Familial breast cancer:

Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.

Update of clinical guideline 14 and 41

Appendix E - Removed sections from CG14 (2004)

Appendix F - Removed sections from CG41 (2006)

Appendix G – Deleted Recommendations from CG14/CG41 (2004 & 2006)

Developed for NICE by the National Collaborating Centre for Cancer

Contents

Appendix E

Removed sections from CG14 (2004) guideline

1 Key priorities for implementation (2004)

Approaches to care

1. Effective care involves a balanced partnership between patients and healthcare professionals. Patients should have the opportunity to make informed choices about any treatment and care and to share in decision making.
2. To ensure a patient–professional partnership, patients should be offered individually tailored information, including information about sources of support (including local and national organisations).
3. Standard written information regarding familial risk and breast cancer risk factors should be developed for use in primary, secondary and tertiary care, to provide consistent advice to women.

Family history and referral

1. When a woman presents with breast symptoms or has concerns about relatives with breast cancer, a first- and second-degree family history should be taken in primary care to assess risk, because this allows appropriate classification and care.
2. Healthcare professionals should respond to women who present with concerns, but should not, in most instances, actively seek to identify women with a family history of breast cancer.
3. Local protocols for the care of women at risk of familial breast cancer should be developed with clear referral mechanisms between primary, secondary and tertiary care, and with appropriate facilities.

Care

1. Access to psychological support and assessment is a key part of the package of care needed for many women covered by this guideline.
2. All women aged 40–49 years satisfying referral criteria to secondary or specialist care (at moderate or greater risk) should be offered annual mammographic surveillance.
3. Mammographic surveillance should only be undertaken after provision of information about its potential advantages and disadvantages for the early detection of breast cancer, and where offered this should be of high quality (equivalent to NHS Breast Screening Programme standard) and audited.
4. Genetic testing is appropriate only for a small proportion of women who are from high risk families.
5. Risk-reducing surgery (mastectomy and/or oophorectomy) is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team.

Important messages to share with women with concerns

- Most women do not develop breast cancer, and of those who do most will not have a known family history of the disease
- For most women increasing in age is the greatest risk factor.
- The great majority of women with a family history of breast cancer do not fall into a high risk category and do not develop breast cancer.
- The great majority of women with a relative with breast cancer are not at substantially increased risk of breast cancer themselves.

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2.1 The guideline (2004)

The guideline is aimed at all health care professionals providing care to women who present with concerns about the risk of developing breast cancer because of a family history.

The guideline aims to provide recommendations to help health care professionals in primary, secondary and tertiary care.

Guideline development methods are NICE development process, which are described in three NICE Guideline Development Process Manuals, available on the NICE website (www.nice.org.uk).

Key features of the guideline are that:

- it is evidence based, where evidence is available
- in areas where evidence is lacking this is made clear, and the consensus methods used are clearly described
- recommendations are explicitly linked to evidence where it is available
- the recommendations, methods and conclusions in the guideline are explicit and transparent.

The full scope of the guideline is presented in Appendix 22.

2.2 Using guidelines

Guidelines are only one type of information that health care professionals may use when making decisions about patient care. It is assumed that this guideline, like all guidelines, will be used by health care professionals who will also bring to bear their clinical knowledge and judgement in making decisions about caring for individual patients. It may not always be appropriate to apply either specific recommendations or the general messages in this document to each individual or in every circumstance. The availability of resources may also influence decisions about patient care, including the adoption of recommendations.

2.3 Responsibility and support for the guideline

The guideline was commissioned by NICE. The development of the guideline was undertaken by ScHARR, University of Sheffield, a provider partner in the National Collaborating Centre for Primary Care (NCC-PC). The guideline development group (GDG) was convened by the NCC-PC. The guideline development group consisted of relevant health care professionals, patient representatives and guideline developers, including a systematic reviewer. The membership of guideline development group is shown in Appendix 21.

2.4 Scope of the guideline

The scope of this guideline was care, and classification, of women at risk of breast cancer because of family history. The guideline covers women aged 18 years and older. It does not cover women who have breast cancer. It does not cover the care and management of men who may be at risk because of family history. The guideline addresses care in primary, secondary and tertiary care in respect of these women. However, the guideline does not cover in detail some aspects of some interventions that may be relevant, for example it does

not address methods of screening in detail as that is outwith the scope. The full scope can be seen in Appendix 22.

2.5 Key clinical questions

The guideline development group identified the potential pathways that women with a family history of breast cancer might take in accessing and moving though health care services. From these pathways they identified potential interventions that might be available and also the decision points where these interventions might have to be considered by women and those involved in their care.
This evidence pathway is presented in Appendix 24, along with the literature search strategies.

2.6 Evidence identification

The development of the clinical guideline took an explicit, systematic approach to evidence identification, consideration and presentation. However it is perhaps worth noting that it is a clinical guideline and is resourced as such rather than a set of exhaustive systematic reviews. The guideline does not set out to undertake comprehensive systematic reviews for each topic area that it covers as this cannot be achieved with the resources available. In this guideline about 30 would have been required. The NICE guideline development process allows the use of existing meta-analyses and systematic reviews where they exist as a basis for evidence statements and recommendations.

The searching provided most of the papers contained in the guideline. This was in spite of the searching for articles that specifically addressed populations with a family history not being straightforward. Many papers addressed breast cancer in populations both with and without family histories and the indexing of papers in databases did not always pick this up, leading to some articles perhaps being missed. We used the expertise available on the group to identify papers that may have been missed as is common practice in NICE and other guideline development and other evidence assimilation processes.

In addition to the guideline scope the GDG identified key clinical questions to be addressed by the guideline these provided a starting framework for considerations of relevance. Late papers have been accommodated in the document and these have been discussed with the GDG to consider what if any impact they have on the recommendations, evidence statements and discussions in the relevant sections.

2.6.1 Search strategies

The search strategies attempted to locate the best available evidence for the interventions identified. It was recognised very early that in many instances this would not be meta-analyses, systematic reviews or RCTs. The searches therefore were wide ranging in the types of study that were searched for.

Searches for studies that included women with a family history of breast cancer, including BRCA1 and BRCA2 carriers were undertaken. However, in many instances studies relevant for family history were not found and therefore studies of general populations of women were also used.
Searches were limited to English language citations.

The databases searched and example search strategies can be found in Appendix 24.

For each intervention the evidence of effectiveness, evidence of harm and cost effectiveness information was sought.

2.6.2 Sifting and reviewing the evidence

Studies retrieved were assessed for their quality and relevance in answering the key clinical questions identified by the clinical working group and the pathways of care exercise.

For studies where our concern is that of what intervention seems to be most effective, then in our assessment of those studies our key concern was the quality of the study in terms of the various aspects of study validity. Firstly, if a study can credibly demonstrate the causal relationship between treatment and outcome then it can be said to have internal validity. Secondly, if the findings can be generalised from the specific study sample to a wider population, then it is said to be generalisable or to have external validity. Thirdly, if the study actually measures what it says it measures then it is said to have construct validity.

Study quality was assessed using modified SIGN checklists.

2.6.3 Synthesising the evidence

Extraction tables and narrative descriptions of studies were used to provide the basis for conclusions about the findings of the body of evidence.

Many meta-analyses and systematic reviews included papers that involved populations of women with a family history and women without a family history, and in many instances did not differentiate in any given conclusions etc. In the guideline if there are papers that were concerned primarily with women with a family history, we have often given a précis of these studies in addition to the meta-analyses/systematic reviews as this population is the one the guideline is primarily concerned with and may have information that is pertinent to this group but lost in the overall findings.

2.6.4 Areas without evidence

The guideline development group used informal consensus methods to derive evidence statements and recommendations in areas where research literature was not available, drawing upon their clinical knowledge and experience. Theses are graded accordingly (D level recommendations).

Although research evidence may be lacking there is a clinical need for this guideline and it is therefore acceptable to present consensus based recommendations for care.

2.7 Evidence grading

Once individual papers had been assessed for methodological quality and relevance in terms of our key clinical questions, they were graded according to the levels of evidence currently used by NICE.

Classification of Evidence

Evidence level	Description
Ia:	evidence from meta-analysis of randomised controlled trials
Ib:	evidence from at least one randomised controlled trial
IIa:	evidence from at least one controlled study without randomisation
IIb:	evidence from at least one other type of quasi-experimental study
III:	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV:	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

This classification is most appropriate for questions of causal relationships, and is usually used to assign studies, dealing with causal relationships, to levels of evidence.

In many areas within this guideline other types of evidence have been used. In many areas the best available evidence comes quite far down the hierarchy. In some instances the most appropriate type of study has been used (e.g. cohort), so despite attracting a 'low' level of evidence in this hierarchy, it is nonetheless the best and methodologically appropriate evidence. Thus the best evidence might not appear to be very strong but this should be seen in terms of a shortcoming of the grading approach rather than a reflection of the evidence available in many instances.

The literature was synthesised, using a qualitative narrative approach, to produce an evidence report. This also included health economics information. This evidence report, with summary evidence statements, was presented to the guideline development group.

2.8 Derivation and grading of recommendations

The derivation of recommendations usually involves assessment of evidence, processes of interpretation and consensus to arrive at recommendations. The mix of evidence, interpretation and consensus will vary between topic areas. The grading of recommendations takes account of this and therefore variation may occur between different groups presented with the same evidence. Whilst evidence statements can be formulated without reference to the context in which clinicians practise, this is not always the case with recommendations.

Recommendations were graded A to D, using the current NICE approach.

Grading of Recommendations	
A	directly based on category I evidence
B	directly based on category II evidence, or extrapolated recommendation from category I evidence
C	directly based on category III evidence, or extrapolated recommendation from category I or II evidence
D	directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence

The NICE guideline development process requires that recommendations are graded on the basis of the evidence that underpins them. The recommendation grading process does not take clinical importance into account. In some instances a lower than expected recommendation grading may be presented, but this will be as a result of extrapolation of higher level evidence, and may for example reflect different populations or settings presented in the evidence and that found in clinical practice in England and Wales.

A low graded recommendation e.g. a D level recommendation does not therefore mean that it is not an important recommendation it only reflects the level of evidence, using the hierarchy described previously, that underpins the recommendation and is not a reflection of its clinical or policy relevance or importance.

2.9 Cost effectiveness review and analysis

NICE guidelines do not currently require a cost impact to be undertaken, which would model the likely cost of implementing all or some of the recommendations. It is recognised that the issue of resource implications of guideline implementation is a major concern. A pilot study to look at methods of undertaking cost impacts of guidelines is currently being commissioned.

2.9.1 Review

Identification of papers

This strategy aimed to identify all relevant studies of cost-effectiveness across the entire scope of the guideline. A literature search was undertaken alongside the clinical literature review. Details of the databases searched and the filters used to identify relevant economic studies are given in Appendix 24. Titles and abstracts were then examined by hand in order to identify cost-effectiveness, cost-utility or cost-benefit studies (CEA, CUA, CBA). Members of the guideline development group provided additional references that had not been identified by the searches.

