed with individual women before surgery.

Evidence from a study of nearly 1000 women at the Mayo Clinic in the USA suggests that breast cancer risk is substantially reduced (by 90%) even with subcutaneous mastectomy.56 This is now being confirmed in BRCA1 and BRCA2 mutation carriers.57

There have been few long term studies of either the physical or psychological sequelae of prophylactic surgery. Some women may be psychologically unprepared for the outcome as cosmesis may not be as a woman expects. The general anaesthetic and surgical risks also need to be taken into account. However, a recent study58 has shown significant benefit to women who choose the option compared to those who do not in terms of anxiety and cancer related worry. It is nonetheless important that a comprehensive protocol for preparing women is in place, including a psychological assessment.59

Increasingly, women at high risk in the UK are opting for preventative mastectomy. This is likely to increase further when genetic testing is more widely available and women at 80-90% lifetime risk of breast cancer are identified. Two recent reports from our own Group and The Netherlands show an uptake of around 50% in unaffected mutation carriers.60 61 Indeed, high risk women are more likely to choose prophylactic surgery than prevention trials.53

Prophylactic oophorectomy (including removal of the fallopian tubes) has been used in women with BRCA1/2 mutations in order to reduce the risk of ovarian cancer. As with mastectomies, the removal of every ovarian epithelial cell cannot be guaranteed, and therefore there is a residual risk of ovarian malignancy. Tobacman et al62 reported primary peritoneal cancer in 3/28 women undergoing prophylactic oophorectomy. Strewing et al63 more recently showed that oophorectomy reduced the risk of ovarian or primary peritoneal cancer by approximately half in a small study. A more recent large multicentre study64 showed that this risk reduction in BRCA1/2 mutation carriers may be as high as 90-95%. It has also been shown that in women with a BRCA1/2 mutation, prophylactic oophorectomy decreases the risk of breast cancer65 and that this risk reduction is unaffected by the subsequent use of HRT. Prophylactic oophorectomy in high risk women may then decrease the risk of both breast and ovarian cancer.

Long term studies are needed to assess the impact of both early detection and preventative treatment on the mortality of women with a high risk of breast cancer.

THE BREAST CANCER GENES
Evidence from the BCLC suggests that familial breast cancer is heterogeneous and that there are a number of different genes involved in predisposition to this disease.66 While a number of different genes have been cloned, work is continuing to localise and clone the remaining genes. The current known genetic conditions and locations of genes is shown in table 2.

BRCA1 and BRCA2
BRCA1 on the long arm of chromosome 17q and BRCA2 on the long arm of chromosome 13q were cloned over five years ago. They are thought to account for over 80% of highly penetrant inherited breast cancer with a combined population frequency of approximately 0.2%.67 The majority of families with breast and ovarian cancers are the result of mutations in BRCA1, with up to 20% resulting from mutations in BRCA2.68

Mutations in both genes confer an increased lifetime risk of breast cancer of 85% with a lifetime risk of ovarian cancer of 60% with BRCA1 and 10-20% with BRCA2.69 70 It is probable that the majority of so-called specific ovarian cancer families are the result of mutations in BRCA1. Supportive evidence for this comes from the long term follow up of apparently site
specific families and new cancers in families from the UKCCCR familial ovarian cancer study. Early evidence from the International Linkage Consortium suggests that although BRCA1 and BRCA2 account for the great majority of families with four or more affected cases under 60 years with breast/ovarian cancer, they account for far less of the predicted hereditary component of smaller families. For instance, a family with two affected sisters under 50 years would have a >50% chance of being the result of a predisposing gene, yet BRCA1/2 mutations only account for about 15% of these families.

A number of different studies have assessed the penetrance of BRCA1 and BRCA2 mutations. These appear to vary with ascertainment; for example, population studies show a lower penetrance than those estimated by the Breast Cancer Linkage Consortium. It has been suggested that a number of low penetrant breast cancer genes may affect the penetrance of BRCA1 and BRCA2 resulting in the variable estimates published. However, communicated risks should be appropriate to the pattern of malignancies within the family being counselled.