Studies that did not appear to be CEA, CUA or CBA were not reviewed. This excluded a number of studies that examined only costs. Only primary studies were included except in the area of mammographic surveillance since in this area there were no studies relevant directly to women with a familial history but a large number of studies relating to the cost-effectiveness of surveillance in other women. Consistent with the clinical review, the IARC screening report (IARC 2002a) was used.

Reviewing the evidence

Eligible papers were assessed using the Drummond checklist (Drummond et al. 1996) for economic evaluations as a basis for review. A narrative was produced for each paper that

reflected these methodological issues and any additional information that was considered relevant to the guideline.

2.9.2 Estimation of cost effectiveness

The scope of the guideline is broad, including the assessment of risk, genetic testing, management strategies including risk reducing surgery, chemo- prophylaxis, and surveillance. Inevitably there are substantial gaps in the economic evidence base. At an early stage the guideline development group identified those areas that they felt were most likely to require additional, primary economic analysis. A decision analytic model was developed as a result of these discussions in order to assess the cost-effectiveness of genetic testing of women at varying degrees of breast cancer risk due to familial history. This model is discussed in more detail in Appendix 20.

2.10 Consensus in recommendations

There may be areas where the group was unable to reach consensus on an area, no matter whether evidence is available or not. Where this has happened it is stated that a consensual recommendation could not be reached, the opposing views are presented and the final decision is left to the user of the guidelines.

Consensus was reached in all recommendations.

2.11 Guideline review

The process of reviewing the evidence is expected to begin 4 years after the date of issue of this guideline. Reviewing may begin earlier than 4 years if significant evidence that affects the guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

3.1 Introduction (2004)

Most women do not develop breast cancer, and of those who do most will not have a known family history of the disease.

Breast cancer is a multifactorial disease which may involve lifestyle, environmental, reproductive as well as genetic factors and as with many other cancers, as yet unknown factors. Even where a woman has a relative with breast cancer it may well be due to chance rather than genetic or shared lifestyle factors.

Some women will have one relative who has had a diagnosis of breast cancer. In many instances these affected relatives will be in the older age range when a diagnosis of breast cancer was given. This type of family history is not that which will increase the risk in women discussed in this document. Rather it reflects that for most women as they get older their risk of breast cancer increases. The family histories that can be considered relevant and pertinent to any increased risk are discussed in the relevant sections where referral criteria are discussed. Therefore it may be helpful to think in terms of relevant (in terms of risk) family histories when the terms family history is used in the guideline.

However for some women with a family history, where there is a cluster of affected family members, there is a considerable degree of worry associated with knowing about the possible increase in risk associated with having a family member who has had breast, or ovarian, cancer. Familial breast cancer typically occurs in women within a family where there have been an unusually high number of family members affected by breast cancer. If there have been more cases of breast or related cancers than would be expected by chance alone, it may be that genes transmitted between generations are sufficient to cause or, more typically, contribute to the development of breast cancer.

In this guideline evidence based information and recommendations for management are presented. An important factor is that of helping concerned women better understand the issues and risks involved. Perhaps even more important is the need to ensure that women are offered appropriate reassurance whenever necessary to prevent unnecessary worry and distress.

3.2 Incidence and prevalence

Breast cancer is the most common cancer in women and accounts for between 18-25% of all female malignancies world-wide (Office for National Statistics 2001, McPherson et al 2000). Although breast cancer incidence and mortality varies considerably around the world, the proportion of women who develop breast cancer is higher in western, developed countries. The lifetime risk (to 85 years of age) of developing breast cancer in more developed countries world-wide has been estimated in the UK at 11% (1 in 9 women) (Office for National Statistics 2001, NHS Cancer Screening Programmes and Cancer Research Campaign 2001). Cancer of the breast is the commonest cancer to affect women in the United Kingdom, accounting for nearly 30% of cases of cancer in women (Office for National Statistics 2001). In 1997 there were 33,100 new registrations of female breast cancer in England and Wales, representing almost 30% of all cancers in women, more than twice as many as for colorectal cancer, the second most common female cancer (Office for National Statistics 2001).

The overall incidence of breast cancer in England in 2000 was 114 per 100,000 female population. Four in five new cases are diagnosed in women over the age of 50, with the

peak in distribution of new cases in the 50-54 age group. The 5-year relative survival rate for women diagnosed with breast cancer was 73% for women diagnosed in 1991-95 and 78% for women diagnosed in 1996-99. This means that three quarters of women diagnosed with breast cancer were still alive five years after their diagnosis (all ONS 2003).

The exact causes of breast cancer remain unclear. However, it has been estimated that up to 27% of women may have an inherited predisposition to breast cancer (Peto & Mack 2000). Nonetheless only 3-5% are likely to carry gene faults which conferred a very substantial (>50%) risk of breast cancer (Claus et al 1994; Ford et al 1998). Media reporting often gives the impression that a greater proportion of cases are linked to genetic inheritance. Since breast cancer is relatively common, it can be difficult for women to know whether any case in a relative indicates a familial inheritance or not. As such, questions about possible familial breast cancer may be expressed to (or raised by) general practitioners, symptomatic breast clinics, breast screening services and others. The size of the demand this puts on health services does not appear to have been accurately assessed in the UK.

3.3 The role of family history

Known risk factors for developing breast cancer relate to an individual's age, lifestyle and environmental factors, reproductive history (for example, early menarche, number of children, late 1st pregnancy), previous benign breast disease and family history (NHS Cancer Screening Programmes and Cancer Research Campaign 2001).

Family history is one of the strongest risk factors for developing breast cancer (Emery et al 2001). Although a woman in the general population aged 70 years of age has a 3% risk of breast cancer in the next 10 years a woman with a BRCA1 mutation has as much as a 15% risk for the next 10 years when aged only 30 years (Ford et al 1998). Whilst the majority of cases of breast cancer arise in women with no apparent family history, between 6-19% of women with breast cancer will have a family history of the disease (Department of Health 2000, Hill et al 1997). This clustering of breast cancer in a family may be due to chance, shared environmental/lifestyle risk factors, or to increased genetic susceptibility.

A large reanalysis of epidemiological data world-wide has found that the probability that women in more-developed countries will develop breast cancer increases according to the number of affected 1st degree relatives (Collaborative Group on Hormonal Factors in Breast Cancer 2001). The probability of a woman aged 20 developing breast cancer by the age of 80 who has no affected relatives is 7.8%, 1 affected relative, 13.3% and 2 affected relatives, 21.1%. Also, the risk of developing breast cancer is greater the younger the relative is when she developed the disease. For example, a woman whose sister developed breast cancer between the ages of 30-39 has a cumulative risk of 10% of developing the disease herself by age 65, but that risk is only 5% (close to the population risk) if the sister was aged 50-54 when breast cancer was diagnosed (McPherson et al 2000). The lifetime risks of breast cancer (to age 80 years), the remaining risk (to 80) and the risk over the next 10 years is shown (Table 1) for the general population (ONS 2001), and for a woman with a mother or sister diagnosed aged 30-39 years (Claus et al 1994 and Collaborative Group on Hormonal Factors in Breast Cancer 2001).

It must be appreciated that the risks derived from the CASH dataset (Claus et al 1994) are from an era when breast cancer was less frequent in the general population (prior to screening and increase in other risk factors such as HRT). At the time of derivation the risks to women with a sister or mother with breast cancer less than 40 years of age represented a true doubling of lifetime risk. This is reflected to some extent in the lack of increase in the last 20 years of life (from the table), which is unlikely to be true. Nonetheless the table demonstrates the 10 year risks at 40 years of age for the woman with an affected relative

being the same or more (using Collaborative Group data) as for the general population a decade later. Indeed recent validation of the risks in a familial screening clinic have shown that the risks are underestimated in the single affected relative category (Amir et al 2003) and use of Collaborative group data may improve risk accuracy in this group. Although lifetime risks are now commonly quoted to 80 years of age (the definition used in these guidelines) these are not available for familial risks beyond 79 years.

Table 1: Lifetime risks of breast cancer [1, 2]

Age in years	Population - 10 year risk[3]	Claus - risk next 10 years[4]	Collaborative Group- risk next 10 years[5]
20	0.1%	0.5%	0.4%
30	0.4%	1.2%	2.2%
40	1.5%	2.7%[7]	4.1%[8]
50	2.8%[6]	4.2%	5.1%
60	2.8%	4.4%	3.8%
70	3.1%	3.5%	4.2%

Notes:

1. All figures rounded to 1 decimal place
2. Cumulative risk figures for this table are presented in Appendix 25
3. Office of National Statistics 2001
4. Claus et al 1994, risks for a woman with a sister or mother with breast cancer aged 30-39 yea
5. Collaborative Group 2001, risks for a woman with a sister or mother with breast cancer aged 30-39 years
6. Entry to NHSBSP
7. Risk level similar to NHSBSP
8. Collab group risk estimate

From Table 1 it can be seen that the risk estimate that gains entry to the NHSBSP is 2.8%. A similar risk estimate for women with a family history was found from Claus at age 40 (2.7%). The corresponding risk estimate from the Collaborative Group was 4.1%. Therefore a risk estimate between 2.7% and 4.1% was thought by the guideline development group to indicate a risk estimate that would be reasonable to justify as moderate risk, hence a figure of 3% was agreed by the guideline development group.

It has been estimated that for a total population of 1 million with an age and sex structure comparable to that of England and Wales there would be 20-40 families whose family history of breast cancer would indicate that members had a high risk of developing breast cancer (R&D Office of Anglia and Oxford 1998). Furthermore, 4,450 women aged 35-49 would be estimated to be at moderate risk of developing the disease, out of a total of 47,000 women at risk.

Family history, however, is not always a reliable indicator of those with gene mutations. Known genetic gene mutations are implicated in only about 2-5% of all cases of breast cancer (NHS Cancer Screening Programmes and Cancer Research Campaign 2001, Department of health 2000). It is not yet known how many breast cancer genes there may be, although two breast cancer genes, BRCA 1 and BRCA2, have been identified and account for a considerable proportion of very high risk families, that is, those with four or more close relatives who have breast cancer (McPherson et al 2000). Certain populations have been found to have different rates of certain genetic alterations. In the Ashkenazi Jewish community three “founder” mutations (two in BRCA1, one in BRCA2) are relatively common and explain almost all the high risk families due to these genes, and other populations have been found to have higher rates of BRCA1 and BRCA2 alterations (e.g. Norwegian, Dutch and Icelandic people). Breast cancer genes may be transmitted through either sex and some family members may transmit the abnormal gene without developing cancer themselves. However, carrying the gene mutation gives a high lifetime risk of developing breast cancer; it is estimated that the risk is as high as 50% of developing the disease by the age of 50, rising to 85% (for some families) by the age of 70 (R&D Office of

Anglia and Oxford 1998). Genetic, or hereditary, breast cancer is usually characterised by early onset, a high incidence of bilateral disease and an association with other malignancies; for instance, inherited factors are thought to contribute to 25-35% of cases diagnosed before the age of 30 (Hill et al 1997). Indeed mutations in the known high risk genes BRCA1, BRCA2 and TP53 have been demonstrated in 20% of a population based sample of women with breast cancer aged 30 years and under (Lalloo et al 2003).