**TP53**
Germline mutations of the TP53 gene on the short arm of chromosome 17 are known to account for over 70% of cases of the Li-Fraumeni syndrome. Early onset breast cancers are common within this syndrome, with the majority of women being diagnosed under the age of 40 years. However, the overall contribution of germline TP53 mutations to familial breast cancer is probably relatively small.

**ATM**
Heterozygous carriers of the ataxia-telangiectasia (ATM) gene are known to be at a five-fold risk of breast cancer. While the initial carrier frequency of this gene was thought to be high, this was based on five complementation groupings. It has since been shown that a single gene on 11q causes the disease. Although initial studies did not indicate that ATM appeared to be a major gene in breast cancer predisposition, there is now emerging evidence that mutations can be associated with high risk in families.

**PTEN**
PTEN (10q) mutations have been found in Cowden syndrome. While this condition is known to be associated with an increased risk of breast cancer, mutations within this gene do not appear to account for high risk families. However, two cases of male breast cancer have been described in association with Cowden syndrome.

**PREDICTIVE GENETIC TESTING**
A predictive test determines whether an unaffected person carries a familial mutation. Many women attend a genetic clinic for the purpose of having a “genetic test” to determine whether they are at increased risk of developing breast cancer and in the majority of cases this test is unavailable and inappropriate. Women in the general population without a family history would have a less than 0.1% chance of carrying a mutation in BRCA1. Therefore a negative screen would not reduce their risks of breast cancer even if the mutation screen were 100% sensitive. Those with a first degree relative with breast cancer diagnosed at 40 years of age, having a 1 in 6 lifetime risk, would not receive any real reduction in their probability of developing the disease and therefore management would not be altered. Even women with a strong family history of breast and ovarian cancer and a 90% sensitivity for mutation testing would not have sufficient risk reduction to cease screening or preventative measures (D F Easton, personal communication).

Predictive testing should therefore only be offered when a pathogenic mutation has been identified within a family. This will allow complete reassurance to those who have not inherited the family mutation and allow informed risk estimates of breast and ovarian cancer to those with the mutation.

The only potential exception to this is within a population with strong “founder” mutations, such as the Ashkenazi population. Within this population, three mutations in BRCA1/2 occur with a frequency of about 2.5% and may account for over 90% of the highly penetrant families. Smaller aggregates of malignancy may also be the result of these founder mutations with the result that mutation screening in unaffected subjects without a known family mutation becomes a useful option.

**UPTAKE OF GENETIC TESTING**
Evidence suggests that about 60% of eligible women undertake a genetic test for breast cancer predisposition. Various theoretical surveys of women who may only be at fairly small risk of carrying a BRCA1/2 mutation would also suggest a high uptake. However, when the poor predictive value of testing unaffected relatives is explained to subjects, the uptake may well be very much lower. The actual uptake in tested families is still much lower than predicted from previous surveys and needs to be extended to families who have not been contaminated by being involved in large scale research. This is now possible with the large number of families in which mutations have been found (approximately 600 in the UK). Little is also known about the outcome of testing. Early results from psychosocial studies suggest that subjects are benefited from a low risk result and may not be adversely affected by a high risk result. From a health economic viewpoint, it is essential to know what options women will undertake. If >50% of women opt for preventive surgery, provisions may need to be made for this. However, the greatest “economic” benefit may arise from a preventive strategy that means that many fewer women have to undergo chemotherapy for metastatic disease.

**CONCLUSIONS**
There have been huge advances in our knowledge of hereditary breast cancer over the last 10-12 years. While it is now possible to offer definitive testing in a few high risk families, much is still to be learnt about the remaining genes that confer low to moderate increases in risk. In the meantime, further evidence has to be gathered as to the efficacy of screening and preventive options. Guidelines for the appropriate management have recently been published for the UK and similar approaches are being used in other parts of Europe and North America. Long term planning within the NHS in terms of manpower and resources is needed to counsel optimally and manage women at high risk of developing breast cancer.

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Risk assessment and management of high risk familial breast cancer

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