3.1.1 Ovarian and prostate cancers: family history issues

The largest proportion of hereditary ovarian cancer cases originate from families with significant family histories; either of ovarian, breast or both cancers. The majority of these families are due to mutations in BRCA1. Therefore a combination of ovarian cancer and breast cancer or multiple cases of ovarian cancer in families implicates a potentially increased risk of breast cancer. Stratton et al. (1999) in a population study of ovarian cancers found that 3% had probable germ-line BRCA1 mutations and that BRCA1 mutations contribute to 5% of all ovarian cancer cases. It is important, however, to distinguish between epithelial ovarian cancer and the rarer germ cell tumours of the ovary in which there is no clear association with an increased risk of either ovarian cancer or of breast cancer in close relatives. There is also evidence to suggest that it is only certain types of epithelial ovarian cancer that confer an increased risk. Mucinous cancers are not associated with BRCA1 or BRCA2 mutations (Werness et al., 2000) and do not appear to increase risk in case control studies for either breast or ovarian cancer (Shah et al., 1994). Borderline tumours of the ovary are also not associated with a significantly increased risk of either BRCA1 or BRCA2 (Stratton et al 1999; Werness et al., 2000) and do not appear to substantially increase the risk of invasive ovarian cancer in relatives (Stratton et al., 1999).

Prostate cancer can be linked with breast cancer in BRCA2 families. A relative risk of 4-5 fold for early onset prostate cancer has been reported and 2-3% of early onset prostate cancer (<55 years) can be due to BRCA2 mutations (Edwards et al 2003). Nonetheless a history of prostate cancer alone in a family will not substantially increase breast cancer risk and even in addition to breast cancer will only add a small amount to the likely hereditary component.

3.4 Impact on individuals with a family history of breast cancer

Understanding the role of inherited gene mutations in familial breast cancer brought promise of genetic testing for breast cancer susceptibility and targeted risk management and preventative strategies. In response, there has been a rapidly increasing demand for information from women with a family history of breast (and/or ovarian) cancers. However, the wider implication of having a family history of breast cancer affects an individual at many levels.

Women may want to know the significance of the family cancers for their personal risk and discuss what they can do to reduce it, but not all family members will be at the same state of readiness to seek risk information (Hagoel et al 2000). Obtaining the necessary family pedigree may be distressing due to the need to contact estranged relatives and to raise painful issues. Decisions about having children and aspects of lifestyle can be affected because of a family history, and those found to carry a genetic mutation may experience guilt about passing a gene to a new generation. Therefore risk counselling is strongly advocated to help prepare counselees for their emotional reactions to genetic testing and decisions about disclosure to the family.

Overall, women attending Cancer Genetics Clinics are not found to be more anxious than other women in the population (Brain et al 2000, Cull et al 1999, Thirlaway et al, Lloyd et al 1996) but they have increased breast cancer specific worries (Lloyd et al 1996). Concerns

that informing women about a high risk of breast cancer could induce or increase anxiety or depression have not been borne out by research studies. A minority of women who had experienced the diagnosis or death of a mother may experience subsequent psychological problems or unresolved grief; daughters who were adolescents or in early adulthood are particularly vulnerable (Wellisch et al 1992, Hopwood et al 1998, Watson et al 1999).

Women state that the value of mammographic surveillance cannot be underestimated, but access is limited for young women at risk and the benefits are currently being researched. Preventive surgery and chemoprevention trials require careful balancing of the possible effects on fertility, body image, menopausal effects and unwanted side effects, leading to potentially difficult decision making.
Men who may be gene carriers are less likely to be tested than women so that information may not be available to unaffected women at risk, and this, together with men's own guilt and anxiety, may affect family dynamics (Dudok de Wit et al 1996).

Ethnic minorities and less well-educated women are under-represented in clinic attendees (Wonderling et al 2001). The number of affected relatives, relationships and position in the family may affect motivation for risk counselling and increased public awareness of cancer genes can lead to further pressure on individuals to deal with their risk.

4.1 Risk estimation (2004)

There are breast cancer risks that all women are exposed to (population level); risks that sub-populations (e.g. certain types of family history) are exposed to and the risks for each individual woman. The risks of breast cancer can be expressed in terms of an age-specific risk (e.g. risk over the next five years), or a lifetime risk (e.g. risk to age 80). Another important measure is the chance that a mutation in a high risk breast cancer gene (BRCA1 or BRCA2) may be present.

In many situations, the breast cancer risk to a woman with a family history of the disease can be estimated straightforwardly from epidemiological studies. These indicate that the risk of breast cancer to a woman with a single affected first degree relative is approximately twice the risk to women in general. The risks are higher if there are more affected relatives, or if the relative(s) is affected at a younger age.

With more complex situations, risks can be estimated by applying risk algorithms, although these models can give inconsistent results and have not been thoroughly evaluated.

Different risks apply to women who are carriers of mutations in the known high-risk genes, BRCA1 or BRCA2. The risk to carriers of BRCA1 mutations have been estimated to be 60-80% by age 70, while the risk to carriers of BRCA2 mutations is somewhat lower and for both genes the risks could be lower in a family with an identified mutation, but little family history. In most instances it is unlikely that a family history of breast cancer will be due to known high-risk genes such as BRCA1 or BRCA2 and we are only beginning to appreciate the contribution of other lower risk genes that may account for more breast cancer overall. In the absence of good epidemiological evidence on these other genes use of existing algorithms for calculating risk is still valid and most will take into account the possibility of such genes being involved.

Epidemiological studies indicate that risks associated with a family history are modified by other known breast cancer risk factors, including age at menopause, parity and breast feeding. It is less clear whether such factors also modify the risks in BRCA1 or BRCA2 carriers.

It must also be remembered risks can be expressed in terms of relative risk or absolute risks. Many research papers often give results in terms of relative risks, one group compared to another, which need to be considered in the context of both absolute and relative risks, especially as the relative risks often sound very dramatic/extreme changes in risk level.

4.2 Risk classification

In this guideline recommendations for care are presented in sections that reflect where the care is likely to be delivered, e.g. primary, secondary or tertiary care, rather than in categories of risk level, e.g. low, medium or high. This is done firstly to reflect service provision as much as possible and secondly to try and avoid problems that previously occurred with the use of low, high and medium risk level descriptions.

In the past, risk categories have been broadly described as 1. “low”, 2. “moderate” and 3. “high” risk. During the guideline development process it became clear that while the latter 2 terms (moderate and high) were generally accepted, the term “low” was misleading and in particular not accepted by patient groups and the lay members of the committee. It was considered misleading as these women are still at increased risk compared to the general

population. Other alternatives were considered, but the group finally felt that definitions should be described on the basis of whether women were cared for in primary, secondary or tertiary care following risk assessment. However it is also recognised that descriptions of women at high and moderate risk will also be necessary in some situations, and that the terms will still be used by many people in the clinical setting. As has been made clear in the relevant sections it is NOT expected that precise risks will be calculated in primary or secondary care, but that health care workers will utilise the algorithms provided. The thresholds for entry to each risk category are based on:

Near population risk:	Women at or near **population risk** of developing breast cancer (that is, a 10-year risk of less than 3% between age 40 and 50 years and a lifetime risk of less than 17%) are cared for in primary care.
Moderate risk:	Women at **moderate risk** of developing breast cancer (that is, a risk of 3–8% between age 40 and 50 years or a lifetime risk of 17% or greater but less than 30%) are generally cared for in secondary care.
High risk:	Women at **high risk** of developing breast cancer (that is a risk of greater than 8% between age 40 and 50 years or a lifetime risk of 30% or greater) are cared for in tertiary care. High risk also includes a 20% or greater chance of a faulty BRCA1, BRCA2 or TP53 gene in the family.

In the context of this guideline

All affected relatives must be on the same side of the family and be blood relatives of the consultee and each other.

In cases of bilateral breast cancer, each breast cancer has the same count value as one relative.

First-degree relatives: mother, father, daughter, son, sister, brother.
Second-degree relatives: grandparents, grandchildren, aunt, uncle, niece and nephew; half sister and half brother.

Third-degree relatives: great grandparents, great grandchildren, great aunt, great uncle, first cousin, grand nephew and grand niece

4.3 Family history taking (2004)

4.3.1 Introduction

Drawing a family tree is the first step in investigating a possible inherited predisposition to breast cancer. This will mean asking a woman to tell you about all their close relatives. It is necessary to know what age they have lived to, what tumours they may have had and the age at which these were diagnosed. Thus a family tree is drawn showing the consulting woman with an arrow and drawing out her first degree relatives (mother, father, sisters, brothers, children); her second degree relatives (grandparents, aunts, uncles, nieces, nephews) and in a thorough history third degree relatives (great grandparents, great aunts and uncles, first cousins). While family history of breast cancer in first degree relatives is nearly always correctly given (the cancer can be verified from pathology records or death certificates) this becomes more problematic for more distant relatives and is particularly a problem for abdominal malignancies and sarcomas (Douglas et al 1999). Verification of family history is an essential part of assessment in a cancer genetics clinic

4.3.4 Summary of evidence relating to recording and assessing family history

A number of studies have been identified which relate to the recording and assessment of family history in women with a family history of breast cancer, although generally, study design lacks rigour.

Four studies have assessed the accuracy of the family histories provided by women with and without breast cancer and have found that reporting of breast cancer family histories is generally reliable (Theis et al, 1994; Parent et al, 1997; Eerola et al, 2000; Husson et al, 2000). Case studies have shown, however, the importance of verifying family histories as a false family history has serious implications for patient management (Kerr et al, 1998). Another study found poor communication amongst families can impede the collection of family history information (Green et al, 1997).

Two studies have evaluated methods of identifying patients at increased genetic risk of breast and other cancers suitable for referral for genetic screening (a postal questionnaire and a family history assessment tool), both of which appeared to be useful instruments (Leggatt et al, 1999 and Gilpin et al, 2000, respectively). A computer support programme for interpreting family histories of breast and ovarian cancer was found to produce more accurate pedigrees, more appropriate management decisions and was preferred by doctors, in comparison to other methods (Emery et al, 2000); doctors found, however that it affected their control of the consultation (Emery et al, 1999).

In terms of evidence relating to psychosocial aspects of recording and assessing family history of breast cancer, 2 surveys have found that collecting family histories and notifying family members about their cancer risk does not appear to cause anxiety (Winter et al, 1996; Leggatt et al, 2000). An RCT, however, found that completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist (Qureshi et al, 2001).

4.3.5 Comment

Family history can be by far the most significant factor in predisposition. About 4-5% of breast cancer is thought to be due to inheritance of a highly penetrant dominant cancer

predisposing gene (Newman et al 1988, Claus et al 1994). However, these type of genes may only account for about 20% of the familial risk as up to 27% of breast cancer is attributable to heritable factors from twin studies (Peto & Mack 2000). If a woman inherits a fault in one of these genes her lifetime risk of breast cancer may be as high as 80-85%. Hereditary factors may play a part in a proportion of the rest, but these are harder to pin down. There are no external markers of risk (no phenotype) to help identify those who carry a faulty gene, except in very rare cases such as Cowden's disease (Nelen et al 1996) and Peutz Jegher disease. In order to assess the likelihood of there being a predisposing gene in a family, it is necessary to assess the family tree. Inheritance of a germ line mutation or deletion of a predisposing gene causes the disease at a young age and often, if the individual survives, cancer in the contralateral (opposite) breast. Some gene mutations may give rise to susceptibility to other cancers, such as ovary, colon and sarcomas (Malkin et al 1990, Leach et al 1993, Papadopoulos et al 1994, Nicolaides et al 1994). Multiple primary cancers in one individual or related early onset cancers in other relatives are, therefore, suggestive of a predisposing gene. To illustrate the importance of age it is thought that over 25% of breast cancer under 30 years is due to a mutation in a dominant gene, whereas less than 1% of the disease over 70 years is so caused (Claus et al 1994). 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 individuals (large families are more informative).

There are very few families where it is possible to be sure of dominant inheritance, but where 4 relatives in the same direct lineage (all related in first degree to at least one other affected individual) have early onset or bilateral breast cancer the risk of inheriting a gene for their offspring is close to 50%. Epidemiological studies have shown that about 80% of gene carriers develop breast cancer in their lifetime. Therefore, unless there is significant family history on both sides of the family, the maximum risk counselled is 40-45% (reflecting the 50% chance of inheriting a gene conferring an 80% risk). Breast cancer genes can be inherited through the father and a dominant history on the father's side of the family would give at least a 20-25% lifetime risk to his daughters. It is important to recognise however, that most family histories of breast cancer are not due to a mutation in BRCA1, BRCA2 or TP53 genes. Some are due to lower penetrance genes which have not yet been discovered and some are simply due to chance, given that breast cancer is a common disease.

4.5 Risk communication

4.5.1 Introduction

Women attending cancer genetics clinics want to discuss their family history, cancer risks and risk management options. However, they may feel unprepared for the consultation due to unfamiliarity with the process and content of genetic counselling, and have unrealistic expectations about access to genetic testing or mammographic surveillance (Hallowell et al 1997c). Lay beliefs about inheritance may interfere with assimilation of risk information and awareness of the family history may result in a fixed perception that risk is high (Richards 1999). Retention and recall of risk values will also depend on the salience of the information for counselees; risk reduction and access to breast screening may take precedence (Hallowell 1997a&b, Richards 1999).

4.5.4 Comment

The transfer of risk information is not straightforward. There is a high degree of uncertainty in the information given in genetic counselling, with respect to the risk of inheriting a predisposing gene, of gene penetrance and hence of developing cancer (Richards 1999). This uncertainty reflects the state of knowledge but is in direct contrast to the needs of counselees, who seek precise information (van Zuuren et al 1997, Julian-Reynier et al 2003 in press). Information can be provided in a number of ways and evidence is conflicting as to the optimal method of risk communication. Categorical risks are criticised for being open to wide interpretation and numerical values may be more difficult for some to understand. Whatever the difficulties, use of numerical risk information may be unavoidable, as this forms the basis for offering risk management (e.g. risk reducing surgery or mammographic surveillance) and decision making about preventive strategies (Fisher 1999 and others).

There has been evaluation of the effectiveness of risk counselling on women's risk accuracy. The apparent precision of numerical information to guide risk management appeals to geneticists and counsellors, but the influence of risk accuracy on health care behaviour and lay beliefs is less clear. Aids to risk communication, such as summary letters, audiotapes and videotapes have shown limited benefit (Cull et al 1998, Evans et al 1994, Hallowell & Murton 1998, Watson et al 1998,) but other strategies, such as visual displays are being evaluated.

9 Audit criteria (2004)

The measures that could be used as a basis for audit are in the table overleaf.

Criterion	Standard	Exception	Definition of terms
Standard written information should be developed for use in primary, secondary and tertiary care	100% of centres to provide this information	Nil	Written information that will provide consistent advice to women, including risk and breast awareness information, lifestyle advice etc
Local protocols should be developed with clear referral mechanisms between primary, secondary and tertiary care and with appropriate facilities	100% of organisations should have local protocols	Nil	
Psychological services available in secondary care	100% of secondary care have a named individual providing psychological support	Nil	
Information should be provided about the potential advantages and disadvantages of mammographic surveillance	100% of women who are offered mammographic surveillance	Nil	Information includes written information and discussion on ▪ Reduced sensitivity in younger breasts ▪ Radiation risks ▪ Possible psychological impact of recall visit
Risk-reducing surgery should be managed by a multidisciplinary team	100% women who have risk reducing surgery		Risk-reducing surgery refers to bilateral mastectomy and oophorectomy A multidisciplinary team should include: ▪ facilities to verify family history and clinical genetic risk assessment ▪ mammography before surgery ▪ psychological assessment and counselling ▪ information about support groups ▪ oncoplastic/breast reconstructive skills

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion plus number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieve

10 Research issues (2004)

This subject would benefit from further research in most areas. The guideline development group identified the following areas which they felt would help improve the evidence base for future versions of this guideline.

1 Validation of risk assessment models is urgently needed.

2 Different risk communication strategies should be evaluated.

3 Prospective studies are needed of the short and long terms psychosocial and sexual impact of risk reducing surgery in women with a family history of breast cancer.

4 Costs and benefits of surveillance in the 30-40 years age groups should be assessed by national pooling of all UK data.

5 The effectiveness of MRI as a surveillance technique, especially in high risk women / gene carriers.

6 The effectiveness of surveillance, in particular mammography, in those aged 40-49 years.

7 Endocrine prevention studies (tamoxifen, aromatase inhibitors) would be valuable.

8 Relative effectiveness of different methods of gene mutation testing.

9 The role and usefulness of computer packages in risk assessment, audit and other aspects of care would be useful.

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Appendix 25 – Risk estimates table

This table is an expanded version of Table 1, section 3.3.

It illustrates the:

- lifetime risks of breast cancer (to age 80 years)
- the remaining risk (to 80)
- risk over the next 10 years

for the general population and for a woman with a mother or sister diagnosed aged 30-39 years.

(all rounded to 1 decimal place)

Age in years	**Population cumulative Risk [1]**	**Population 10 year risk [1]**	**Claus cumulative risk [2]**	**Claus risk next 10 years [2]**	**Collaborative Group-Cumulative risk [3]**	**Collaborative Group- risk next 10 years [3]**
20	0	0.1%	0	0.5%	0	0.4%
30	0.1%	0.5%	0.5%	1.2%	0.4%	2.2%
40	0.5%	1.5%	1.7%	2.7%	2.6%	4.1%
50	2.0%	2.8%	4.4%	4.2%	6.7%	5.1%
60	4.8%	2.8%	8.6%	4.4%	11.8%	3.8%
70	7.6%	3.1%	13%	3.5%	15.6%	4.2%
80	10.7%		16.5%		19.7	

Notes:
1.Office of National Statistics 2001
2.Claus et al 1994
3.Collaborative Group 2001

Appendix 26: Breast cancer risk categorisation (2004)

General Comments

1 The guidelines aim to generate three risk categories: near-population, moderate and high.

2 The starting point for this classification was that the high risk category should include women with either (a) a 30% chance of developing breast cancer by age 80 or (b) a >8% chance of developing breast cancer over the next ten years or (c) one of whose affected relatives has a >20% chance of harbouring a deleterious BRCA1 or BRCA2 mutation. The moderate risk women should include other women with a >3% risk of breast cancer over the next ten years.

3 The immediate risk of breast cancer clearly depends on the exact age of the woman since the incidence rates increase with age. However, since the main issue at least for the moderate risk category was early screening, the woman was assumed to be aged below age 50 for this purpose. For simplicity, the woman is assumed to be age 40. Different criteria would arise if the exact age of the woman is considered (see below).

4 The probability of a BRCA1 and BRCA2 mutation refers to their affected relative rather than the woman themselves. Usually (in a previously untested family) this will equate to a probability of the woman themselves of 10% or more. It was expressed in this way because the testing is organised by family and almost always involves testing an affected person first. Note that probability is intended to refer to the probability of a mutation being present, not the probability of a mutation being found on a specific test.

5 The categories are based only on family history. Other factors (reproductive, hormonal etc.) affect the risk and can be incorporated but this was considered beyond the scope of this classification.

6 Family history is intended to cover breast cancer (in men and women) and ovarian cancer. It does not cover other cancers, even though some (e.g. prostate, pancreas) would affect the carrier probabilities. Similarly, there is no consideration of the histological type of the cancer (e.g. where ER positive or negative) although this also affects the carrier probabilities. The assumption is that these could be incorporated into counselling at secondary/tertiary level.

7 The cancer risks for women with specific family history can be derived either from empirical studies (mostly case-control studies) or statistical models. Case-control studies provide direct estimates of risk for women with certain common types of family history (essentially based on number of affected first degree relatives), and in that context are preferred. However they cannot deal with the full complexity of the family history (for example, the pattern of disease among second or more distantly affected relatives, their ages etc). Statistical models such as Claus, BRCAPRO and more recently the Tyrer-Cuzick and Boadicea models have the advantage that they can compute risks for any type of family history (and, in the case of BRCAPRO and Boadicea, BRCA1/2 carrier probabilities). The disadvantage of the modelling approach at the current time is that none of the models have been extensively validated and, in the case of BRCAPRO and Claus, the models are unduly simplistic and can give risk estimates that are not

consistent with empirical observations. Where possible we have used the Collaborative Group paper as the basis of the risk categorisation.

8 Since empirical risks are generally based on first degree relatives only, some adjustment is appropriate for practical use. Thus for example the risk to a women with an affected mother but no affected second degree relatives is lower that the risk based on their first degree family history alone. This is somewhat problematic for defining simple risk categories, since the extent of the adjustment will depend on the whole pedigree and, more subtly, on the accuracy of the information about more distant relatives.

9 A complication in defining absolute risks is that most risk estimates have been based on studies and rates from some time ago. Thus the Collaborative Group analysis derived absolute risk estimates based on 1998-1990 rates, and models (e.g. Claus, Boadicea) use rates from a similar period.

Moderate risk category

Single Affected Relative

The following table gives the estimated risks over the next years, for unaffected women of given ages with an affected first degree relative, based on the estimated relative risks from the Collaborative Group paper applied to 2001 population rates.

Age of women	**Population**	**Age at diagnosis of affected 10 relative**			
		Case<40	40-49	50-59	60+
20	0.0665%	0.36%	0.19%	0.18%	0.13%
30	0.438%	2.2%	1.2%	1.2%	0.85%
40	1.493%	4.1%	2.9%	3.2%	2.5%
50	2.765%	5.1%	5.6%	4.2%	4.2%
60	2.838%	3.8%	3.8%	4.1%	3.8%
70	3.134%	4.2%	4.2%	4.5%	4.2%

For women aged 40, the ten year risk is close to 3% for women with a 1st degree relative diagnosed up to age 60. If, however, the risks are based on 1990 rates, only women a first degree relative diagnosed below age 40 would qualify. The same would apply if the criterion were raised to, say, 3.5% to reflect the increase in incidence.

Another issue that the breast cancer incidence rates in the next ten years will increase with the age of the woman, within the 35-50 age-group, and that the categorisation should in theory reflect this. Peto has argued that the risk of breast cancer is approximately constant (at about 3.5% p.a.) after the age of diagnosis of the first case. Most data (including the Collaborative Group re-analysis) seem to be broadly consistent with this. So one could argue that a more consistent definition of the moderate risk category would be: any women older than the age at diagnosis of her affected 1st degree relative. In the guidelines, a fixed age cut-off was preferred for simplicity.

For women with only an second (or more distant) degree relative affected, excess risks will be reduced by (at least) a factor of 2 under any plausible model. On this basis, no woman

would qualify as moderate risk (except possibly women with a second degree relative diagnosed below age 30, for which the data are poor).

Two affected relatives

The Collaborative Group paper quotes a relative risk of ~ 8 fold for women <50 with two first degree relatives affected over age 50. This would be sufficient to get them into the moderate risk group.

Some data (e.g. from the Swedish population register) suggests this risk may be exaggerated. It is unclear on the basis of these data whether there should be an age at diagnosis cut-off. For the purposes of the guidelines, the moderate risk group is taken to include any women with two affected 1st degree relatives at any age.

There is a discrepancy here with the Claus model. Under the Claus model, the risk drops markedly for cases aged over 60. This has to do with the shape of the incidence curve for carriers of the postulated "susceptibility allele" in this model (the probability of an affected women diagnosed with breast cancer, who has an affected relative diagnosed at the same age, carrying the susceptibility allele drops from over 30% at ages 50-59 to approximately 10% at ages 60-69. This is probably a weakness in the model, reflecting its attempt to model risk in terms of a single high risk gene. The Boadicea model does not exhibit this behaviour and gives risks exceeding the 3% threshold at all ages of diagnosis.

For women with one 1st and one 2nd degree relative we do not have direct estimates. On the basis of the Boadicea (polygenic) model, the relative risk for such women would be close to 3, and would therefore qualify (Antoniou et al, 2002). The Claus model also indicates that such women qualify (for ages at diagnosis below 60).

Similar arguments apply to women with two 2nd degree relatives (e.g. grandmother and aunt). Heuristic arguments would suggest that these have half or less of the excess risk of the former group and would not generally qualify as moderate risk. Both the Claus and Boadicea models agree with this. However, women with two second degree relatives diagnosed at a young age would qualify. These include women with two second-degree relatives diagnosed below age 50. For consistency with the high-risk category, this group is taken to include cases where the average age at diagnosis is below 50.

Bilateral breast cancer

There is large volume of data indicating that the risks are greater to the relatives of bilateral cases. Based on the study of Hemminki et al, based on the Swedish registry, which is the largest, the overall RR of breast cancer in daughters of bilateral breast cancer cases is 3 fold, and is ~2.6 fold even for cases diagnosed over age 60. The most the most logical criterion would be to include all first degree relatives of bilateral cases as moderate risk. This is consistent with the argument that (from a genetic viewpoint) a bilateral case should count as two cancers. Although some criteria have included an age cut-off. the number of women presenting with an affected bilateral case where both cancers were diagnosed over 50 is likely to be small.

Male Breast Cancer

The evidence for an increased risk associated with a first degree relative with male breast cancer has been found in many studies, with relative risks typically >2 fold. There are few data on the effect of age, though the largest study (Rosenblatt et al.1991) study did estimate a 3 fold relative risk for cases <60 and a lower relative risk for older cases. A cut-off of <60

is defensible, but no age cut-off would be simpler and more consistent with the specialist referral.

Ovarian Cancer

Most data suggest that the increased risk associated with a family history of both breast and ovarian cancer is mostly due to BRCA1 and BRCA2 mutations.

A complication here is that the effect of age at breast cancer diagnosis on BRCA1 prevalence is much stronger than for BRCA2 or for the familial risks. Thus the prevalence in cases drops from ~5% in the 30-39 age-group to less than 1% in the 50-59 age-group. Nevertheless, the prevalence among cases with a family history of ovarian cancer will be substantial even for older cases (although this will also depend on the age of diagnosis of the ovarian cancer, another complication). For example, even for cases aged 60-69 at diagnosis with an affected relative with ovarian cancer aged 40-49, the probability of a BRCA1 mutation is of the order of 10% (based on various calculations, including the estimates of Antoniou et al, 2003 and Boadicea predictions). On this basis, women in this category should be included as moderate risk regardless of the age at diagnosis of the breast cancer.

The logical criterion here would be all women with two 10 (or one 10, one 20) affected relatives with breast cancer and/or ovarian cancer.

High risk Category

2 case families

2 1st degree relatives. It is clear that the two cases at any age does not qualify for the high risk category, on the basis of an 8% risk over the next ten years (the Collaborative Group paper estimates a risk of ~5%) or on the basis of mutation carrier probability. Two cases at any age might qualify on the basis of a cumulative risk of 25% by age 80.

According to the collaborative group paper, the ten-year risk would exceed 8% if one case is diagnosed below age 40. Thus, women with two relatives affected at a sufficiently young age would qualify as high risk. It is uncertain where the correct age cut-off should be. For the purposes of the guidelines, an average age of 50 has been chosen.

One 1st and one 2nd degree relative. Again there is uncertainty in this situation. A single gene model such as Claus would predict a similar risk to that for 2 1st degree relatives and so would include, but a more complex model such as Boadicea predicts substantially lower risks. For the purpose of the guidelines the same average of 50 criterion has been adopted for consistency, but this requires further research.

Ovarian cancer

Here it is clear that, on the basis of known BRCA1/2 risks, at least for ovarian cancers diagnosed in the 40-49 age-group, the carrier probability will exceed 20% for families with two ovarian cancers. For families with or one breast cancer and one ovarian cancer diagnosed in the 40-49 age-group, the carrier probability may be approximately 20% (~17% on the basis of recent BRCA1/2 risks; Antoniou et al, 2003). By similar arguments, the carrier probabilities will be too low if the breast cancer case is diagnosed above age 50.

The carrier probabilities are lower if ovarian cancer is diagnosed below age 30 (rare) or above age 50 (for BRCA1) or 60 (for BRCA2).

Male breast cancer

Similar arguments apply for male breast cancer. 5-10% of cases harbour a BRCA2 mutation, so a single case would not be sufficient for high risk, but a male breast cancer in conjunction with a female case (possibly at any age) would be sufficient.

Families with 3+ cases

Calculations based on a variety of models indicate that families with 3 cases (for example, mother, sister and aunt) do not necessarily qualify as high risk on any basis, whilst families with three cases diagnosed at a young age (for example, below age 50) do qualify. For the purposes of the guideline we have chosen an arbitrary cut-off of an average of less than 60 years.

Families of Ashkenazi Jewish descent

Families of Ashkenazi Jewish descent are treated differently because the BRCA1/2 carrier probabilities are higher. Systematic studies indicate carrier probabilities in excess of 20% for breast cancer cases diagnosed below age 40 (but not at older ages) and for ovarian cancer cases. It should be noted that Ashkenazi Jewish women do not generally have a higher risk of breast cancer than other women in the U.K. The reason for referral in this case related solely to the greater BRCA1 carrier probabilities.

Appendix F

Removed sections from CG41 (2006) guideline

1. Introduction (2006)

The Familial Breast Cancer Guideline (NICE) was published in 2004. The recommendation made on the use of MRI in diagnosing breast cancer was as follows:

On the basis of current evidence, MRI and ultrasound should not be used in routine surveillance practice but may have a role in problem-solving mammographically detected abnormalities.

(Note: several MRI studies have already been presented at major cancer meetings and will report in the next 2 years. This recommendation should be reviewed when they become available.)

These studies have now been published and this review updates the evidence. Guidance on other issues was not considered by this review and remains current.

Recent evidence has suggested that MRI screening increases the sensitivity of breast cancer screening at the expense of specificity.[Leach et al., 2005] This additional sensitivity has the potential to identify cases sooner which ought to lead to more promising prognoses. Furthermore, a hastening of a correct identification can prevent disutility associated with false negatives prior to their eventual diagnosis. Similarly, evidence has suggested that the sensitivity of the mammography options is partially compromised in younger groups, due to breast tissue density issues. [Kerlikowske et al., 1996] The benefit of MRI screening has to be contrasted between different groups of women, and then compared with the cost implications that MRI screening has, both in the screening programme (such as the cost of those incorrectly brought back for further investigation) and in the wider National Health Service.

The primary question that this investigation is looking to answer is whether MRI screening can be recommended on clinical and cost-effectiveness grounds in particular populations of women

3. Evidence statements

1 MRI in combination with mammography has increased sensitivity relative to mammography alone in surveillance for breast cancer in women at high risk of familial breast cancer and particularly BRCA1 & BRCA2 carriers. (Ib)

2 Four out of five studies showed that mammography had a greater specificity than MRI in the high risk group. (Ib)

3 Mammography has been shown to be a useful adjunct to MRI in the high risk group, particularly for BRCA2 carriers because of their high incidence of ductal carcinoma insitu (DCIS). There is also some evidence that within the BRCA2 population mammography has a higher sensitivity than MRI in detecting DCIS.(Ib).

4 In two studies there was a greater differential in sensitivity in favour of MRI over mammography in BRCA1 carriers. (Ib)

5 No studies were found comparing the diagnostic sensitivity of digital mammography versus MRI in women at high risk of FBC

6 Digital mammography has increased sensitivity over film-screen mammography in the surveillance of women from the general population under 50 years of age, pre-menopausal & peri-menopausal and those with dense breast tissue. (Ib)

7 No economic evaluations were identified that dealt with the cost-effectiveness of surveillance tools in those at a familial risk of breast cancer.

8 A cost utility model developed for this work showed that a combined approach of annual mammography and Magnetic Resonance Imaging (MRI) is a cost-effective intervention in all women with a BRCA1 mutation aged 30–49 (Ib)

9 A cost utility model developed for this work showed that the use of a combined approach of annual Magnetic Resonance Imaging and mammography is a cost- effective intervention in non-BRCA1 women aged 30-39 with an 8% or greater 10- year risk (Ib)

10 A cost utility model developed for this work showed that the use of a combined approach of annual Magnetic Resonance Imaging and mammography is a cost- effective intervention in non-BRCA1 women aged 40-49 with a 20% or greater 10- year risk (Ib)

3.1. Responsibility and support for guideline development (2006)

3.1.1. The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to the National Institute for Health and Clinical Excellence (NICE).

3.1.2. The Technical Team

The Technical Team had the responsibility for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The Technical team working on this guideline consisted of the:

- Information Scientist, who searched the bibliographic databases for evidence to answer the questions posed by the Guideline Development Group (GDG)
- Reviewer, with a knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG.
- Health Economist who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness
- Project Manager, who was responsible for organising and planning the development, for meetings and minutes and for liaising the Institute and external bodies.

3.1.3. The Guideline Development Group (GDG)

Guideline Development Groups are not committees but working groups. The aim is to get the range of experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations who were sent the draft scope of the guideline and some guidance on the expertise needed. From the nominations, three consumer representatives and the following healthcare professionals joined the GDG.

The GDG members of the original guideline were re-convened under the same chairmanship. Because of the topic to new members were invited to join

4. Clinical Effectiveness of MRI

4.1. Methods

The question being addressed - is as follows:

"**What is the effectiveness and cost effectiveness of MRI versus mammography versus MRI and mammography in surveillance for breast cancer in women at increased risk compared to the general population?"**

Population: Asymptomatic women at an increased risk of breast cancer

Intervention: MRI or MRI & mammography (digital or film)

Comparator: Mammography (digital or film)

Outcomes: sensitivity, specificity, cases identified, positive predictive values,

negative predictive values, mortality, cost effectiveness

Inclusion criteria: RCT's, cohort or case-control studies evaluating MRI Vs mammography (X-ray mammography is the gold standard) or MRI and mammography Vs mammography in the detection of breast cancer in asymptomatic women with an increased risk of breast cancer.

Exclusion criteria: Insufficient information to allow construction of 2x2 table,. women without an increased risk of breast cancer (unless reported by sub group), computed radiography.
It was not within our remit to consider quality of life issues surrounding the use of MRI. However, this may be a question to be addressed when the full guideline is updated.

The search strategy used in the original guideline was repeated and updated from December 2002 when the last searches were conducted. Foreign language papers were excluded.

The Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), CENTRAL, Medline, Embase, Cinahl, & PsycInfo databases were searched from 2003 until 30th November 2005. The abstracts were read and 17 papers obtained. 12 papers were rejected because they were not relevant or did not meet the inclusion criteria. 5 papers were included for review that assessed the diagnostic accuracy of MRI vs mammography in women at increased risk of developing breast cancer.

Areas without evidence:

It was anticipated that we would not find studies on the accuracy of digital imaging in an increased risk population group. Therefore we included any studies conducted in a normal population where subgroup analysis had been undertaken in the under 50 age group

An additional search was carried out for diagnostic studies of digital mammography in an average risk breast cancer population. The databases above were searched between 2003 and 22nd December 2005. Foreign language studies were excluded.

Seven studies were obtained. Five studies were excluded because they were not relevant or did not meet the inclusion criteria. Two papers were included for review because they had carried out subgroup analysis in the population of interest to this guideline.

Where possible the data from each of the included studies have been reproduced in a 2x2 table to give figures of the true positive, false positive, false negative and true negative results of the diagnostic tests undertaken.

4.2. MRI Evidence

MARIBS study (Leach et al 2005)

Table 1 Sensitivity and Specificity Table adapted from MARIBS study [Leach et al., 2005]

	Mammography			MRI			MRI & mammography		
	All women	*BRCA1*	*BRCA2*	All women	*BRCA1*	*BRCA2*	All women	*BRCA1*	*BRCA2*
No. women	649	139	86	649	139	86	649	139	86
No positive screens True positive									
False positive	121	30	13	344	76	41	428	95	51
No negative screens True negative									
False negative	21	10	6	8	1	5	2	1	1
Sensitivity %	40%	23%	50%	77%	92%	58%	94%	92%	92%
Specificity %	93%	92%	94%	81%	79%	82%	77%	74%	78%
predictive value % positive	10%	9%	32%	7%	14%	15%	7%	11%	18%
negative	99%	97%	97%	99%	100%	97%	100%	100%	99%

The MARIBS study was a multicentre prospective cohort study of 649 women aged

35-49 years with a *BRCA1*, *BRCA2*, *TP53* mutation or strong family history of breast cancer. Annual screening of MRI and mammography was carried out for 2-7 years (1881 screens). A total of 35 cancers were diagnosed. 19 by MRI only, six by mammography only and eight by both, with two interval cases. 11 invasive cancers were less than 10 mm in greatest dimension. Of these, six were detected by MRI, three by mammography, one by both modalities, and one interval case. Four invasive cancers were between 10-14 mm. Three were detected by MRI and one by both modalities. Five invasive cancers were between 15-19 mm. Four were detected by MRI and one by both modalities. Nine cancers were 20 mm

or larger in dimension, six were detected by MRI and three by both modalities. There were six cases of ductal carcinomas in situ (DCIS), of which four were less than 10 mm in diameter. Three were detected by mammography, two were detected by both modalities and one was an interval cancer. Of the 29 invasive cancers, three were grade 1, seven were grade 2, 19 were grade 3. Of cancers detected by screening or in a screening interval, 21 of 26 were node negative.

Sensitivity was significantly higher for MRI than for mammography and was particularly pronounced in *BRCA1* carriers (13 cancers). The authors note that MRI is able to detect tumours earlier in their development compared with mammography, although mammography is relatively good at detecting DCIS compared with MRI. In spite of annual screening with two modalities, some large, node positive tumours were identified. This reflects the rapid growth characteristics of cancers in women with germline mutations.

Overall the study shows that the combination of MRI with mammography is the most effective screening examination for *BRCA1* and *BRCA2* carriers and the full high-risk cohort studied here. The authors also conclude that their results suggest that MRI screening would be of most benefit to *BRCA1* carriers.

MRISC study (Kriege et al 2004)

Table 2 Sensitivity and Specificity Table adapted from [Kriege et al., 2004]

	Mammography	MRI
Total screens	4169	4169
No positive screens True positive	18	32
False positive	207	420
No negative screens True negative	3917	3704
False negative	27	13
Sensitivity %	40	71
Specificity%	95	90
predictive value %		
True	8	7
Negative	99	100

Women who had a cumulative lifetime risk of breast cancer of 15 percent or more were included in this cohort study [Kriege et al., 2004]. 1909 asymptomatic women including: 358 carriers of germline mutations, 1052 high risk (30-50% cumulative lifetime risk), 499 moderate risk (15-30% cumulative lifetime risk) were screened, with a mean follow-up of 2.9 years. Among the women examined by both methods at the same screening visit, 45 tumours were detected including 6 ductal carcinomas in situ (DCIS). Five patients were excluded from analysis.

Of the invasive cancers 19 were 1cm or less in diameter, 14 were between 1-2 cm, 11 were more than 2 cm in diameter. Six of the 42 invasive tumours with known axillary status were node positive.

11 grade 1 cancers were found in women at high risk (68.8%), 6 in moderate risk women (75.0%), 2 in mutation carriers (10.5%).

One Grade 2 cancer was found in women at high risk (6.2%), 2 in moderate risk (25.0%), 5 in mutation carriers (26.3%).

Four Grade 3 tumours were found in women at high risk (25.0), 1 in moderate risk (12.5%), 12 in mutation carriers (63.2%).

The authors comment that larger tumours were found in women with *BRCA1*, *BRCA2* and *TP53* mutations than the other two risk groups in the study, suggesting that more frequent screening is necessary for this group of women.

The study found that the sensitivity of MRI was higher than mammography, but that the specificity and positive predictive value were lower. MRI detected 20 cancers (including 1 DCIS) that were not found by mammography, and the stage of these cancers was favourable, 11 of the 19 invasive tumours being less than 10 mm.

The study also showed that mammography had a higher sensitivity than MRI for detecting ductal carcinoma in situ (DCIS) 83% (five out of six cancers detected), compared with 17% (one out of six) for MRI. In this study, screening with MRI led to twice as many unneeded additional examinations compared with mammography (420 versus 207) and three times as many unneeded biopsies (24 versus 7). The authors conclude that the MRI can detect breast cancer at an earlier stage in women at risk for breast cancer.

Warner et al study 2004

Table 3 Sensitivity and Specificity Table adapted from [Warner et al., 2004].

	Mammography				MRI			
	Year 1	Year 2	Year 3	Total	Year 1	Year 2	Year 3	Total
Total screens	236	136	85	457	236	136	85	457
No positive screens True Positive	5	3	0	8	11	5	1	17
False positive	1	0	0	1	15	4	1	20
No negative screens True negative	222	129	83	434	208	125	82	415
False negative	8	4	2	14	2	2	1	5
Sensitivity %	38	43	0	36	85	71	50	77
Specificity %*	99.6	100	100	99	93	97	99	95.4
Predictive value % True	83	100	N/A	88	42	56	50	46
Negative	97	97	98	97	99	98	99	99
Abbreviations: MRI magnetic resonance imaging; N/A not applicable *Definition of specificity is based on biopsy rates								

A cohort study of 236 asymptomatic women with *BRCA1* or *BRCA2* mutations underwent 1-3 annual screenings [Warner et al., 2001]. The study found that MRI was more sensitive for detecting breast cancer than mammography or CBE alone.
22 cancers were detected in total; 16 invasive, 6 ductal carcinoma in situ (DCIS). There was one interval cancer.

All six of the DCIS cancers were found in the *BRCA2* group. Four in year 1, (two detected by MRI, tumour size between 3.0-4.0 cm, one detected by mammography, tumour size not given because specimen consisted of few small scattered foci, one detected by both modalities, tumour size 1.5 cm). One in year 2, (detected by mammography, no remaining cancer was observed at time of excisional biopsy). One in year 3, (detected by MRI, tumour size 6.0 cm).

Nine invasive cancers in year 1 were detected. Six had tumour sizes between 0.5-

1.0 cm (3 detected by MRI, 1 detected by mammography, 2 detected by both modalities), three had tumour sizes of 1.5-2.0 cm (2 detected by MRI, 1 by neither (ultrasound.)) Six invasive cancers were detected in year two. Three had tumour sizes of 0.6-1.0 cm (3 detected by MRI), three had tumour sizes of 1.5-2 cm (2

detected by both modalities, 1 by neither (ultrasound). One cancer was node positive.

The study shows that the addition of annual MRI to mammography improves the sensitivity of surveillance for detecting early breast cancers. The authors suggest that mammography appears to be a useful adjunct to MRI for *BRCA2* carriers because of the high incidence of ductal carcinoma insitu (DCIS) in this group.

The authors note that MRI recall rates decreased from 26% on the first round of screening to 13% on the second round and 10% on the third. The authors conclude that the study supports the position that MRI-based screening should be used for breast cancer surveillance for *BRCA1* and *BRCA2* mutation carriers. Further research is required to demonstrate whether this modality lowers breast cancer mortality before it can be recommended for general use.

Kuhl et al study 2005

Table 4 Sensitivity and Specificity Table adapted from [Kuhl et al., 2005].

	Mammography				MRI				MRI & Mammography			
	All	Risk 20%	Risk 20-40%	Mutation Carriers	All	Risk 20%	Risk 20-40%	Mutation carrier	All	Risk 20%	Risk 20-40%	Mutation carrier
Total screens	1701	352	751	167	1701	352	751	167	1701	352	751	167
No positive screens True positive	14	3	5	2	39	6	20	8	40	6	20	8
False positive	45	11	18	5	39	10	16	4	55	14	14	9
No negative screens True negative	1364	302	676	154	1370	354	678	155	1354	299	673	150
False negative	29	3	15	6	4	0	0	0	3	0	0	0
Sensitivity %	32.6	50	25	25	90.7	100.0	100.0	100.0	93.0	100.0	100.0	100.0
Specificity %	96.8	96.5	97.4	96.9	97.2	97.4	97.7	97.5	96.1	95.5	97.0	94.4
Predictive rates % Positive PV	23.7	21.4	21.7	28.6	50.0	42.9	55.6	66.7	42.1	30.0	51.2	47.1
Negative PV	97.91	99.0	97.4	96.8	99.7	100	100	100	99.7	100	100	100

This cohort study comprised of 529 asymptomatic women who were suspected or proven to carry a breast cancer susceptibility gene [Kuhl et al., 2005]. A total of 1542 surveillance rounds were completed with a mean follow-up of 5.3 years. This study found that in patients at high familial risk for breast cancer MRI had the highest sensitivity, specificity and positive predictive rates for the detection of cancer. Forty three cancers were identified in the total cohort (34 invasive, 9 ductal carcinoma in situ (DCIS)). Forty of the forty three were diagnosed by imaging studies. Two cancers were palpable at the time of diagnosis (one at the regular screening interval, one was an interval cancer diagnosed in between screening rounds). These two clinically palpable cancers were also visualised by MRI but not mammography.

Nineteen cancers were diagnosed by means of MRI only. These included five intraductal (all high grade) and 14 invasive cancers with a median size of 7.5 mm. All fourteen invasive cancers were staged pT1 and all had negative axillary lymph
nodes.

14 cancers diagnosed by mammography. These included three intraductal and ten invasive cancers with a median size of 12.0 mm, four were node positive.

39 cancers were detected by MRI. These included eight intraductal and 31 invasive cancers with a median size of 11.0 mm, five were node positive.

This study found that MRI had the highest sensitivity, specificity and positive predictive value for the detection of invasive as well as intraductal cancer. The addition of mammography to MRI did not improve sensitivity to a statistically significant degree. The authors conclude that compared with mammography, surveillance with MRI allows an earlier diagnosis of familial breast cancer and at an earlier stage. The specificity of MRI was equivalent to that achieved with mammography, which the authors suggest is due to the highly experienced readers used in the study. The number of cancers in the subgroup at moderate risk was too low to make valid recommendations regarding which surveillance modalities to recommend. The findings of this study lead the authors to recommend that MRI should be an integral part of surveillance for women at high familial risk, particularly in documented mutation carriers, but also for women without documented mutation The authors also note that further work is required to assess the risk/benefit ratio of mammography and MRI in young *BRCA1* mutation carriers who may exhibit an increased radiosensitivity.

International Breast MRI Consortium Working Group study (Lehman et al 2005)

Table 5 Sensitivity and Specificity Table adapted from [Lehman et al., 2005]

	Mammography	MRI
Total screens	367	367
No of positive screens True Positive	1	4
False positive	3	20
No of negative screens True negative	360	343
False negative	3	0
Sensitivity %	25.0	100.0
Specificity %	99.0	95.0
Predictive rates % Positive Predictive value	25.0	17.0
Negative predictive value	99.0	100.0

This prospective study compared the performance of screening mammography with MRI on 367 asymptomatic high risk women age 25 or above [Lehman et al., 2005]. The objective of this study was also to ascertain if imaging and biopsy procedures are reliable and do not result in excessive false positive examinations. Imaging results recommended 38 biopsies of which 27 were performed. 4 cancers were detected overall, all were detected by MRI, and mammography detected 1 of these. The biopsy recommendation rates for MRI and mammography were 8.5% (95% CI 5.8-11.8) and 2.2% (95% CI 0.1-4.4), respectively. Twenty four women underwent biopsy based on a positive MRI and four based on a positive mammogram. Of the lesions that were identified as malignant, two were identified in women with scattered fibroglandular density, and two were identified in women with heterogeneously dense breast tissue. Three of the four lesions were identified as infiltrating ductal carcinomas ranging in size from 5 mm to 13 mm, and one lesion was DCIS. All were lymph node negative.

The limitations of this study are that only one screening round was undertaken and no follow-up was carried out to identify potential false negative MRI results or delayed diagnoses of those who declined biopsies. The authors conclude that although the specificity of MRI has been challenged they found only 5% of women underwent benign biopsy and the PPV of biopsies performed was 17%. They recommend that MRI should be considered as a complement to mammography.

4.3. Digital mammography Vs film mammography Evidence

DMIST study (Pisano et al 2005)

There was insufficient data provided to construct a 2 x 2 table.

This prospective study was conducted to assess whether the use of digital mammography had a higher sensitivity than film mammography [Pisano et al., 2005].

The results from 42,760 asymptomatic women entered into the trial were reported. Sub group analysis was undertaken in the following: under 50 age group, pre- menopausal and peri-menopausal n=15803, and those with heterogeneously or extremely dense breasts n=19897. In the entire population the diagnostic accuracy of digital and film mammography was similar. The accuracy was significantly higher for digital mammography in the under 50 age group, women with dense breasts and pre-menopausal & peri-menopausal women.

A total of 335 cancers were diagnosed. Of these 254 (75.8%) were diagnosed within

365 days after study mammography and 81 (24.2%) were diagnosed between 366-

455 days after study mammography.

In the pre-menopausal & peri-menopausal subgroup film mammography identified seven (2.1%) invasive cancers, four (1.2%) ductal carcinoma in situ (DCIS), three were node positive. Digital mammography identified 19 (5.7) invasive cancers, 14 (4.2%) DCIS, five were node positive.

In the heterogeneously dense or extremely dense breast subgroup, film mammography identified 12 (3.6%) invasive cancers, seven (2.1%) DCIS, five were node positive. Digital mammography identified 26 (7.8%) invasive cancers, 14 (4.2%) DCIS, five were node positive.

The authors conclude that digital mammography was significantly better than conventional film mammography at detecting breast cancer in these groups. The cancers detected by digital mammography and missed by conventional mammography included many invasive and high-grade in situ cases. The authors conclude that this justifies the use of digital mammography in these groups.

Oslo II study (Skaane et al 2004)

This randomised controlled trial [Skaane and Skjennald, 2004] was conducted to compare cancer detection rates, recall rates and positive predictive value of film mammography (FM) with digital mammography (DM). 25,263 women aged 45-69 years were randomised to either film or digital mammography. Sub group analysis was carried out on the 45-49 age group (n=7607). 17 cancers were detected with FM (10 invasive cancers, seven DCIS). The median size of invasive cancers detected by FM was 11mm. 8 cancers were detected with DM (six invasive cancers, two DCIS). The median size of invasive cancers detected by DM was 10 mm.

Recall rates in both groups were significantly higher with DM than FM ($P<0.05$), but positive predictive value was not significantly different. In the 45-49 age group the cancer detection rate was nearly equal for the two modalities ($P=0.686$.) The authors state that a limitation of the study was that comparisons between FM and DM were available only during review of positive mammograms. Low recall rates and no follow-up for probably benign lesions might have caused cancers represented by a positive score on images in either modality to be dismissed at consensus meetings, where decisions about which women should continue in the screening programme and which be recalled for diagnostic workup were taken. Follow-up for two years would be necessary to detect incorrectly dismissed cancers and to evaluate interval cancers in a subsequent screening round.

The number of breast cancers in the group was small and the authors state that the results do not permit any final conclusions regarding the comparison of FM and DM in women younger than 50 years.

5.5. References

Reference List

Amir, E., Evans, D. G., Shenton, A., Lalloo, F., Moran, A., Boggis, C., Wilson, M., & Howell, A. 2003, "Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme", *J Med Genet*, vol. 40, no. 11, pp. 807-814

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, nton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 72: 1117-1130

Berrington de Gonzalez A, Reeves G (2005) Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. *Br J Cancer* 93: 590-596

Breast Group of the Royal College of Radiologists (1989) Radiological nomenclature in benign breast change. *Clin Radiol* 40: 374-379

Claus EB, Risch N, Thompson WD (1994) Autosomal dominant inheritance of early- onset breast cancer. Implications for risk prediction. *Cancer* 73: 643-651

European Commission. ASQRAD - Assessment system for the quantification of radiation detriment. EUR 16644, CEPN-L95/2. 1996. Luxembourg, European Commission.

Griebsch, I. Cost-effectiveness of contrast enhanced magnetic resonance imaging Vs X-ray mammography of women at a high risk of breast cancer (MARIBS). 2006. Unpublished Work

Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V (1996) Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA* 276: 33-38

Kerlikowske K, Salzmann P, Phillips KA, Cauley JA, Cummings SR (1999) Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. *JAMA* 282: 2156-2163

Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, Manoliu RA, Kok T, Peterse H, Tilanus-Linthorst MM, Muller SH, Meijer S, Oosterwijk JC, Beex LV, Tollenaar RA, de Koning HJ, Rutgers EJ, Klijn JG (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 351: 427-437

Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, Kuhn W, Schild HH (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 23: 8469-8476

Law J (1995) Risk and benefit associated with radiation dose in breast screening programmes. *Br J Radiol* 68: 870-876

Law J, Faulkner K (2002) Two-view screening and extending the age range: the balance of benefit and risk. *Br J Radiol* 75: 889-894

Law J, Faulkner K (2001) Cancers detected and induced, and associated risk and benefit, in a breast screening programme. *Br J Radiol* 74: 1121-1127

Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, Gilbert FJ, Griebsch I, Hoff RJ, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Thompson D, Warren RM (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 365: 1769-1778

Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, Pisano E, Schnitt SJ, Gatsonis C, Schnall M, DeAngelis GA, Stomper P, Rosen EL, O'Loughlin M, Harms S, Bluemke DA, International B (2005) Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer* 103:
1898-1905

National Institute for Clinical Excellence 2004, *Familial Breast Cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and terttiary care*, National Institute for Clinical Excellence, London, Clinical Guideline 14

Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M (2005) Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 353:
1773-1783

Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. (2002) Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* 158: 220-235

Salzmann P, Kerlikowske K, Phillips K (1997) Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. *Ann Intern Med* 127: 955-965

Skaane P, Skjennald A (2004) Screen-film mammography versus full-field digital mammography with soft-copy reading: randomized trial in a population-based screening program--the Oslo II Study. *Radiology* 232: 197-204

Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, Cutrara MR, DeBoer G, Yaffe MJ, Messner SJ, Meschino WS, Piron CA, Narod SA (2004) Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 292:
1317-1325

Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, Goel V, Ramsay E, Chart PL, Cole DE, Taylor GA, Cutrara M, Samuels TH, Murphy JP, Murphy JM, Narod SA (2001) Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol* 19: 3524-3531

Young, K. C., Faulkner, K., Wall, B., and Muirhead, C. Review of radiation risk in breast screening. No 54. 2003. NHSBSP.

Appendix G

Updated recommendations from CG14/CG41 (2004 & 2006)

Recommendation from 2004/2006	Updated recommendations for 2013	Reason for change
• Support mechanisms (e.g. risk counselling, psychological counselling and risk management advice) need to be identified and should be offered to women not being offered mammographic surveillance who have ongoing concerns. (D). **[2004]**	• Offer support (for example, risk counselling, psychological counselling and risk management advice) to women who have ongoing concerns but are not eligible for surveillance additional to that offered by the national breast screening programmes[1]. **[2004, amended 2013]**	Recommendation amended to refer to national breast screening programmes and to apply to all types of surveillance.
• Before decisions on surveillance are made, written patient information and discussion should be offered. This should: • reflect the possible reduced sensitivity of mammographic detection of the younger age group with dense breasts and the increased potential for further investigations (C) • discuss the potential advantages and disadvantages of breast surveillance for early detection of breast cancer, including ○ radiation risks (C) ○ the possible psychological impact of a recall visit (D). **[2004]**	• Before decisions on surveillance are made, discuss and give written information on the benefits and risks of surveillance, including: - the possibility that mammography might miss a cancer in women with dense breasts and the increased likelihood of further investigations **[new 2013]** - possible over diagnosis - the risk associated with exposure to radiation - the possible psychological impact of a recall visit. **[2004,**	Recommendation amended to account for changes in the surveillance recommendations.

[1] National Breast Screening Programmes:

- England - NHS Breast Screening Programme (NHS Breast Screening Programme (NHSBSP))
- Wales - Breast Test Wales (Breast Test Wales: Home page)
- Northern Ireland – Breast Screening Programme (Breast Screening)

	amended 2013]	
• At entry to an MRI surveillance programme, and at each subsequent change in the programme, women should be provided with a documented plan which includes: - a clear description of the method(s) and intervals, including the risks and benefits - the reasons for any changes to the surveillance plan - sources of support and further information. **[2006]**	• At the start of a surveillance programme and when there is a transition or change to the surveillance plan, give women: - information about the surveillance programme, including details of the tests, how often they will have them and the duration of the programme - information about the risks and benefits of surveillance - details of sources of support and further information. **[2006, amended 2013]**	Recommendation amended to apply to all types of surveillance.
•	• Ensure that women know and understand the reasons for any changes to the surveillance plan**. [2006, amended 2013]**	Recommendation was previously part of the above recommendation but was made into a separate recommendation.
• MRI of both breasts should be performed to high quality standards ensuring both high temporal and spatial resolution. Dynamic sequences are recommended post contrast. They should be double-read where possible. **[2006]** •	• Ensure that MRI surveillance includes MRI of both breasts performed to national breast screening programme standards. **[2006, amended 2013]**	Recommendation amended to include reference to national breast screening programme.

Recommendation from 2004/2006	Updated recommendations for 2013
• MRI and any accompanying mammography data should be collected for audit purposes to support a national database. **[2006]** • When mammography is recommended in women under 50, digital mammography should be used in preference to conventional mammography at centres where this is available to NHS Breast Screening Programme standards. **[2006]** • Women who have been referred to a clinical genetics centre who are not known to have a genetic mutation should be offered an assessment of their 10-year breast cancer risk using a validated risk assessment tool (for example Tyrer-Cuzick or BOADICEA; Antoniou, 2004, Amir, 2003) to assess whether they are or will be eligible for MRI. **[2006]** • Women who are known to have a genetic mutation should be offered annual MRI surveillance if they are: - *BRCA1* and *BRCA2* mutation carriers aged 30–49 years - *TP53* mutation carriers aged 20 years or older. **[2006]** • MRI surveillance should be offered annually when indicated: From 30-39 years: - to a women at a 10 year risk of greater than 8%[2] From 40-49 years: - to a women at a 10 year risk of greater than 20%, or - to a women at a 10-year risk of greater than 12% when mammography has shown a dense breast pattern[3]. **[2006]**	• When women not known to have a genetic mutation are referred to a specialist genetics clinic, offer them assessment of their carrier probability using a carrier probability calculation method with acceptable performance (calibration and discrimination) to determine whether they meet or will meet the criteria for surveillance. (An example of an acceptable method is BOADICEA) **[new 2013]** • Offer annual mammographic surveillance to women: - aged 40-49 years at moderate risk[4] of breast cancer - aged 40-59 years at high risk[5] of breast cancer but with a 30% or lower probability of a *BRCA* or TP53 mutation. - aged 40-59 years with a greater than 30% probability of being a *BRCA* carrier[6] - aged 40-69 years with a known *BRCA1* or *BRCA2* mutation. **[new 2013]** • Offer mammographic surveillance as part of the population screening programme to women: - aged 50 years and over with a greater than 30% probability of being a TP53 carrier[7] - aged 60 years and over at high risk[5] of breast cancer but with a 30% or lower probability of a *BRCA* or TP53 mutation. - aged 60 years and over at moderate risk[4] of breast cancer

[2] A 10-year risk of 8% aged 30–39 and a 10-year risk of 12% risk aged 40–49 years would be fulfilled by women with the following family histories:

- 2 close relatives diagnosed with average age under 30 years*
- 3 close relatives diagnosed with average age under 40 years*
- 4 close relatives diagnosed with average age under 50 years*

*All relatives must be on the same side of the family and one must be a mother or sister of the woman

[3] As defined by the 3-point mammographic classification used by UK breast radiologists (Breast Group of the Royal College of Radiologists 1989] mammographic classification used by UK breast radiologists (Breast Group of the Royal College of Radiologists 1989]

[4] Lifetime risk of developing breast cancer is at least **17% but less than 30%**

[5] Lifetime risk of developing breast cancer is at least 30%. High risk group includes rare conditions which carry an increased risk of breast cancer, such as Peutz-Jegher syndrome, (STK11), Cowden (PTEN), Familial diffuse gastric cancer (E-Cadherin).

[6] Surveillance recommendations for this group reflect the fact that women who at first assessment had a 30%-or greater BRCA carrier probability and reach 60 years of age without developing breast or ovarian cancer will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance.

[7] Surveillance recommendations for this group reflect the fact that women who at first assessment had a 30%-or greater TP53 carrier probability and reach 50 years of age without developing breast cancer or any other TP53 related malignancy will now

• Women who have not been tested but have a high chance of carrying a BRCA1 or TP53 genetic mutation should be offered annual MRI surveillance from 30–49 years if they are at: - a 50% risk of carrying one of these mutations in a tested family, or - a 50% risk of carrying a BRCA1 or TP53 mutation in an untested or inconclusively tested family with at least a 60% chance of carrying a BRCA1 or TP53 mutation (that is, a 30% risk of carrying one of these mutations themselves). **[2006]** • Mammographic surveillance should not be available for women younger than age 30 years. (D) **[2004]** • For women aged 30-39 years of age satisfying referral criteria for secondary or specialist care, mammographic surveillance should be carried out: - only as part of a research study (ethically approved) or nationally approved and audited service. (D) and - individualised strategies should be developed for exceptional cases, such as: • women from families with BRCA1, BRCA2 or TP53 mutations. (C) • women with equivalent high breast cancer risk. (D). **[2004]**	- aged 60 years and over with a greater than 30% probability of being a *BRCA* carrier[6] - aged 70 years and over with a known *BRCA1* or *BRCA2* mutation. **[new 2013]** • Consider annual mammographic surveillance for women: - aged 30-39 years at high risk[5] of breast cancer but with a 30% or lower probability of a *BRCA* or TP53 mutation - aged 30-39 years with a greater than 30% probability of being a BRCA carrier[6] - aged 30-39 years with a known *BRCA1* or *BRCA2* mutation - aged 50-59 years at moderate risk[4] of breast cancer. **[new 2013]** • Do not offer mammographic surveillance to women: - under 29 years and under - aged 30 -39 years at moderate risk[4] of breast cancer - aged 30-49 years with a greater than 30% probability of being a *BRCA* carrier[6] - of any age with a known TP53 mutation[7]. **[new 2013]** *MRI surveillance* • Offer annual MRI surveillance to women: - aged 30-49 years with a greater than

have a lower than 30% carrier probability and should no longer be offered MRI surveillance.

• All women satisfying referral criteria to secondary or specialist care (at moderate risk or greater) should be offered mammographic surveillance from age 40 years. (C). **[2004]** • For women aged 40–49 years at moderate risk or greater, mammographic surveillance should be: - annual - to NHS Breast Screening Programme standards - audited - part of the NHS Research and Development Health Technology Assessment programme evaluation of mammographic surveillance of women younger than 50 with a family history wherever possible - only undertaken after provision of written information about the positive and negative aspects of surveillance. (D). **[2004]** • For women aged 50 years and older, surveillance should be: - as part of the NHS Breast Screening Programme, screened every 3 years (C) - more frequent mammographic surveillance should take place only as part of a research study (ethically approved) or nationally approved and audited service (D) and - individualised strategies should be developed for exceptional cases, such as: o women from families with BRCA1, BRCA2 or TP53 mutations (C) o women with equivalent high breast cancer risk (D). **[2004]** • If ongoing assessment of surveillance efficacy for women younger than age 50 years subsequently shows it is not cost effective, surveillance should be stopped. (D). **[2004]** • On the basis of current evidence, MRI and ultrasound should not be used in routine surveillance practice but may have a role in problem-solving mammographically detected abnormalities. (D) **[2004]** (Note: several studies have already been presented at major cancer meetings and will	30% probability of being a *BRCA* carrier[6] - aged 30-49 years with a known *BRCA1* or *BRCA2* mutation. - aged 20-49 years with a greater than 30% probability of being a TP53 carrier[7] - aged 20-49 years with a known TP53 mutation. **[new 2013]** • Consider annual MRI surveillance for women aged 50 – 69 years with a TP53 mutation. **[new 2013]** • Do not offer MRI to women at moderate risk or high risk of breast cancer but with a 30% or lower probability of a *BRCA* or TP53 mutation. **[new 2013]** • Do not offer MRI to women: - aged 20-29 years with a greater than 30% probability of being a *BRCA* carrier[6] - aged 20-29 years with a known BRCA1 or BRCA2 mutation. **[new 2013]** • Do not offer MRI to women aged 50-69 years and over: - with a greater than 30% probability of being a TP53 carrier[7] unless mammography has shown a dense breast pattern - with a greater than 30% probability of being a *BRCA* carrier[6], unless mammography has shown a dense breast pattern • with a known BRCA1 or BRCA2 mutation, unless mammography has shown a dense breast pattern. **[new 2013]** • Ensure that individual strategies are developed for all women having mammographic surveillance and that surveillance is: - to national breast screening programme standards - audited - only undertaken after written information is given about risks and benefits**. [new 2013]** • Do not routinely offer ultrasound surveillance to women at moderate or high risk of breast cancer but consider it: - when MRI surveillance would normally be offered but is not suitable (for example, because of

report in the next two years. This recommendation should be reviewed when they become available).	claustrophobia) - when results of mammography or MRI are difficult to interrupt. **[2013]** • Do not offer surveillance to women who have undergone a bilateral mastectomy**. [new 2013]** • Review eligibility for surveillance if family history changes (for example, if another member of the family develops breast cancer or a mutation is identified). **[new 2013]** • For women under 50 years who are having mammography, use digital mammography at centres providing digital mammography to the national breast screening programme standards. **[new 2013]**

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